Pain Research and Management

Shared Mechanisms of Chronic Pain and Emotional-Motivational Problems: From Basic Science to the Clinics

Lead Guest Editor: Susanne Becker
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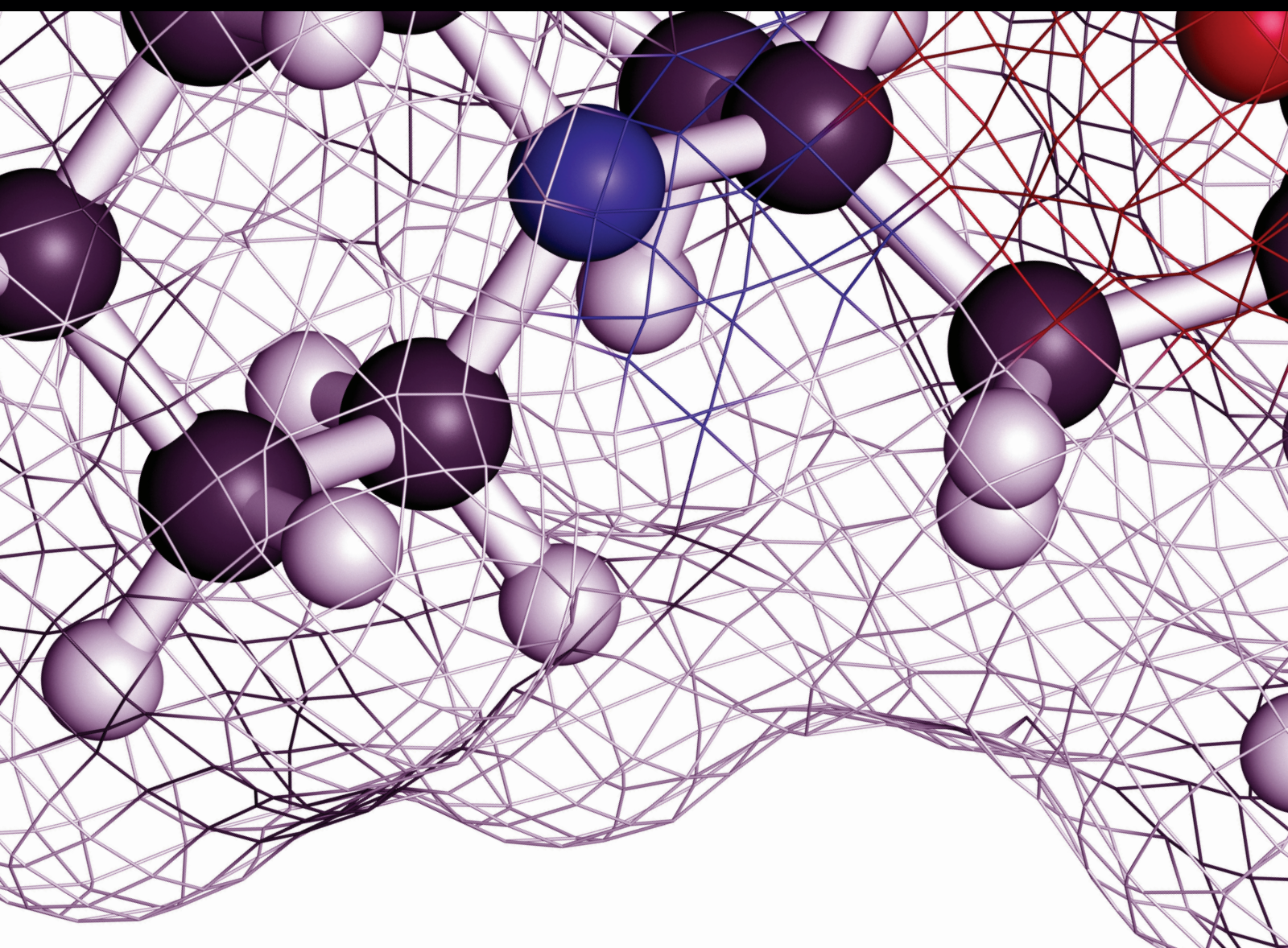

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Editorial Board

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Editorial

Shared Mechanisms of Chronic Pain and Emotional-Motivational Problems: From Basic Science to the Clinics

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Chronic pain is often associated with altered emotional and motivational states. High comorbidities between chronic pain and affective disorders are a well-known phenomenon. Many overlaps in the neural processing of pain, motivation, and emotion have been reported. For example, multiple brain regions that are involved in the processing of pain are also implicated in the processing of affective, motivational, and emotional events. Similarly, dysfunction of mesolimbic circuitry, which results in impaired motivated behavior, and which has been discussed as a causal mechanism in affective disorders, has been observed in chronic pain patients. Accordingly, it has been proposed that altered functioning of brain affective and emotional circuits may contribute to pain chronification. Apart from these neurophysiological overlaps, pain, motivation, and emotion show many similarities and interactions on a psychological level. For example, pain is a typical stressor that shifts motivational systems by urging initiation of protective behaviors (e.g., escape, avoidance, and hypervigilance). In addition, positive and negative emotional experiences as well as cognitive processes can modulate the perception of pain. Well-known examples of such cognitive-emotional pain modulation are placebo and nocebo effects that can lead to inhibition and facilitation of perceived intensity and unpleasantness of pain which can be mediated by anxiety. Based on these observations, it is conceivable that the multidimensional treatments incorporating pharmacological and nonpharmacological approaches of both pain and motivational-emotional disturbances could result in fruitful synergies.

To understand such interactions and possible shared mechanisms, a multidisciplinary view on the phenomenon of chronic pain and altered emotional-motivational processing is needed. The aim of the present special issue was to provide a platform to integrate such multidisciplinary views, discussing recent advances from basic to clinical research and giving the reader insights into the intersection between chronic pain, emotion, and motivation, as well as in the mechanisms of comorbid affective disorders and possible new applications in pain therapy.

The special issue comprises eight articles providing, on the one hand, a broad overview on emotion and motivation in chronic pain together with a focus on underlying mechanisms and highlighting translational approaches. On the other hand, specific outstanding phenomena and contexts are discussed in reviews and supported by original research articles reporting novel insights. Specifically, S. Becker et al. provide a review on the current state of the art on emotional and motivational pain processing, focusing on observations suggesting that in chronic pain a shift toward negative emotional-motivational processing occurs. By discussing various factors that might contribute to such a shift, for example, altered reward processing and goal regulation, a translational view is presented, emphasizing the great potential of translational approaches. Focusing on one of the most important brain structures in the context of emotional-motivational processing, namely, the amygdala, J. M. Thompson and V. Neugebauer provide a comprehensive overview of the role of the amygdala neurocircuitry

in pain, together with pain-related changes of this neurocircuitry. Importantly, possible pharmacological strategies targeting corticoamygdala dysfunction and pain-related amygdala hyperactivity are discussed from the perspective of basic and clinical science.

Three more reviews focus on phenomena related to emotional-motivational pain mechanisms pain. A.-K. Bräscher et al. review the literature on placebo hypoalgesia and nocebo hyperalgesia as forms of emotional-motivational pain modulation, concluding that the role of learning processes in this context is currently underestimated. Although the role of learning in placebo and nocebo effects is acknowledged, it appears neglected in human research. X. Fuchs et al. focus in their review on the role of emotion and cognition in phantom limb pain. Although perceptual and disability-related factors seem to be in forefront of factors affecting phantom limb pain, emotional factors, such as comorbid depression and anxiety, perceived stress, and cognitive factors, such as catastrophizing and maladaptive coping, affect severity of phantom limb pain and disability induced by the pain. Concentrating on children and adolescents with chronic pain, K. E. J. Mano delineates that anxiety is a crucial factor in paediatric chronic pain, with a comorbidity higher than in adults with chronic pain. They identify school as the major source of anxiety in children with chronic pain and discuss possible shared mechanisms of school anxiety and chronic pain as well as current approaches of assessing school anxiety.

Focusing on paediatric chronic pain as well, M. Pavlova et al. provide original data investigating the role of anxiety and depression in the relationships of chronic pain and sleep disturbances in young chronic pain patients (8–18 years of age). Paediatric pain is often associated with sleep problems, and the authors of this article show that this relationship is mediated by depressive and anxiety symptoms.

Two additional research articles investigated the role of affective-motivational and cognitive processes in physical functioning in chronic pain patients. R. Esteve et al. demonstrated that activity patterns in patients with chronic musculoskeletal pain are affected by patients' self-regulation of goals. Specifically, optimism affects this relationship, with higher levels of optimism being related to persistence, flexible goal management, and commitment to new goals, which in turn are associated with higher positive affect, persistence in finishing tasks despite pain, and less avoidance behavior. Last, O. Rasouli et al. hypothesized that higher cognitive load interferes with motor control, namely, postural control, in patients with fibromyalgia and chronic fatigue syndrome. Although this hypothesis could not be confirmed, both groups of patients displayed impaired postural control compared to healthy participants, and this impairment was correlated with perceiving fatigue related to their disorder.

In conclusion, this special issue highlights the complexity of chronic pain conditions and discusses the contribution of emotional, motivational, and cognitive factors. Understanding overlapping neural mechanisms that promote chronic pain will lead to improved prevention and treatment of chronic pain.

Conflicts of Interest

The editors declare that there are no conflicts of interest.

Susanne Becker
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Research Article

A Concurrent Cognitive Task Does Not Perturb Quiet Standing in Fibromyalgia and Chronic Fatigue Syndrome

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Background and Objectives. Cognitive complaints are common in fibromyalgia (FM) and chronic fatigue syndrome (CFS). Fatigue as well as pain may require greater effort to perform cognitive tasks, thereby increasing the load on processing in the central nervous system and interfering with motor control. *Methods*. The effect of a concurrent arithmetic cognitive task on postural control during quiet standing was investigated in 75 women (aged 19–49 years) and compared between FM, CFS, and matched controls ($n = 25$/group). Quiet standing on a force plate was performed for 60 s/condition, with and without a concurrent cognitive task. The center of pressure data was decomposed into a slow component and a fast component representing postural sway and adjusting ankle torque. *Results*. Compared to controls, CFS and FM displayed lower frequency in the slow component ($p < 0.001$), and CFS displayed greater amplitude in the slow ($p = 0.038$ and $p = 0.018$) and fast ($p = 0.045$) components. There were no interactions indicating different responses to the added cognitive task between any of the three groups. *Conclusion*. Patients displayed insufficient postural control across both conditions, while the concurrent cognitive task did not perturb quiet standing. Fatigue but not pain correlated with postural control variables.

1. Introduction

Executive function generally requires concerted cognitive and motor ability. In patients suffering pain and fatigue, there is evidence of cognitive difficulties as well as motor control deficits [1, 2], and patients often complain about increased effort and difficulty performing cognitive tasks [3, 4]. Cognitive dysfunctions, including working memory impairment, attention deficit, and less efficient information-processing capacity, are core symptoms reporting pain and fatigue conditions, specifically in chronic fatigue syndrome (CFS) and in fibromyalgia (FM). These patients are often more troubled by cognitive difficulties than by other symptoms [5]. Neuroimaging has demonstrated functional and structural alterations in the central nervous system (CNS) and a pattern of increased neural recruitment during cognitive tasks in both CFS [6] and FM [7]. Increased effort in these patients to perform is reported after physical as well as mental exertion, and is seen as lingering postexertional fatigue [8, 9]. Whether a greater mental effort and increased neural recruitment during cognitive tasks may interfere with motor control remains to be shown.

Possible consequences of pain and fatigue on motor function are often forgotten but need to be recognized. Cognitive neuroscience has shown that pain and fatigue are overlapping symptoms between different conditions and diagnoses and may be an effect of chronification with changes in similar regulatory mechanisms in the central nervous system (CNS), particularly in domains not under voluntary control [10]. This may affect certain aspects of motor performance, as sensory motor learning requires ability to maintain and update internal models. This is a prerequisite for prediction of action, necessary to allow a series of events to be contained without the need of

voluntary control [11]. Perception of pain and fatigue may interfere with this process as deficits in balance and postural steadiness have been demonstrated in patients with FM as well as in CFS [12, 13] with similar deficits found in dynamic postural control at gait initiation [14].

Notably, brain-body-environment interactions and perception-action links are common basis for behavior without representational separation between domains [15]. Deficits in either domain may thus affect performance when executed concurrently due to sharing of neural networks between cortical areas [16]. Attention and sensory integration are essential to produce appropriate motor output such as balance control [17]. In some populations, particularly the fragile elderly, the risk of falling increases with the addition of a concurrent task such as talking while walking [18], and execution of multiple tasks is a major risk factor for falls [19]. Notably, there is some evidence suggesting premature aging of brain areas in both FM and CFS [20, 21], which may affect the execution of multiple tasks in persons with these diagnoses.

The addition of a cognitive task while maintaining postural control in quiet standing is thus expected to increase the load on central processing and therefore affects the ability to sustain postural equilibrium. In healthy persons, the controlling strategy appears to tighten to maintain postural equilibrium when a cognitive component is added. As an effect, postural sway may decrease [22]. In contrast, elderly with risk of falling display increased rather than decreased postural sway [23].

A dual task paradigm is generally used to study the interference between postural control and cognitive loading [17], and was therefore considered appropriate to investigate motor responses during quiet standing in FM and CFS. To find whether patients with FM and CFS would respond either similarly to healthy young individuals with reduced postural sway [24] or similar to elderly with increased postural sway [23] and greater regulatory force [25], both the controlled and the controlling parameters need to be assessed [26]. That is, on the level of performance and on the level of control of posture. A means to asses this is via structural data analyses by decomposition of ground reaction forces registered by a force platform. In addition to measures in the time domain that describe the magnitude of these components, additional measurements in the frequency domain are necessary to define the control strategies [27, 28]. Impaired postural control and the effect of added cost of a concurrent task may be expressed as deviations in both components in both the time and frequency domains.

Given the evidence that pain as well as fatigue affects motor and cognitive ability and findings of reduced postural stability, cognitive complaints, problems with sensory integration, and signs of premature aging in patients with FM and in patients with CFS, it was hypothesized that a cognitive task would cause an increased load on central processing in both patient groups. This would cause reduced drive for maintaining satisfactory postural control. Hence, postural sway was expected to increase, similar to in elderly [25].

2. Methods

A cross-sectional case-control study was designed to investigate the effect of a concurrent cognitive task on postural control parameters during quiet standing. Seventy-five females, aged 19–49 years, participated in this study (Table 1). The number of participants was estimated based on a previous study, using a similar protocol, on schizophrenic patients with 30 participants divided into two groups [29]. In the present study with three groups and less severe conditions, the number of participants was increased to 25 in each group. Inclusion criteria were young to middle aged females, as diagnoses of CFS and FM are predominant in women within this age span. Patients diagnosed with both FM and CFS were excluded. Eighty-seven patients were found eligible for participation, and those interested were referred by their attending physician and included consecutively during a period of 20 months. Thirty-two declined and data from four were excluded due to unsatisfactory quality. One patient with FM did not complete the test due to pain. Data were used from 25 patients diagnosed with CFS according to the Centers for Disease Control and Prevention criteria [30] and 25 patients diagnosed with FM according to the American College of Rheumatology (ACR) 1990 criteria [31]. Diagnoses were determined in collaboration between a rheumatologist, psychiatrist, and neurologist at the National Competence Centre for Complex Symptom Disorders. Condition severity was determined by the Fibromyalgia Impact Questionnaire (FIQ) and the Chalder Fatigue Scale. Twenty-five healthy control (HC) persons recruited from students and staff of the hospital and university constituted an age- and gender-matched control group with no history of chronic pain or fatigue. Exclusion criteria for all were diagnosed psychiatric disorder, clinical depression, neurological condition, musculoskeletal disorder, vestibular deficits, or uncorrected reduced vision potentially interfering with postural control. Verbal and written information was given, and written informed consent was obtained from each participant. The study was registered in Clinical Trials (NCT01686074) and approved by the Regional Ethical Committee for Medical and Health Research Ethics (2012/679/REK midt) and conducted according to the Declaration of Helsinki.

2.1. Data Acquisition. Participants performed two different trials of quiet standing with open eyes on a firm surface: a baseline condition without a concurrent cognitive task and an experimental condition with a concurrent cognitive task. The concurrent task consisted of counting backward aloud from 150 in steps of 7, designed to ensure actual execution of the cognitive task and minimize verbalization to prevent rhythmic counting and breathing, potentially influencing quiet standing performance [32]. Three-dimensional (3D) ground reaction forces were registered at 100 Hz with a Kistler force plate (9260AA6; Kistler Instruments AG, Switzerland).

Each test was performed once, for 60 seconds [33], without shoes, feet parallel, and arms folded across the chest.

Table 1: Characteristics of the participants in each group.

Variables	HC ($N = 25$)	CFS ($N = 25$)	FM ($N = 25$)
Age (years)	34.4 (7.9)	34.0 (8.9)	38.6 (8.0)
Weight (kg)	68.0 (9.8)	71.6 (12.9)	75.4 (14.3)
Height (cm)	167.2 (7.1)	169.1 (5.4)	168.5 (6.0)
BMI (kg/m^2)	24.3 (3.5)	25.2 (5.1)	26.5 (4.5)
Education (years)	16.1 (2.3)**	13.4 (2.5)**	13.5 (2.2)**
Pain level[a]	0.08 (0.28)*,**	1 (1.16)*	3.7 (1.8)**
Fatigue level[a]	0.6 (0.8)**	3 (1.8)**	3.2 (2.2)**
Chalder score	5.8 (5.7)*,**	25.4 (3.8)**	21.1 (5)*
FIQ	—	—	56.9 (13)

Data are presented as means (SD). HC: healthy control; CFS: chronic fatigue syndrome; FM: fibromyalgia; FIQ: Fibromyalgia Impact Questionnaire. [a]Level of pain and fatigue on the day of testing registered upon arrival to the lab. *Significance level 0.05; **significance level 0.01.

Feet width was individually standardized as the distance equal to half the shoulder width between the acromial processes and marked on the platform to ensure the same foot position for both conditions. All participants started with the baseline condition to ensure equal potential learning and/or fatigue effect. Instructions were to step onto the platform, stand still and relaxed without moving the head or extremities, or talk except articulating the numbers. A red cross (21 × 21 cm), 4 m away at eye level, served as a visual reference point for postural control. To establish a steady, quiet stance, the participant was informed that the test was commenced 10 s before the recording started and that it was finished 3 s after the data collection was completed. One-minute seated rest was provided between the conditions.

2.2. Data Analysis. Fifty-eight seconds of data were used from each trial, excluding one second at the start and end of the recording to avoid potential electronic noise from the start and stop key. Data were analyzed in MATLAB (R2014a; MathWorks Inc., Natick, MA). The preprocessed center of pressure (CoP) signals (2nd order Butterworth, 8 Hz, low pass, zero lag) was decomposed into a slow component and a fast component according to the concept of instant equilibrium forces [26]. Instants of equilibrium points in the signal, when the total horizontal force equals zero, were identified, and the CoP positions at these instants were determined and interpolated by a cubic spline function for estimation of the trajectory of the slow component. The slow component is ascribed to the movement of the center of mass (CoM) of the body, that is, postural sway. Deviation of CoP from the approximated trajectory of the slow component was determined as an estimation of the trajectory of the fast component. The fast component can be attributed to the torque created by the movement of the ankle joint to control postural sway [26].

Amplitude and frequency parameters were computed for the slow and fast components. Amplitudes were calculated by computing the 95% confidence ellipse area (mm^2), defined from the first two principal components of each of the slow and fast components [34]. The two radii of the ellipses were defined by the mediolateral (ML) and anteroposterior (AP) directions. The frequency content of the slow and fast components in the ML and AP directions were estimated by the Fourier analysis of the characteristics of the power spectral density using Welch's periodogram method [34].

2.3. Statistical Analysis. The statistics were performed using the SPSS statistical software (Version 22; IBM Corporation, USA). Normal distribution was verified with P-P plots, and histograms were inspected for control of skewness and kurtosis. A mixed-design analysis of variance (ANOVA) was used to analyze the effect of group, condition, and interaction (group × condition), with group ($n = 3$; HC, CFS, and FM) as the between-subjects factor and condition ($n = 2$; baseline and experimental) as the within-subjects factor. Sphericity was determined according to Mauchly's test. Wilks' lambda was used for multivariate exact statistics for between-subjects effects. Pairwise comparisons with Bonferroni corrections were performed to identify significant differences between groups and between conditions. Pearson correlations were used to investigate the influence of pain, fatigue, and education on postural control variables in the patient groups. Age, weight, and BMI did not differ between the three groups (Table 1), and there were no correlations between these variables and the outcome variables. Therefore, they were not included as covariates. Partial eta-squared ($\eta^2 p$) was used for effect size. The alpha level was set at $p < 0.05$.

3. Results

Overall, there were no statistical differences between CFS and FM, and both groups displayed generally similar and greater amplitudes and lower frequencies for the slow component as well as the fast component compared to HC, across both conditions (Figures 1 and 2; Table 2). Differences in strategy for postural control as an effect of the added concurrent cognitive task could not be inferred from single variables as there were no significant interactions between group and condition on any variable. Table 2 shows the results of the main effects and post hoc comparisons. Across patient groups, there were some scattered correlations between fatigue variables with postural control, but no correlations with pain variables.

3.1. The Slow Component. The analysis showed that *amplitude (AP and ML)* differed between groups: $F_{2;71} = 3.96$, $p = 0.023$, $\eta^2 p = 0.100$ (Figure 1). Significant main effects of the group were found for amplitude in both the AP ($p = 0.044$) and the ML ($p = 0.020$) directions. Post hoc analyses showed greater amplitude for CFS compared to HC in the AP ($p = 0.038$) and the ML ($p = 0.018$) directions, but no differences were found between FM and HC (Figure 1; Table 2).

The analysis showed that *frequency* differed between groups: $F_{2;71} = 7.03$, $p = 0.002$, $\eta^2 p = 0.162$ (Figure 1). Significant main effects of the group were found for frequency in both AP ($p < 0.001$) and ML ($p < 0.001$) directions. Post hoc comparisons showed similar and lower frequency for both FM and CFS compared to HC in both the AP and the ML directions ($p < 0.001$ for all) (Figure 1; Table 2).

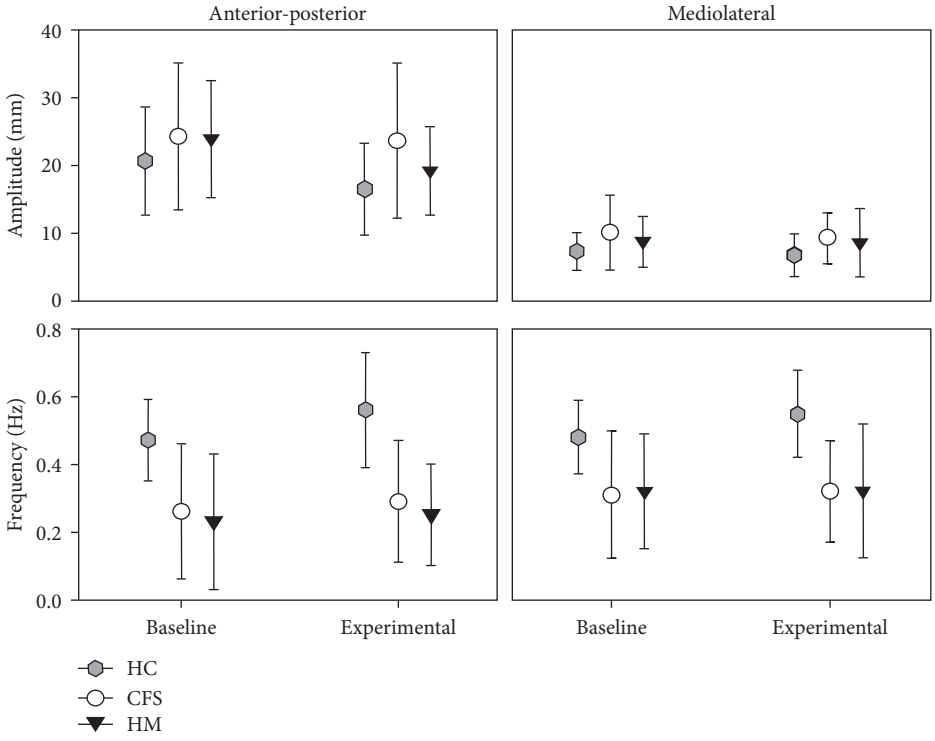

Figure 1: Estimated group means (standard error) of the slow component derived from the center of pressure data representing postural sway during quiet standing in both anteroposterior and mediolateral directions. Baseline and experimental conditions with the concurrent cognitive task are shown.

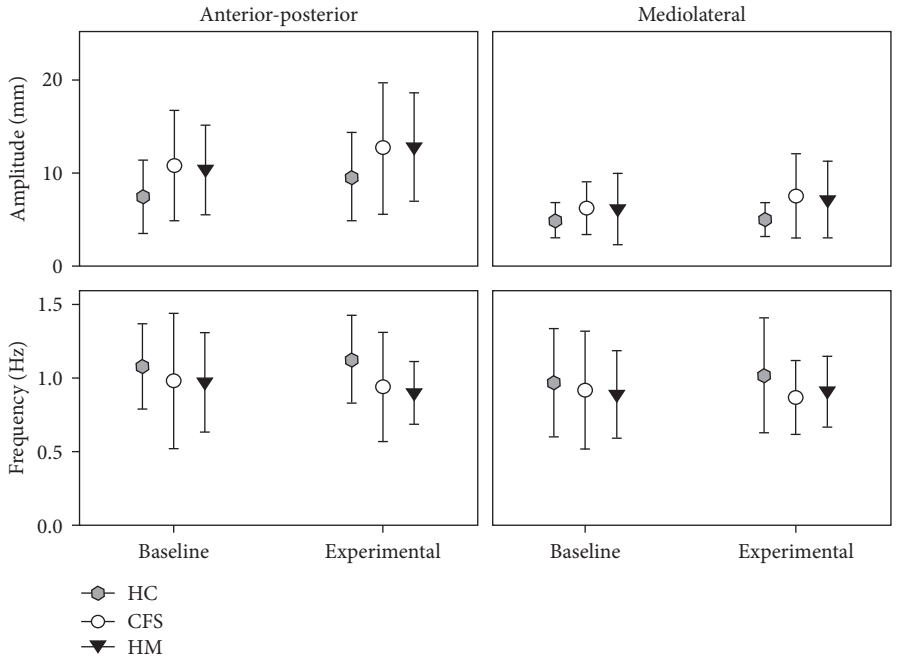

Figure 2: Estimated group means (standard error) of the fast component derived from the center of pressure data representing adjusting ankle torque during quiet standing in both directions. Baseline and experimental conditions with the concurrent cognitive task are shown.

As an effect of condition, the amplitude in the AP direction decreased ($p = 0.006$) with the experimental task, whereas the frequency increased in both the AP ($p = 0.02$) and the ML ($p = 0.030$) directions.

3.2. The Fast Component. The analysis showed that *amplitude (AP and ML)* differed between groups: $F_{2;71} = 4.38$, $p = 0.016$, $\eta^2 p = 0.110$ (Figure 2). There was a significant main effect of the group for amplitude in the AP ($p = 0.033$) and

Table 2: The results of repeated-measures ANOVA for each variable.

	Variable	Group * condition	Condition	Group	Post hoc
Area	CoP	$F(2, 81) = 0.45$	$F(1, 81) = 0.76$	$F(2, 81) = 6.16^{**}$	HC-CFS**, HC-FM*
	Postural sway	$F(2, 81) = 0.20$	$F(1, 81) = 4.32^{*}$	$F(2, 81) = 5.08^{**}$	HC-CFS**
	Adjusting ankle torque	$F(2, 81) = 2.41$	$F(1, 81) = 15.93^{**}$	$F(2, 81) = 5.97^{**}$	HC-FM**
Postural sway	Amp-AP	$F(2, 81) = 0.84$	$F(1, 81) = 6.92^{*}$	$F(2, 81) = 4.36^{*}$	HC-CFS*
	Amp-ML	$F(2, 81) = 0.41$	$F(1, 81) = 0.71$	$F(2, 81) = 4.90^{*}$	HC-CFS*
	F-AP	$F(2, 81) = 1.61$	$F(1, 81) = 13.08^{**}$	$F(2, 81) = 22.08^{**}$	HC-CFS**, HC-FM**
	F-ML	$F(2, 81) = 1.24$	$F(1, 81) = 5.67^{*}$	$F(2, 81) = 16.01^{**}$	HC-CFS**, HC-FM**
Adjusting ankle torque	Amp-AP	$F(2, 81) = 1.07$	$F(1, 81) = 12.38^{**}$	$F(2, 81) = 4.89^{*}$	HC-FM*
	Amp-ML	$F(2, 81) = 0.70$	$F(1, 81) = 4.79^{*}$	$F(2, 81) = 4.99^{**}$	HC-CFS*, HC-FM*
	F-AP	$F(2, 81) = 0.82$	$F(1, 81) = 0.53$	$F(2, 81) = 2.51$	—
	F-ML	$F(2, 81) = 0.77$	$F(1, 81) = 0.01$	$F(2, 81) = 1.55$	—

CoP: center of pressure; Amp: amplitude (mm); F: frequency (Hz); AP: anteroposterior; ML: mediolateral; conditions: baseline and experimental conditions with the concurrent cognitive task; HC: healthy control; CFS: chronic fatigue syndrome; FM: fibromyalgia; * $p < 0.05$; ** $p < 0.010$.

the ML ($p = 0.031$) directions. Post hoc analysis showed a greater amplitude only in the ML direction and only for CFS ($p = 0.045$) compared to HC (Figure 2; Table 2). A multivariate analysis for the AP and ML directions showed that *frequency* did not differ between groups: $F_{2;71} = 0.20$, $p = 0.820$, $\eta^2 p = 0.006$.

As an effect of condition, the amplitude increased only in the AP direction ($p = 0.005$) as a response to the experimental task, whereas the frequency did not change significantly (Figure 2; Table 2).

3.3. Correlations. Across patient groups, the frequency in the AP direction in the slow component increased with fatigue before the test across both conditions (baseline $r = 0.306$, $p = 0.030$; experimental $r = 0.329$, $p = 0.020$). In the experimental condition, the frequency in the AP direction in the slow component also increased with fatigue after the test ($r = 0.332$, $p = 0.019$) and with Chalder's fatigue score ($r = 0.350$, $p = 0.001$). In the experimental condition, Chalder's fatigue score also correlated positively with the frequency in the ML direction in the slow component ($r = 0.318$, $p = 0.024$). At baseline, the amplitude in the AP direction in the fast component correlated with fatigue before the test (baseline $r = 0.405$, $p = 0.003$). Pain variables, including FIQ, and education did not correlate with postural control.

4. Discussion

This study is, to our knowledge, the first that collectively evaluated the effect of a concurrent cognitive task on postural control in quiet standing in patients with FM and CFS compared to controls. The study comprised both the fast and the slow components derived from CoP measurements, defining the controlling variable (attributed to adjusting ankle torque) and the controlled variable (ascribed to postural sway), respectively. The results supported our hypothesis only in part, showing unsatisfactory postural control in both patient groups, characterized by larger amplitudes and lower frequencies for the slow and fast component in both the anteroposterior and mediolateral directions during both conditions, with and without a concurrent cognitive task. There were no significant differences between the patient groups, but the CFS group performed in general worse than the FM group when compared to controls. We found no interactions that supported different patterns of postural control strategies in response to the added cognitive task in any of the patient groups compared to controls. As seen in Figures 1 and 2, the profiles of the responses are similar for all groups.

Both patient groups displayed larger amplitude in the slow component, which represents the movement of the body's CoM, thus indicating larger postural sway. This suggests worse performance in patients. Both patient groups also displayed larger amplitudes in the fast component, which is attributed to lateral forces that controls the position and movement of CoM. This suggests a deficit in control where the ankle torque is too large relative to the frequency. Notably, the frequency of the fast component was similar across all three groups. In theory, if the torque is too large relative to the frequency, it will cause greater postural sway as CoM is pushed too far in one direction before a counteracting force is created [29]. Alternatively, larger postural sway may be due to that the timing of the adjusting ankle torque was not sufficiently synchronized to correct the drift of CoM at the right moment. This assumption fits with the Drift-and-Act Hypothesis, which proposes that postural control includes a sequence of drift-and-act episodes where the body deviates from the vertical line until the sensory information has been processed in the CNS and a corrective action is initiated [35].

Our hypothesis that the amplitude of the slow component would increase and amplitude and frequency in the fast component decrease in patients as an effect of the concurrent cognitive task, indicating larger postural sway and reduced drive to maintain adequate postural control, was not supported. Even though patients in general displayed larger amplitudes relative to the frequency in the fast component, and larger amplitudes and lower frequencies in the slow component, the intrinsic patterns at baseline and in the experimental task followed a similar profile in all groups. This implies that the nature of the response to an added cognitive task was not different in patients compared to

controls. Similar responses in healthy subjects to added cognitive loading during quiet standing were presented in previous studies, showing reduced CoP area [36] and sway amplitude [37] and increased sway frequency [32]. CoP is a measure of the migration of the total reaction force across the support surface and postural sway is the parameter that the system needs to control. In addition to measures used in these previous studies mentioned above, the present study also assessed the fast component in the CoP signal, which is interpreted as the lateral and controlling force that can be attributed to ankle torque [26]. Increased amplitude in the fast component confirmed the assumption of upgraded control with a concurrent cognitive task in quiet standing, proposed by Dault et al. [32]. This furthermore supports the assumption that arousal and postural control are related and that a concurrent cognitive task can increase arousal and attention compared to only quiet standing without an additional task, thus upgrading the control [38].

Performing a concurrent cognitive task in quiet standing increases the load on central processing [37], and was expected to negatively affect postural control in the patients. Although the amplitude of the slow component was generally larger in patients, it decreased while performing the concurrent cognitive task, which reflects a normal response to an added or increased cognitive load [37]. This normal response in patients may be explained by that the level of difficulty for either the cognitive or the postural task was too low to challenge control. Other explanations may be that patients were, despite their diagnoses, in relatively good shape and participated on a good day. We noted several cancellations due to feeling too unwell to come to the lab, and one patient who was unable to finish the test due to pain. Thus, a more challenging test may, or may not, trigger responses similar to in elderly with risk of falling, that is, larger amplitude in the slow component and reduced amplitude and/or frequency in the fast component. That the cognitive task did not cause increased amplitude in the fast component may also be explained by the "posture first principle" [39] as attention is typically aimed toward postural control at the cost of other tasks, to secure stability, provided a sufficient level of control.

The generally worse performance in patients compared to controls may be explained by several factors. Deficits in the sensory motor processing [40] and neurological symptoms such as muscle weakness and poor balance [41] have been reported in both FM and CFS. Evidence of the accelerated age-related decrease in white and gray matter in the CNS has been shown in both patient groups [20, 21], suggesting reduced ability in central processing comparable to elderly persons, including cognitive dysfunction that links to postural instability [42]. Reduced attentional and cognitive capacity as a result of pain and fatigue may contribute to explain the generally reduced postural control displayed in patients in the present study [43]. Multiple factors could potentially contribute to explain the reduced control of standing posture, more specifically, delayed triggering of a corrective action, and a slow action process [1, 44].

In the present study, we could however not find any correlations between pain, before or after the test or for FIQ, with any of the postural control variables. Fatigue before and after the test as well as the Chalder Fatigue Scale did in contrast correlate with several, but apparently scattered, postural control variables. Two correlations were found at baseline, while four were found in the experimental condition. Of those, two were for the same variable, frequency for the slow component in the AP direction, which suggests that the correlations were not totally random. It was however counter intuitive that the correlations with fatigue were positive for frequency, as frequency was generally lower in patients. Higher frequency and larger amplitude do however add up to higher velocity, and velocity is shown to be the most important cue that the system uses for control of posture rather than position or acceleration [45]. For a full explanation of the nature of postural control deficits, several different measurements may have to be considered.

Post hoc comparisons revealed larger and other differences for postural control in patients with CFS than in patients with FM when compared to controls. This finding was in line with shown correlations between fatigue and postural control. Notably, there is up to 70% diagnostic overlap between CFS and FM [46], indicating that fatigue is common also in FM. Note that education did not correlate with postural control variables in the present study. Thus, fatigue rather than pain or cognition may explain demonstrated deficits in postural control.

Although the response to the concurrent cognitive task in patients did not indicate reduced control as expected, the number of correlations between fatigue and postural control variables increased. Importantly, there is a link between mental fatigue and cognition, at least in CFS [3]. Previous studies seem to point to different cognitive deficits in these patient groups that may depend on fatigue. Slow information processing has been demonstrated in patients with CFS, while patients with FM display impaired ability of attention [5]. A review of the current research on neuropsychological functioning in CFS shows that slowed processing speed, impaired working memory, and poor retention of information are the most prominent features of cognitive dysfunction [47]. Note, however, that more recent research in cognitive neuroscience claim that overlapping symptoms between these conditions may be an effect of chronification with changes in similar regulatory mechanisms in the CNS [10]. Essentially, described discrepancies between cognitive difficulties in FM and CFS may thus owe to different study methods in different studies rather than true differences in underlying deficits. Recent studies support the findings of motor and cognitive affection both in patients with CFS [1] and FM [2], but hitherto no specific or unique patterns of cerebral changes have been found that distinguish these conditions from each other.

Future research on the effect on postural control of concurrent tasks should increase the level of task difficulty to challenge capacity in the patients. Future research should also study the interrelationship in central processing between pain and fatigue with cognition and motor control.

The present results should be interpreted with reservation to the following limitations: we did not assess the cognitive functioning, and medications were not controlled

beyond the use of analgesics for pain. Verbalization and respiratory pattern, as potential interference with postural sway, was not monitored. Although the cognitive task was designed to minimize verbalization, to prevent rhythmic counting and thereby rhythmic breathing, the frequency of verbalization was not standardized or controlled for. A relatively small sample size may limit external validity due to the great heterogeneity of symptoms in both CFS and FM.

5. Conclusion

The intrinsic patterns at baseline and in the experimental condition followed a similar profile in all groups, without any interactions that supported different postural control strategies in response to the concurrent cognitive task in patients. Both patient groups did however display insufficient postural control compared to control persons, generally characterized by larger amplitude and lower frequency in the slow component representing postural sway, and larger amplitude in the fast component attributed to adjusting ankle torque. It is proposed that a mismatch between the magnitude and frequency of the controlling ankle torque induced greater postural sway in patients. The CFS group displayed greater differences than the FM group compared to controls, suggesting a somewhat worse general performance. Correlations between fatigue and postural control but not between pain and postural control indicate that fatigue is the explaining factor for reduced postural control in both groups. There were no statistical differences between patient groups.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Emotional and Motivational Pain Processing: Current State of Knowledge and Perspectives in Translational Research

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Pain elicits fear and anxiety and promotes escape, avoidance, and adaptive behaviors that are essential for survival. When pain persists, motivational priority and attention shift to pain-related information. Such a shift often results in impaired functionality, leading to maladaptive pain-related fear and anxiety and escape and avoidance behaviors. Neuroimaging studies in chronic pain patients have established that brain activity, especially in cortical and mesolimbic regions, is different from activity observed during acute pain in control subjects. In this review, we discuss the psychophysiological and neuronal factors that may be associated with the transition to chronic pain. We review information from human studies on neural circuits involved in emotional and motivational pain processing and how these circuits are altered in chronic pain conditions. We then highlight findings from animal research that can increase our understanding of the molecular and cellular mechanisms underlying emotional-motivational pain processing in the brain. Finally, we discuss how translational approaches incorporating results from both human and animal investigations may aid in accelerating the discovery of therapies.

1. A Shift to Negative Emotional-Motivational Processing in Chronic Pain

Pain is much more than the conscious perception of a sensory event. It is aversive and inseparably linked to emotion as reflected in the generally accepted definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. In chronic pain, a high comorbidity with affective disorders such as depression and anxiety has been reported [2]. It has been hypothesized that in chronic pain, a predominance of processing of negative emotional information might underlie emotional-motivational problems such as depression and anxiety. Research on pain has shifted in the last couple of decades from a strong focus on nociception toward a broader perspective that includes factors such as pain-relevant emotion and motivation that may contribute to the development and maintenance of chronic pain [3, 4].

A central feature of pain is that it is a strong stressor and motivator that can induce fear and anxiety and urges escape and avoidance responses. Acute pain is physiological by acting as an alarm system, thereby preventing further damage and promoting behavior directed toward healing. However, in chronic pain, fear, anxiety, and escape and avoidance responses become maladaptive, often resulting in impaired functionality, social withdrawal, anxiety, and depression [5]. The idea that chronic pain is related to a negative emotional-motivational shift is intriguing because it provides an explanation for dysfunctional processes related to reward, learning, goal regulation, and avoidance and approach behavior. However, investigating the mechanisms underlying a shift to negative emotional-motivational pain processing is challenging. Animal models allow important insights into

neurobiological mechanisms; however, assessment of emotional-motivational aspects of pain is not comprehensive. In contrast, subjective experiences can be easily assessed in humans, but uncovering underlying neurobiological mechanism is more difficult. Translational approaches offer benefits linking these two domains.

In this review, we focus on emotional-motivational factors possibly underlying a shift towards negative processing in chronic pain, bringing together information from animal and human research. Reward processing, learning, goal regulation, and related pain avoidance behavior are such factors that seem to play a prominent role in pain and that are likely altered in the proposed shift. Possible synergies of translational research are highlighted, along with approaches on how preclinical research can be informed by human studies and vice versa.

2. Human Studies to Investigate an Emotional-Motivational Shift Towards Negative Affective States in Chronic Pain

Human behavior is directed by goals in a broad array of domains (e.g., social, work-related, health). Thus, understanding an individual's response to acute and ongoing pain requires thorough examination of the motivational dynamics between this pain and other demands. Self-regulation theories, describing the processes by which one attempts to gain control over behavior, thoughts, feelings, desires, and actions in the service of goal attainment [6, 7] provide useful insights into a range of phenomena including avoidance behavior and attentional processes [8]. An important aspect of self-regulation is how people modulate negative states, including pain, in the process of goal pursuit. Ongoing pain is often perceived as a barrier to the pursuit of valued goals [9]. The presence of ongoing pain results in perceived or anticipated discrepancies between actual and desired behavioral outcomes, resulting in negative effect. In an early state, patients with persistent pain are often motivated to stay committed to earlier (prepain) life goals and performance standards [10]. This is reflected by task persistence despite pain, which requires cognitive shielding and effort mobilization [11]. For example, attention will be focused on goal-relevant information, whereas distracting pain information will be inhibited [12]. In case of repeated goal failure, however, a motivational shift towards pain-related goals might occur, which often becomes a very dominant goal in patients' goal hierarchy. Individuals then prioritize effort towards goals such as getting rid of or acquiring control over the ongoing pain problem, which is often reflected by increased problem-solving attempts and avoidance behavior [13], which are often maladaptive in ongoing and chronic pain. Such motivational shift is typically associated with a narrowed focus of attention toward pain-related information, increased accessibility of negative information, and worrying [10, 14]. Repeated failure of problem-solving attempts and attainment of valued goals might, at some point, start inducing feelings of helplessness and hopelessness and associated states of depression and anhedonia. According to Brandtstädter and Rothermund [11], such (temporary) states may be adaptive, because they urge reappraisal of the current situation and disengagement from inefficient effort mobilization to unattainable goals. Goal disengagement is reflected by devaluation of blocked goals, acceptance, and a shift of attention from narrowly focused and top-down towards more holistic, broad-based, and bottom-up, allowing activation of alternative goals that may be more feasible and less affected by pain.

In addition to goal regulation, self-regulation theories consist of many factors, such as reward processing, learning, and approach and avoidance. All these factors, in themselves, have suggested mechanisms likely involved in an emotional-motivational shift in chronic pain. For example, reward processing has been dissected into dissociable components of wanting, that is, the motivation to obtain a reward, and liking, that is, the hedonic experience of such a reward [15]. Both components can be differentially affected by pain [16, 17]. Pain has been reported to increase wanting while leaving liking unaltered [5, 18]. This mismatch may reflect a drive to compensate for a negative emotion induced by pain, but being unsuccessful to increase pleasure. In chronic pain, a similar mismatch could represent unsuccessful coping attempts, and the lack of increased pleasure following "trying harder" could potentially lead to phenomena like learned helplessness [16]. Learning comprises several processes that are mechanistically very different in promoting behavior and/or perception. For example, operant learning results from the consequences of a behavior where the desired consequences lead to an increase in the probability that preceding behavior will be shown again (i.e., reward), while undesired consequences lead to a decrease of this probability (i.e., punishment) [19]. In contrast, respondent or Pavlovian learning is the process, by which a formerly neutral stimulus comes to elicit a response that is similar as a response elicited by a naturally meaningful stimulus. Pain is a meaningful stimulus, eliciting, among other reactions, fear. If this pain is repeatedly coupled to a neutral stimulus, for example, a specific situation or movement (which does not cause the pain directly), this conditioned stimulus (CS) can then elicit fear [20]. Approach and avoidance can be the results of such learning. For example, one can learn to avoid pain- or fear-inducing situations. Avoidance leads to particularly robust behavior. Because of avoidance, a person does not experience that a feared stimulus is no longer harmful or threating, potentially delaying recovery. Such processes are well known in pain [21, 22].

The theoretical framework presented here, providing insight in how people struggle to make sense of unwanted experiences and how they avoid, adapt, or alter the perceived causes of those experiences, offers an excellent starting point to investigate emotional-motivational shifts in chronic pain at behavioral and psychobiological levels in humans. These processes are related to subjective experience and higher cognitive function, rendering human research an essential part in advancing knowledge on the emotional-motivational shift in chronic pain.

2.1. Research in Healthy Volunteers

2.1.1. Reward Processing. Pain and reward or pleasure has been suggested to be the two ends of a continuum, with emotion as a common currency that allows the comparison between stimuli [23]. This assumption suggests that pain and reward/pleasure affect each other. Indeed, pleasure and appetitive motivation induced by pleasant odors, pictures, or music as well as monetary rewards inhibit acute pain [24–27]. An interesting case of reward is pain relief. Pain relief is strongly sought-after when in pain and can become an all-dominant goal in chronic pain. Relief from an aversive state is generally associated with rewarding experiences. For example, food tastes better when one is hungry [28, 29], and the pleasure of pain relief is known to almost everybody. In line with the results on effects of pleasure and (monetary) reward on pain perception, pain relief as reward induces endogenous pain inhibition over and above the physical pain reduction [30].

The idea of a hedonic continuum with pain and reward/pleasure at its ends is supported by the observation that brain processing of pain and reward widely overlap [31]. But, only few studies so far investigated the mediating mechanisms between interactions of pain and reward. One study demonstrated that dopamine mediates pain inhibition induced by reward [27]. Dopamine mediated not only the pain-inhibiting effects of reward, but also the pain-facilitative effects of punishment suggesting that dopamine mediates motivated behavior triggered by stimuli of positive and negative valence [32]. With respect to endogenous opioid activation, it has been observed that responses in the periaqueductal gray and ventral striatum to rewarding stimuli at the age of 14 years predicted the presence of pain complaints in adolescents two years later, with much stronger effects for carrier of the T-allele of the rs563649 polymorphism of the human mu-opioid receptor (OPRM1) gene [33]. Carriers of the T-allele of this polymorphism shown increased responsiveness to a number of noxious stimuli, including ischemic, mechanical, and thermal stimuli applied to various anatomical sites [34]. At the circuit level, the orbitofrontal cortex mediates reward-induced pain inhibition through altered functional connectivity with the rostral anterior insula, anterior-dorsal cingulate cortex, and primary somatosensory cortex [35]. In line with these results, Talmi et al. [36] showed that increased activation in the insula was associated with prioritizing pain avoidance over obtaining a monetary reward, and this increased activation was related to increased activation in the orbitofrontal cortex. Pain relief (although not implemented as reward) is associated with increased activation in the nucleus accumbens as well as in the ACC [37–39]. The ACC has a high density of opioidergic receptors, leading to the hypothesis that opioidergic mechanisms in the ACC might be related to the endogenous pain inhibition related to rewarding pain relief, which is supported by preclinical studies (see below). In humans, this was demonstrated by positron emission tomography (PET) showing an association of opioidergic receptor activation in the ACC with perceived reductions in pain induced by placebo interventions [40–42].

2.1.2. Learning. Learning processes can affect the pain experience via different routes. One possibility is through operant learning, that is, learning based on reward, affecting the perception of pain. Few studies investigated this route by using, for example, verbal reward in terms of praise to increase or decrease participants' ratings of experimental pain [43, 44]. However, it is conceivable that in those studies, only participants' rating behavior was changed (as this was what was reinforced), but not necessarily the perception of pain. But, by operant learning, also pain-related evoked brain potentials [45] and facial pain expression [46] can be increased or decreased. Instead of using extrinsic reinforcement, such as verbal reinforcement or smileys, pain relief can be used as intrinsic reinforcement, that is, within the pain system. As such, rewarding pain relief appears particularly well suited to induce operant learning processes, which has been shown in several studies, confirming that (partial) pain relief can lead to learned changes in pain perception in humans [47–49] and in animals (e.g., [50]; see Section 3 below).

A different route is fear learning that affects pain processing. Learned fear of pain is related to facilitated sensitization and decreased thresholds for pain [51–53], interference with habituation to repeated pain stimuli [54], enhanced somatosensory processing at pain-relevant body locations [55, 56], and impaired acuity of perceptual discrimination [57]. Pain-related fear conditioning has also been shown to induce increased tension in muscle responses [58].

2.1.3. Goal-Regulation, Approach, and Avoidance. The effect of motivational context on pain processing has been the topic of increasing experimental research endeavors. For instance, it has been demonstrated that experimentally inducing the goal of pain avoidance in healthy volunteers significantly enhanced existing attentional biases to visual cues signaling imminent pain [59]. Durnez and Van Damme (2015) [60] found that experimentally induced expectation of pain on a specific body location enhanced somatosensory processing at that body location relative to other locations in a Tactile Change Detection (TCD) task, especially in participants who were motivated to actively avoid painful stimulation by a specified motor action. Durnez and Van Damme [61] further demonstrated that using similar experimental manipulation of motivation, participants actively attempting to avoid pain showed prioritization of somatosensory stimuli over visual stimuli in a bimodal Temporal Order Judgment (TOJ) task. It has also been found in an experimental study with healthy volunteers that after losing control over pain administration, persistent attempts to regain control were associated with more fear of pain and performance costs on a secondary cognitive task, suggesting narrow attentional focus on pain [62]. All this experimental work suggests that alterations in goal priorities, such as a strong motivational focus on pain control or avoidance, might substantially enhance attentional focus on pain.

Some experimental work studying the effects of competition between pain-related goals and nonpain goals is

available. It has been shown that concurrent pursuit of a salient goal significantly reduced attentional bias towards visual cues signaling impending experimental pain [63]. Furthermore, Karsdorp et al. [64] used a dot probe paradigm to assess attentional bias in which stimuli predicting experimental pain were put in competition with stimuli associated with a temporary nonpain goal. They found preferential attending to goal-related information over pain-related information, especially in those participants high in self-reported trait attentional control. Furthermore, increasing the motivational salience of a distraction task during cold pressor pain enhanced distraction effectiveness, particularly in participants scoring high on catastrophic thinking about pain [65]. There is also increasing evidence that induction of a nonpain goal may counteract pain-related avoidance behavior. In a study by Van Damme et al. [66], healthy volunteers were presented trials of two different tasks, of which one could result in the administration of a painful stimulus, and they were free to perform or not these trials. In half of the sample, a competing goal was induced by instructing participants that they could win monetary rewards by performing the pain task. The findings showed that this competing goal resulted in less avoidance of the painful task and in a significant reduction of the association between fear of the pain stimulus and avoidance of the painful task. Similar findings were reported in a study by Claes et al. [67]. Using a voluntary joystick paradigm, they conditioned one movement to be pain-inducing and another movement to be safe. In half of the sample, the pain-inducing movement was also associated with obtaining a financial reward. In those participants, the pain-related movement was performed more frequently, and the typical slowing of movements signaling pain was attenuated, although pain-related fear remained unaltered. These findings were replicated in a study by Claes et al. [68]. They used the same procedure, but additionally categorized participants based on their self-reported goal priority (avoiding pain versus seeking reward) and found that the effect of the concurrent goal on pain avoidance behavior was most pronounced in those participants who prioritized reward seeking, and less pronounced in those participants prioritizing pain avoidance. This is also in line with another study which experimentally manipulated goal pursuit during the performance of cognitive tasks while being exposed to pain and found that participants persisted longer in an achievement relative to a hedonic (avoiding pain) goal context [69].

2.2. Research in Chronic Pain Patients

2.2.1. Reward Processing. Although studies are still scarce, research suggests changes in brain functions in individuals with chronic pain [3, 70]. Impairment of reward-related decision-making has been reported in patients with chronic back pain and complex regional pain syndrome (CRPS) [71]. Studies have shown that chronic pain is likely to be accompanied by a hypodopaminergic state [32]. A decrease in D2-receptor binding [72–75] and presynaptic activity [76, 77] in the striatum has been observed at rest and after painful stimulation in humans using PET. This might also play a critical role in chronic pain. Further, altered responses in the nucleus accumbens to the cessation of a painful stimulus were found in patients with chronic pain versus healthy controls using fMRI [37]. Moreover, variations of the activity in the nucleus accumbens during reward processing significantly predicted anhedonia, that is, the inability to perceive pleasure, which has been suggested to be associated with chronic pain in some patients independent of depression [78, 79]. In addition, chronic pain patients have been shown to exhibit less robust activation in brain regions associated with affective and cognitive pain-modulatory processes, specifically the ventral tegmental area, to the anticipation of pain (pain onset) and the anticipation of pain relief (pain offset) [80].

2.2.2. Learning. The few available data on respondent conditioning in patients with chronic pain suggest that pain responses can be easily conditioned on multiple levels of the nervous system and can lead to enhanced pain perception and maladaptive brain changes, and that chronic pain patients acquire conditioned fear responses faster and extinguish them more slowly [58, 81, 82]. In patients with chronic low back pain compared to healthy individuals, a positive correlation of brain responses in the amygdala and insula and their connectivity with conditioned fear of movement has been observed [83]. Moreover, in patients with irritable bowel syndrome (IBS) compared to healthy individuals, increased cerebellar responses to both pain-associated and safety conditioned stimuli (CSs) during fear learning have been found. With respect to fear extinction, chronic pain may be characterized by impaired extinction of pain-related fear generalization [84] and enhanced reactivations of extinguished conditioned fear responses [85–87]. This may indicate a preservation of pain disability in chronic pain by persistent excessive protective behavior, which seems to be related to an individual's awareness of the association between the CS and the pain, which is the unconditioned stimulus [88, 89].

Moreover, along an operant conditioning model of pain [90], increases or decreases of pain perception can serve as implicit reinforcers: in this context, fibromyalgia patients without comorbid IBS did not learn pain habituation but showed increased sensitization compared to healthy controls, and those with comorbid IBS showed neither sensitization nor habituation learning [49]. Mechanisms of operant conditioning of sensitization or habituation may thus be differentially altered in chronic pain.

In addition, respondent and operant processes interact and may induce motivational biases forming habitual behaviors and a shift from more ventral to dorsal striatal circuits similar to addictive processes [91]. Thus, in chronic pain, fear of pain may then motivate behaviors that lead to pain relief, which is experienced as rewarding. However, this still needs to be tested in an experimental fashion. Moreover, brain changes during fear-conditioned predictions such as reduced PFC responses during extinction learning may

hinder learning of new predictive stimulus properties. This includes those that are important to reduce pain and could thus contribute to the development and persistence of chronic pain, but also this still needs to be determined.

2.2.3. Goal Regulation, Approach, and Avoidance. One of the most significant alterations resulting from chronic pain conditions is the disruption of appropriate and valued (goal-directed) behavior [92–94]. Changes in approach and avoidance tendencies are discussed as central components in the development and maintenance of chronic pain [95]. The competition between pleasure-related cues and pain can drive decisions and guide approach or avoidance behavior, which can already be observed at stages of acute pain. Pain-related fear needs to be considered within a motivational context to avoid or control pain with often competing existing goals [10, 13, 96–100]. Patients with chronic pain often experience difficulties in weighing the value of pain avoidance versus the withdrawal from valued activities [16, 101–103]. This would be especially important in the case when pain relief becomes more important than other rewards.

Correspondingly, it has been proposed that individuals with chronic pain are often stuck in (largely unsuccessful) attempts to get control over their pain [14] and that this makes them chronically vigilant to pain-related information [104]. A recent study indicated that individuals with chronic pain give indeed high priority to pain control goals and often see pain control as a necessary condition to attain other goals [105]. There is also accumulating evidence that chronic pain patients might be characterized by biased attention to pain-related information [106]. However, empirical research on the link between shifts in motivational priority and attentional processing is scarce [12]. One study, though, showed that a strong focus on problem-solving attempts towards pain was associated with more catastrophic thinking about pain and greater attention to pain [107].

3. Preclinical Investigations of Emotional-Motivational Pain Processing

Although most animal studies of pain rely on measurements of evoked mechanical and thermal responses, the need for evaluation of affective/motivational and cognitive aspects of pain and the underlying molecular, cellular, and circuit mechanisms is increasingly being recognized [108]. Complementary to human studies, animal investigations have demonstrated a critical role of corticolimbic circuitry in the processing of acute and chronic pain, which is involved in the evaluation of changing goals and competing motivations and facilitates decisions on avoidance, coping, and adaptive behavior. During acute pain states, corticolimbic circuitry promotes self-regulation of pain [109] through the engagement of descending pain-modulatory pathways or through the inhibition of the affective/emotional response to pain.

3.1. Animal Studies of Pain-Motivated Behavior. Mesolimbic reward/motivation circuitry, consisting of dopaminergic neurons in the ventral tegmental area and their projections to the nucleus accumbens in the striatum, is activated by rewards including food, drink, warmth, and so on and by drugs of abuse. Electrophysiological studies in animals, typically demonstrate inhibitions of midbrain dopamine neurons by aversive stimuli, consistent with the role of these neurons in reward coding [110–112]. However, a proportion of dopaminergic neurons can be excited by noxious or alerting stimuli [113–115]. In addition, some reward coding dopamine neurons were found to increase their activity at the offset of a noxious stimulus [116, 117], suggesting a "rebound" response to relief of pain. Therefore, mesolimbic neurons respond to alerting, aversive, and rewarding stimuli, including relief reward [118], and encode their salience and motivational value. These heterogeneous populations of neurons project to different brain regions in the striatum, prefrontal cortex, hippocampus, and amygdala to initiate specific motivated behavior and to promote learning.

Recently, measurements of dopamine transients in response to painful pinch of the rat's tail using fast scan cyclic voltammetry (FSCV) demonstrated increased dopamine release in the dorsal striatum and in the core of the nucleus accumbens [119], suggesting saliency coding. In contrast, dopamine levels were suppressed during the painful stimulus in the shell region of the nucleus accumbens and increased after pain offset [119, 120]. Behavioral studies in rats with sustained postsurgical, neuropathic, inflammatory, or bone cancer pain demonstrate that relief of pain with nonopioid interventions elicits conditioned place preference (CPP) only in injured but not sham-operated animals [50, 121–127]. These findings demonstrate that pairing of the pain-relieving treatment with a CPP chamber provides a learning experience and promotes motivation to seek pain relief. CPP is accompanied by release of dopamine in the NAc and blockade of dopamine receptors in the nucleus accumbens blocks CPP from pain relief [50]. These studies establish the role of mesolimbic dopamine signaling in pain and pain relief as alerting and emotional signals that promote learning and shape behavioral response.

3.2. Aversive Aspects of Pain. The prefrontal cortex (PFC) plays a major role in motivated behavior, decision-making, emotional processing, and cognition and is therefore critically involved during acute and chronic pain. The PFC provides top down control of the sensory and affective dimensions of pain and has functional connections with the mesolimbic dopamine circuitry, amygdala, and hippocampus. In rodents, PFC can be subdivided into the anterior cingulate (ACC), prelimbic (PL), and infralimbic (IL) cortices, each providing unique pain-modulatory functions. In the ACC, long-term potentiation (LTP) is believed to enhance pain responses and facilitate the interaction between chronic pain and anxiety [128]. Optogenetic stimulation of the inhibitory neural circuitry of the ACC leads to decreased neuronal activity in the ACC and reduction in pain behavior [129]. Pharmacological studies demonstrating CPP in rats with neuropathic pain following microinjection of morphine in the ACC indicate that these pain inhibitory circuits are

likely the targets of exogenous opioid analgesics [130]. In addition, blockade of opioid ACC circuits prevented CPP elicited by nonopioid therapy, suggesting that endogenous opioid ACC circuits may be necessary for relief of pain aversiveness in general [130].

In the rodent PL, chronic neuropathic pain was shown to inhibit firing of pyramidal neurons as a result of feed forward inhibition mediated by GABAergic interneurons [131]. Consequently, optogenetic activation of parvalbumin-positive GABAergic neurons decreased pain responses and produced CPP, while optogenetic inhibition of these cells increased pain responses. Moreover, antinociceptive effects were also observed following selective activation of the projections from PL to NAc, suggesting regulatory role of the PL on mesolimbic dopamine circuitry and affective/motivational symptoms of pain [132].

The PFC also receives reciprocal inputs from the amygdala and the hippocampus, the brain regions essential for consolidation of emotional memories and fear conditioning. Synaptic plasticity in both regions has been observed in rodent models of neuropathic pain [133, 134]. Deactivation of the PFC through increased inputs from the basolateral amygdala has been demonstrated in a model of arthritic pain [135, 136]. Conversely, the PFC projects to and modulates the activity of a specific population of inhibitory cells in the amygdala, the intercalated cells, that control the function of amygdala pain output cells. However, more research needs to be done to unravel the precise neural circuitry that drives specific pain-related behavior.

Preclinical research therefore supports a critical role of the corticolimbic neural circuits involving endogenous dopamine and opioid neurotransmission in adaptive behavior, learning, and decision-making in the context of pain [137]. Corticolimbic circuits integrate pain-related experiences with other competing motivational goals, allow evaluation of the costs and benefits, and underlie selection of appropriate behavioral actions. The reported results in animals are therefore well in line with result in humans. The engagement of corticolimbic circuits in endogenous pain adaptive mechanisms also implies that diminished ability of these circuits to control emotional pain processes may underlie the transition to chronic pain [138].

3.3. Aberrant Corticolimbic Circuitry and Transition to Chronic Pain. Animal pain studies are typically conducted at early times following injury (less than one month) and cannot be classified as truly chronic and analogous to chronic pain conditions in patients. However, several recent studies have extended this time period in order to identify neural mechanisms that occur late after the initial insult and may therefore represent mechanisms underlying the shift from sensory to emotional pain processing. Hubbard et al. [139] and Seminowicz et al. [140] have investigated pain behavior and brain changes during a 4-month period following nerve injury in rats. At this late time point, they observed the emergence of anxiety behavior that coincided with the occurrence of volumetric changes in the PFC of injured rats. It is likely that molecular and cellular modifications in the brain precede these larger-scale volumetric changes and the emergence of comorbid behaviors such as anxiety, depression, and cognitive impairments. Indeed, expression of genes encoding dopamine and kappa opioid receptors in the rat nucleus accumbens was reduced 28 days but not 5 days following nerve injury [141]. Coincidently with these molecular changes, altered functional connectivity between the NAc and dorsal striatum and cortex was also observed only at the later time point. Moreover, fMRI BOLD activity in the NAc and prefrontal areas was associated with tactile allodynia on day 28 after nerve injury [142]. Therefore, reorganization of the brain during transition from acute to chronic pain has been demonstrated in animal pain models. These preclinical investigations are beginning to identify molecular underpinnings of the shift from nociceptive to emotional pain processing in chronic pain.

4. Translation of Preclinical Findings to Clinical Applications

Research in animals allows invasive mechanistic investigations that can be performed in a relatively homogenous population under calibrated and controlled conditions without the interference of confounding factors such as use of medications, different life styles, and so on present in human studies. Animal research has significantly contributed to our understanding of basic anatomy and neural mechanisms of pain processing. For example, the descending opioid-sensitive pain-modulatory pathways from the periaqueductal gray area (PAG) and rostral ventromedial medulla (RVM) were first identified in rodents and cats [143–145]. It was later discovered that electrical stimulation of PAG produced naloxone-reversible analgesia in patients with intractable pain [146, 147]. This success in predicting clinical responsiveness based on preclinical findings demonstrates translational relevance of animal research. However, limitations of animal research must also be acknowledged.

First, animal pain models cannot directly replicate the full complexity of the human pain experience and are intended to inform about potentially important neural mechanisms. Second, animal research is conducted in homogenous populations, offering an advantage in robustness of the effect size, but also potentially limiting the generality of the effect. Several examples have shown differences in pain responses between different species or even between different rodent strains [148, 149]. Another obstacle specifically in investigating chronification of pain in animals is the relative inability to assess pain-related emotional states. Researchers have used open-field, forced-swim, or elevated plus-maze tests to evaluate anxiety- and depressive-like behaviors in animals with persistent pain [150, 151]. Burrowing, home-cage monitoring, and voluntary wheel running have been used to assess the well-being of animals [152, 153]. Recently, operant assays such as conditioned place preference/avoidance [154] and place escape avoidance paradigm (PEAP) [155] were adopted to evaluate affective-motivational aspects of acute and ongoing pain. Although

these measures are indirect and limited in comparison to the whole array of affective, emotional, and well-being assessments available in human research, they provide important mechanistic information about emotional-motivational and cognitive aspects of pain. An important issue for future research is thus to increase correlation between human and animal studies. Such complementary research is necessary to identify the cellular and molecular mechanisms that promote transition to chronic pain and determine whether these mechanisms can be targeted therapeutically.

5. Conclusions

Chronic pain is different from acute nociception or subacute persistent pain. Unrelenting pain loses its alerting and motivational utility and becomes a constant burden that disrupts goal-directed behavior. Patients with chronic pain are often more vigilant to pain-related information and shift their motivational priority to pain control goals. The affective and motivational disturbances play a critical role in reward, learning and information processing, goal regulation, and avoidance behavior. These observations suggest a complex interplay between motivational and emotional factors, whose interrelations and relevance shift in chronic pain. Related variables such as valuation of stimuli, desires, and needs vary largely inter- and intraindividually depending on a specific situation.

Consistent with these psychological signs of chronic pain patients, neuroimaging studies have demonstrated changes in brain anatomy and function, that generally reflect a shift from predominantly nociceptive to more affective and emotional processing [156]. Altered structure and function in emotional-motivational frontostriatal brain circuits have been shown to predict the transition from subacute to chronic back pain. Specifically, increased functional connectivity in between the nucleus accumbens and the ventromedial PFC predicted this transition [157] as well as higher incidence of white matter and functional connections between medial prefrontal cortex, NAcc, and amygdala [138, 158]. Both these functional and structural alterations predicted pain persistence over one year, suggesting that the development of chronic pain is predetermined by neuroanatomical and neurofunctional factors outside core nociceptive processes. Importantly, the relevance of nonnociceptive frontostriatal circuits in pain modulation has been confirmed in healthy volunteers [109, 159]. In addition, altered dopamine and opioid activity have been shown using PET imaging. Research in humans, however, is limited when it comes to the investigation of underlying neurophysiological mechanisms. Despite great advances in technical possibilities, brain imaging is still restricted to a coarse resolution compared to the density of neurons, and invasive procedures are only possible in very rare cases.

Animal research has confirmed the role of corticolimbic circuits in affective and motivational aspects of pain and provided more fundamental insights into neurobiological mechanisms. Thus, electrophysiological, FSCV, and behavioral measurements demonstrate a role of dopamine signaling for pain and pain relief. Other investigations show the requirement of endogenous opioid activity in the ACC for relief of pain following opioid or nonopioid therapy. With the development of new techniques, including genetic approaches, it is now possible to investigate the impact of chronic pain on specific cells in neuronal circuits. Translationally relevant animal models and measures that are based on clinical observations will be able to provide mechanistic insights into neural circuitry in chronic pain and help to identify novel therapeutic options for patients.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Review Article

Psychological Factors Associated with Phantom Limb Pain: A Review of Recent Findings

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Phantom limb pain (PLP) is a common phenomenon occurring after the amputation of a limb and can be accompanied by serious suffering. Psychological factors have been shown to play an important role in other types of chronic pain, where they are pivotal in the acquisition and maintenance of pain symptoms. For PLP, however, the interaction between pain and psychological variables is less well documented. In this review, we summarize research on the role of emotional, motivational, cognitive, and perceptual factors in PLP. The reported findings indicate that emotional factors modulate PLP but might be less important compared to other types of chronic pain. Additional factors such as the amount of disability and adjustment to the amputation appear to also play a role. Bidirectional relationships between stress and PLP have been shown quite consistently, and the potential of stress and tension reduction in PLP treatment could be further exploited. Little is known about the role of cognitive variables such as attention or expectation. Catastrophizing seems to aggravate PLP and could be targeted in treatment. Body perception is altered in PLP and poses a potential target for novel mechanistic treatments. More research on psychological factors and their interactions in PLP is needed.

1. Introduction

The amputation of a limb represents a serious disruption of body integrity and is associated with a number of negative consequences, particularly disability and postamputation pain. Although severe chronic residual limb pain is rare (occurring in less than 10% of the amputees), the majority of amputees (above two-thirds) report at least mild residual limb pain [1]. As a consequence of changes in the posture and strain of the remaining body parts, secondary pain is reported by a high proportion of the amputees, with high rates (more than 20% each) of pain in the remaining limbs, the shoulders, and the neck or the upper back [2, 3]. Almost all amputees also report about ongoing awareness of a phantom limb, with 60–80% complaining about phantom limb pain (PLP), that is, a painful sensation perceived in the amputated limb and thus located outside the physical borders of the body [4–6]. PLP usually begins early after an amputation (e.g., [7]), and in most amputees, PLP becomes chronic with a large variability in intensity, frequency, and quality [6, 8]. PLP leads to personal suffering [9], reduced quality of life [10], and impairs sleep [6]. PLP is still a challenge for pain research and treatment.

Neuroplastic changes occurring in the brain after an amputation have been a major focus in PLP research for the last two decades (for reviews, see [11, 12]). In contrast, less research has focused on psychological factors, and although they play an important role in other types of chronic pain, for example, chronic musculoskeletal pain (e.g., [13–15]), their role in PLP remains less well studied and less well understood (e.g., [16]). Furthermore, review articles directly addressing psychological factors in PLP are rare. Sherman

et al. [17] and Hill [18] reviewed and critically discussed evidence from earlier studies and showed that PLP cannot be related to unresolved grief due to limb loss, denial, psychosomatic manifestations, pathological misinterpretation of somatic sensations, or personality disorders (e.g., [19–21]). The proposed relationship between personality factors and PLP could not be substantiated ([17]; for a discussion, see [18]).

Since the reviews cited above [17, 18] have been published two and three decades ago, respectively, the present work focuses and summarizes the research on the role of psychological variables from the late 90s to the present. We further focus on emotional factors, motivational aspects such as stress and stress coping, cognitive factors, and the role of body perception in the development and maintenance of chronic PLP and its potential for treatment approaches.

2. Emotional Factors

Much research on emotional processing in chronic pain has focused on comorbid anxiety and depression, which have a high prevalence in chronic pain (cf. [22–24]). For example, a health survey in a representative German sample [25] found an interview-based [26] prevalence of 8.1% for chronic pain disorder. Compared to the healthy population, the 12-month prevalence for anxiety disorders was significantly elevated in both male (33% versus 7%, odds ratio = 5.65) and female (37% versus 20%, odds ratio = 2.69) chronic pain patients. Mood disorders were also significantly more prevalent in chronic pain patients compared to pain-free participants (men: 30% versus 7%, odds ratio = 5.48; women: 30% versus 15%, odds ratio = 2.69). In line with the role of anxiety and mood disturbances (especially depression) in chronic pain, similar relationships can also be expected for chronic PLP. In the following sections, we will summarize findings on the role of depression and anxiety in PLP and will show that it is important to take specific characteristics of the sample into account, especially whether the sample consisted of amputees in early or later stages after amputation and whether concomitant pain was present.

2.1. Depression and Anxiety in Early-Stage Amputees. Especially in early stages after amputation, comorbidity rates of mental disorders in amputees can be related to factors other than PLP. Factors like chronic diseases leading to the amputation, traumatization, secondary pain, disability caused by the amputation, and adaptation to the new situation can give rise to anxiety and depression independently of PLP. The modulation of pain by emotional factors may therefore be different in early and late stage amputees. For example, Shukla et al. [27] reported high rates of depression (about 50%) and anxiety (above 35%) in amputees in the postoperative phase, regardless of PLP. In contrast, in samples that were more heterogeneous in age, time since amputation, or the cause of amputation, prevalence rates for depression and anxiety were lower than the rates reported by Shukla et al. [27] for recently amputated participants. For example, a prevalence of 19% was reported for depressive symptoms [28] and of 24% for both depression and anxiety symptoms [29]. In these studies, the association of depression and anxiety with PLP (which is most prevalent shortly after amputation [1]) has not been specifically investigated. Consequently, recent amputations should be seen as a special case, and in fact, there is evidence that depression in the postamputation phase is more strongly related to concerns about disability than PLP [28, 30, 31]. However, a different relationship has been observed for preamputation anxiety. Raichle et al. [32] investigated the relationship between overall anxiety levels prior to lower limb amputation and PLP and found that they were positively related particularly with PLP intensity (up to five days after amputation), even when postoperative analgesic medication was controlled for. The analysis of the interplay between emotional states and PLP can be better determined in later stages, when disability and adaptation to the new situation are no longer dominating topics. However, even in later stages, PLP is frequently related to disability and it is important to consider both disability- and pain-related issues.

2.2. Depression in Later Stages after Amputation. As already stated, symptoms of depression are common in the acute phase after an amputation. However, several studies showed that the rates of depressive symptoms decline during the following years. Horgan and MacLachlan [33] published a review on psychosocial adjustments following lower limb amputations and concluded that depression in the first years after amputation is most strongly associated with disability and that, by two years after amputation, depression rates have dropped to a level comparable to those of healthy people. However, even at later stages, it is important to distinguish between disability, somatic symptoms, pain, and depression. Whyte and Niven [31] used the Beck Depression Inventory (BDI [34]) to assess depressive symptoms in a sample of amputees with PLP in the chronic stage. They observed a significant positive correlation of PLP and BDI scores; however, they found that this correlation was mainly driven by PLP being correlated with items of the BDI that assess performance or somatic symptoms that are often seen in chronic pain. The problem that the BDI (and possibly other depression scales as well) tends to overestimate depression in samples with physical diseases and chronic pain has been pointed out before [35]. This highlights that the diagnostic instrument needs to be taken into account in the interpretation of studies on amputees and that psychopathology might be overestimated due to somatic symptoms associated with amputations. Desmond and MacLachlan [36] used the Hospital Anxiety and Depression Scale (HADS [37]) to screen for anxiety and depression and the Impact of Event Scale [38] to assess the severity of posttraumatic stress. They tested a sample comprising exclusively older male amputees ($N = 582$) with long-standing traumatic amputation (at least 10 years). Importantly, the HADS specifically excludes items concerning intrusions or physical symptoms of depression to avoid confounding when assessing groups with somatic disorders. In this homogeneous sample, the authors found elevated scores for depression, anxiety, and

posttraumatic stress. In the amputee sample, values potentially indicating clinically relevant depression were observed three times more often than expected for the normal population. This study also found differential associations between psychological distress and postamputation pain: amputees showed higher values in depressive symptoms, avoidance, and intrusions if they suffered from either residual limb pain or residual limb pain *and* PLP but not if they suffered from PLP alone, indicating that chronic PLP might be different from other postamputation pain in terms of psychological distress. However, it is not entirely clear which factors caused the differences between the subgroups. The authors assumed that residual limb pain more strongly conflicts with prosthesis use so that their results might have been associated with activity restriction-induced negative affect [39]. Desmond and MacLachlan's [36] results suggest that PLP and depression are—if at all—only weakly associated if residual limb pain is accounted for. However, their sample consisted of former military service members who were mostly male, at younger age when serving, and suffered from traumatic limb loss in the line of duty with no preceding pain or diseases, and thus, these findings should not be generalized to other populations. Another study [40] reported the results of a survey that used a stratified sample of 914 amputees, which might provide more general norms. To assess depressive symptoms, the authors used the Center for Epidemiological Studies Depression Scale [41], which is also better suited for assessing depression in populations with chronic health problems. Pain bothersomeness was assessed individually for PLP, residual limb pain, and back pain. There was a significant correlation between pain bothersomeness and depressive symptoms within each of the groups. Depressive symptoms were almost three times more likely to be present in subjects who were extremely bothered by PLP than in subjects reporting not to be bothered. However, this association was even stronger in residual limb pain and back pain. Another study [42] compared depression and anxiety between PLP patients and other patients suffering from nonphantom neuropathic pain caused by trauma or surgery. Like another study mentioned above [36], this study used the HADS. This study found that amputees with PLP showed fewer symptoms of both depression and anxiety compared to patients with other types of neuropathic pain; however, residual limb pain was not accounted for. Fuchs et al. [43] reported on affective distress and pain-related interference as assessed by the West Haven-Yale Multidimensional Pain Inventory [44], a questionnaire assessing different dimensions of pain-related burden, in large samples of patients with chronic back pain and musculoskeletal pain compared to three amputee groups with (a) none but PLP, (b) non but residual limb pain, and (c) both PLP and residual limb pain. In line with the results from other studies [36, 40, 42], persons with either PLP or residual limb pain showed less affective distress and pain interference compared to chronic back pain or musculoskeletal pain patients. Concurrent PLP and residual limb pain was associated with higher burden compared to the groups that reported only one type of postamputation pain. However, even the amputees suffering from both pain types always showed less-intense burden than patients with chronic back pain or musculoskeletal pain. In a longitudinal study, Castillo et al. [45] assessed depression and pain in subjects with lower limb trauma at 3, 6, 12, and 24 months after injury. Pain predicted depression, but depression did not predict pain. It is important to note, however, that not all subjects in this study were amputees and that the study also did not make a distinction between PLP and other types of limb trauma-associated pain.

Taken together, these studies suggest that the association between pain and depression might be weaker in PLP than in other chronic pain conditions, including residual limb pain. In addition to a differentiation between specific pain types in amputees, it is important to consider the diagnostic tools and the composition of study samples.

2.3. Anxiety in Later Stages after Amputation. Anxiety is assumed to be both an etiological and a maintaining factor of chronic pain, especially as it is associated with avoidance of activity and perceived disability [46]. Similar to depression, anxiety symptoms are common in an early stage after amputation [27, 29], and anxiety levels decline in the first years after amputation [29, 33]. However, anxiety does not appear to be exclusively related to PLP shortly after amputation. Horgan and MacLachlan [33] stated that anxiety in acute amputees mainly relates to changes in body image, altered social role and social discomfort, and adaptation to a new identity. The preoccupation of amputees with topics relating to identity and social functioning (rather than pain) was also found in a qualitative study that explored amputees' experiences using a semistandardized interview [47]. Similar to what has been observed for depression, Whyte and Niven [31] also found that, in an early phase after amputation, anxiety was mainly correlated with somatic symptoms (e.g., insomnia) but not necessarily with pain.

There are only few studies on the association of anxiety and PLP after the immediate consequences of an amputation have subsided. The study by Desmond and MacLachlan [36] showed that compared to pain-free amputees, anxiety levels were higher in long-term amputees with chronic PLP or residual limb pain. However, those levels were still within the range of the healthy population. In their longitudinal study, Castillo et al. [45] showed that, in a late, chronic phase of pain following lower-extremity trauma, subsequent pain was predicted by anxiety but not by depression. However, as mentioned above, this study included amputees and non-amputees and did not differentiate between PLP and other types of pain.

3. The Role of Stress and Tension in PLP

Stress is thought to play a key role in the development and maintenance of chronic pain. As outlined in the diathesis-stress model of chronic pain [46, 48], various dysfunctional affective, cognitive, and behavioral responses mediate the relationship between stressors and pain symptoms in chronic pain patients. It has been proposed that similar to other types of chronic pain, stress can trigger pain episodes

in PLP [24, 49]. Although some studies can be found, which will be discussed in the following paragraphs, there is generally less research on the role of stress in PLP compared to more common types of chronic pain (e.g., chronic back pain or headache [24]).

Sherman and colleagues conducted several studies on this topic and proposed that there are complex interactions between the central nervous system, sympathetic arousal, and characteristics of the residual limb [50]. For example, Sherman and Bruno [51] showed that the temperature of the residual limb compared to the intact limb is decreased in amputees with PLP, which has been related to decreased near-surface blood flow. The authors further showed a significant relationship between the extent of temperature differences and PLP quality such as burning, tingling, and throbbing. Discharges of peripheral input can be mediated by autonomic nervous system activity which could explain why situational (external) stressors and internal states (e.g., tension and anxiety) interact and trigger PLP episodes. In fact, Sherman et al. [52] demonstrated that there is a close temporal relationship between PLP and involuntary contractions of residual limb muscles: muscle activity bursts, which were recorded using surface electromyographic signals, preceded the experience of PLP. Involuntary contractions of residual limb muscles have been directly related to anxiety, tension, and stress [53]. This relationship is also supported by studies using relaxation-focused interventions to reduce PLP: In a review, Sherman [54] suggested that most treatments for PLP show success rates of 30% or below that might be merely due to placebo effects; only treatments reducing tension showed better effects and can be considered as successful treatments. Preliminary beneficial effects have also been shown for biofeedback. In a case study, total and enduring relief of PLP and an increasing temperature of the residual limb were observed following a residual limb EMG and temperature biofeedback training [55]. In another study, improvements in pain of at least 30% were observed in 6 out of 7 patients after six sessions of residual limb temperature biofeedback training [56]. However, this study lacked a control group, and better controlled studies on biofeedback in PLP are needed to evaluate its effectiveness.

Angrilli and Köster [57] experimentally investigated the effect of stress induction on amputees with and without PLP. Stress was induced in the amputees by means of three different induction methods: (a) having them deliver a free speech about memories of the amputation, (b) applying a cold pressor pain test, and (c) performing a mental arithmetic task. As measures of sympathetic stress responses, the authors recorded the heart rate and blood pressure levels. Amputees with PLP showed stronger psychophysiological stress reactions compared to amputees without PLP only in the free-speech task. This study thus suggests that amputees with PLP show enhanced stress responses, at least when the stressors are autobiographic and specific (e.g., reminders of their pain or amputation), similar to findings in chronic musculoskeletal pain patients [58]. Moreover, the results support the hypothesis that distressing pain memories (see below) play a role in PLP [59–61]. Heightened stress reactivity in amputees with PLP has also been demonstrated on a cortical level. Using electroencephalography, Larbig et al. [62] showed that PLP patients display increased cortical activity when presented with verbal pain-associated material.

The studies described above support the notion that PLP relates to both peripheral and central arousal and that PLP episodes might be influenced by emotional distress. Katz [63] proposed a model explaining the close connection between cognitive and affective processes and PLP. In amputees, the threshold for somatic sensations in the phantom limb might be lowered due to the loss of inhibitory control. The underlying mechanisms are proposed to be identical to those when healthy participants experience somatic sensations while affectively aroused. The reduced threshold for sympathetic activation might allow even events of much lower salience to trigger somatic sensations in the phantom limb, which further indicates that brain regions involved in cognitive and affective processes might contribute to a sympathetic-efferent/somatic-afferent cycle of activity. Interestingly, sympathetic arousal might also play a role in other chronic pain conditions and might further be related to maladaptive plasticity in the brain. For example, in patients suffering from complex regional pain syndrome (CRPS), sympathetic blocks have been shown to restore the organization in the primary somatosensory cortex [64]. CRPS is a condition characterized by ongoing pain perceived in upper or lower extremities, which shares similarities with PLP, as in terms of neuroplastic changes in the sensorimotor cortex [65, 66]. However, up to now, the contribution of sympathetic arousal to PLP remains largely unexplored.

How do these laboratory findings on the interaction between stress, peripheral or central arousal, and PLP relate to more naturalistic contexts and to daily life stressors? Giummarra et al. [67] developed a structured questionnaire on specific triggers of PLP episodes and investigated their frequency of occurrence in a sample of 264 amputees. Although behavioral triggers (e.g., trying to use the phantom) and stimulation of the residual limb (e.g., movement, touch, or pressure) were the most common trigger categories (50% and 37%, resp.), emotional triggers such as emotional distress, exhaustion, or thinking of the missing limb were still reported by 23% of the amputees. Moreover, 20% reported influences of the weather and another 11% reported about referred sensations originating from the intact limb. These results support the notion that PLP episodes often follow emotional distress and that residual limb activity interacts with PLP experience [52, 57]. However, these data are based on cross-sectional and subjective reports and may therefore be prone to memory biases or express implicit theories rather than actual events. Instead of using cross-sectional questionnaire data, Arena et al. [68] conducted a longitudinal study employing pain and stress diaries. Twenty-seven male amputees with PLP completed the diaries four times a day for six months. The authors performed a cross-lagged correlation analysis to detect relationships between stress and PLP over time. A significant relationship between stress and PLP was found in 74% of the amputees. The authors observed that, (a) in 63% of the sample, stress and pain covaried simultaneously, (b) in 44%, a change in pain preceded a change in stress, and (c) in

37%, a change in stress preceded a change in pain. This study thus supports the interpretation that even on the level of daily life stressors, there is a bidirectional relationship between PLP and stress. Taken together, findings from the laboratory and naturalistic observations are well in line with each other and support the role of stress in PLP.

Another reference to altered stress processing in PLP comes from studies investigating the importance of traumatization due to limb loss and initiated the developments of novel treatments of PLP [69]. Preliminary data indicate that a trauma-focused psychological treatment, aiming at traumatic amputation-related memories, successfully reduced PLP [70], probably due to the improvement of regulation of sympathetic arousal [71]. Consequently, an eye movement desensitization and reprocessing treatment, which has been applied in the treatment of posttraumatic stress disorder, showed promising effects in reducing PLP-associated suffering [72], although the specificity of this intervention needs to be clarified.

4. Cognitive Factors

Pain experience can be modulated by cognitive factors such as attention, memory, expectations, beliefs, appraisals, and (cognitive) coping strategies [24, 73, 74]. For many of these factors, little is known about how they specifically modulate PLP [18]. Although we do not know how attentional processes modulate PLP, some indirect indications exist. For example, hypnosis alters attentional processes and can be efficient in modulating both acute and chronic pain (for reviews, see [75, 76]). A reduction of PLP by hypnotherapy has been shown in a case study [77], although more studies are needed. Placebo effects, which are partly based on expectation [78], can also be used to alleviate neuropathic pain [79] and might potentially be effective in PLP although this has not been tested. Finally, the literature shows detrimental effects of catastrophizing on PLP, which are probably also mediated via attentional and expectation processes [80]. In the following sections, we will review relevant findings on memory, coping styles, and catastrophizing and their importance for PLP.

4.1. Memory for Pain. Several theories of chronic pain suggest that both declarative and nondeclarative memory processes contribute to the development and maintenance of chronic pain via neuroplastic changes in the nervous system [81–83]. One example for this process is central sensitization, referring to a hyperexcitability of the central nervous system and associated lowered pain thresholds [84]. In different groups with chronic pain, structural and functional reorganization within pain-processing brain areas has been shown, which might represent a neural correlate of pain memory [81, 85, 86].

For amputees in particular, memory processes have been discussed for both nonpainful phantom sensations and PLP. Katz and Melzack [61] and Katz [87] proposed a crucial role of *somatosensory memories* for both PLP and nonpainful phantom phenomena (e.g., phantom limb awareness or phantom sensations). Anderson-Barnes et al. [88] suggested that phantom sensations could be explained by *proprioceptive memories* and that they might become associated with pain perceived before the amputation by means of learning mechanisms. Due to tumor, vascular disease, or injury, an amputation is often preceded by pain in the affected limb. Katz and Melzack [61] suggested that pain prior to the amputation is encoded and can later be triggered, for example, by peripheral input stemming from the residual limb. This triggered preamputation pain is then experienced as PLP. Maladaptive plasticity that is positively correlated with PLP [65] can be seen as neural underpinning of pain memory in amputees. These processes might be more severe if chronic pain has already been present prior to amputation [81, 85, 86], potentially influencing the formation of a pain memory. The theory of a relationship between preamputation pain (that leaves behind a memory trace) and PLP is supported by retrospective reports that have shown similarities between memories referring to somatosensory perceptions in the affected limb in the phase before amputation and later phantom sensations [60, 61]. For example, in the study by Katz and Melzack [61], almost 60% of the amputees who reported having had pain before the amputation also reported that similar pain qualities continued or recurred later on in the phantom limb. However, reports about preamputation pain that were gathered retrospectively might be prone to memory bias. Prospective studies, on the contrary, give more valid information on the relationship between preamputation pain and PLP and showed that PLP during the first six months, but not long-term PLP, was predicted by pain before amputation [89, 90].

Finally, in line with the observation that chronic pain patients often complain about forgetfulness, impairments of both working memory and long-term memory have been discussed for chronic pain (for reviews, see [91–93]). Although empirical studies have used various methods and have found heterogeneous results when testing memory performance, reviews and meta-analyses indicate that chronic pain patients show poorer performance on memory tests [91–93]. In a recent review, Mazza et al. [91] have argued that poor performance in working and long-term memory tests of chronic pain patients might be related to impaired encoding and/or retrieval processes. In addition, this study also indicated a memory bias towards selectively remembering pain-related events. Whether processes of working memory or long-term memory are also associated with PLP has not yet been systematically studied.

4.2. Coping Strategies. The general term *pain coping* describes functional or dysfunctional styles to deal with pain after it has been attended to and interpreted (appraised) as being a threat [94, 95]. Pain coping can be divided into cognitive and behavioral strategies and also includes catastrophizing, which will be discussed in detail in the following section. Cognitive coping strategies comprise, for example, distraction from a sensation or reinterpretation of pain [96]. Examples for behavioral coping strategies are increasing or decreasing social or physical activity or seeking social or

medical support [94, 96]. Hill [96] systematically described coping styles in amputees with PLP by having sixty male PLP patients complete the Coping Strategies Questionnaire [95]. Using principal component analysis, she found that the factor structure in PLP patients resembled the one originally discovered by Rosenstiel and Keefe [95] in a sample of chronic back pain patients. In the study by Hill [96], three main components were found—cognitive coping, helplessness, and pain denial—which explained about 20% of the variance in both PLP and psychological distress. In addition, most of the variance in these variables was accounted for by catastrophizing, representing a core facet of the helplessness factor. The author concluded that the repertoire of PLP sufferers contains only a limited amount of coping strategies that actually help to alleviate distress and pain and that successful coping rather means *not* to catastrophize. In a later study by Hill et al. [97], catastrophizing explained 26% of the variance in PLP, whereas other strategies only explained 3%. Interestingly, although male and female amputees do not differ in respect of PLP prevalence when the cause of amputation is controlled for, females report greater levels of pain interference [98]. This sex effect might contribute to differences in reported strategies to cope with PLP, with women showing significantly higher degrees of catastrophizing than males [98].

The conclusion that PLP patients use rather few coping strategies was confirmed by another study applying a different methodological approach. Whyte and Niven [99] had 89 amputees collect diary entries assessing PLP and coping strategies once per hour for one week. Instead of using standardized questions, coping strategies were captured using a free format. Analyses revealed that the amputees used a limited number of strategies that could be classified into distraction, relaxation, seeking support, exercise, manipulation of the residual limb, and drug or alcohol use. Importantly, none of the reported strategies was shown to be effective in reducing PLP. This study thus confirms that PLP sufferers tend to use less effective coping strategies.

4.3. Catastrophizing. Pain catastrophizing is a maladaptive cognitive coping style that is characterized by an exaggerated, negative orientation towards pain and anticipation of negative outcomes. There is evidence that catastrophizing predicts chronic pain and associated impairment [94, 100, 101]. Several studies found that catastrophizing was significantly positively correlated with the magnitude of PLP in amputees [80, 96, 97, 102–105]. Jensen et al. [103] found that between one and six months after amputation, the change in PLP and depressive symptoms could be predicted by catastrophizing and lack of social support and overtly solicitous responses from family members. In a later study [102], these results were replicated for a period of 12 and 24 months after amputation. Surprisingly, in these studies, more intense catastrophizing was associated with an *improvement* of PLP and depression symptomatology six and 24 months after amputation. These results, at first glance, seem contradictory; however, they might be explained by regression to the mean artefacts, caused by the strong correlation between PLP, depression, and catastrophizing at the first time point in the studies, and thus, there was little room left for the patients to further aggravate at the second time point. Hence, the lagged relationships in these two studies do not necessarily indicate that catastrophizing predicts improvement of PLP. Rather, the results highlight the importance of taking the initial magnitude of pain into account. Another longitudinal study supporting the aggravating effect of catastrophizing on PLP was performed by Richardson et al. [104]. These authors found that catastrophizing before the amputation significantly predicted PLP six months after the amputation, whereas pain before the amputation was only weakly related to later PLP.

Relationships between catastrophizing and PLP have been investigated in two studies by Vase et al. [80, 105]. In the first study [105], catastrophizing accounted for 35% of the variance in PLP after statistically controlling for depression and anxiety. In addition, catastrophizing correlated positively with wind-up-like pain, elicited by pinprick stimulation applied to the residual limb. Wind-up is a dynamical pain phenomenon which is usually assessed by repetitive application of moderately painful stimuli of equal intensity. Due to temporal summation processes, stimuli are perceived as increasingly painful. However, strong enhancement in perceived pain in this paradigm indicates exaggerated summation or sensitization processes, which have previously been reported for chronic pain patients [106, 107]. Vase et al. [105] suggested that catastrophizing and wind-up might interact and contribute to PLP. In the second study [80], the authors used electroencephalographic recordings of cortical responses to noxious and nonnoxious stimuli presented at the amputees' affected and nonaffected limbs. For stimuli presented on the affected side, there was a significant correlation between catastrophizing and the power at the N/P135 dipole, suggesting an origin of cortical activity in the area of the secondary somatosensory cortex. The authors concluded that this finding might be explained by the fact that catastrophizing implies hypervigilant attention to noxious and nonnoxious stimuli. Another study showed that catastrophizing is not only related to PLP but also to disability as it predicted physical and psychosocial disability in amputees [108].

5. Changes in Body Perception and Their Relationship to PLP

The changes in physical integrity after amputation are accompanied by alterations in cortical body representation and body perception. Moseley et al. [109] introduced the body matrix concept, describing a widely distributed frontoparietal brain network involved in processing a combined representation of body and space for maintaining homeostatic control and enabling protective behavior. Amputation-induced changes in this network and their behavioral and perceptual consequences have been repeatedly studied in the past (e.g., [110–113]).

Previous studies have shown that brain changes in amputees with PLP compared to amputees without PLP are pronounced and that PLP intensity is positively

correlated with shifts in sensorimotor body representation (e.g., [65, 114]). These reorganization processes appear to be mirrored in altered body perception. For example, reorganization in the primary sensory cortex is not only correlated with PLP but also with the experience of a telescopic distortion (e.g., [115]), that is, the perception that the phantom limb shortens or, in extreme cases, retracts into the residual limb over time. Other cognitive alterations were observed for functions involving spatial transformations of body parts that appear to involve posterior and superior parietal regions and intraparietal regions (cf. [116]). Thus, amputees with PLP perform worse when they have to mentally rotate their limbs (e.g., [117]), and a negative association between performance in mental limb rotation and the frequency of PLP has been shown [118]. This suggests that phantom sensations in general [119] and PLP in particular are associated with impairments in the body schema, describing a flexible central representation of body posture that is needed for action. Since mental rotation of body parts involves motor imagery processes [120], and since the associated neural mechanisms are different in amputees with PLP compared to amputees without PLP [121], these results highlight the impaired mentalization of motor execution specifically for painful phantom limbs. Consequently, it has been suggested that the central body representation itself should be a target of therapeutic approaches [122], and thus, novel treatments aim at normalizing the underlying processes [123–130]. Interestingly, the amputees' body perception might be important for the effectiveness of these treatments [6, 127].

The PLP-specific alterations in body representation also have consequences for higher-order emotional and cognitive processes. In a nationwide study, Bekrater-Bodmann et al. [4] surveyed a large cohort of amputees for the presence of residual limb pain and PLP and additionally for their body-related dream content. Specifically, they assessed the proportion with which the amputees dreamed of themselves as being impaired (i.e., amputated) versus having an intact (i.e., nonamputated) body. The majority of amputees recalled their body appearance in dreams as intact, even decades after the amputation. PLP correlated positively with the recall of an impaired body in dreams, indicating that suffering in the awake state influences body representation in dreams. This relationship was rather unspecific because for residual limb pain, the same relationship was found. However, although dream content is rather difficult to interpret, these results suggest that the impaired physical body has a higher salience in postamputation pain sufferers than in pain-free amputees. In line with this notion, there is new evidence that PLP is related to implicit attitudes towards amputated bodies in general. By using an lmplicit Association Test, Macauda et al. [131] showed that amputees implicitly prefer intact bodies. In fact, amputees did not differ from a nonamputated control group. Interestingly, PLP intensity was significantly and positively correlated with the preference for intact bodies. It remains open how these findings are related to those from an earlier study [132] in which amputees were instructed to draw their body images and in which amputees suffering from PLP drew their bodies as intact more often than amputees without PLP. To which extent this is mediated by emotional factors remains to be determined. Prospective studies need to carefully consider and examine the complex interplay between PLP, body-related higher-order cognitions, and emotional processing.

6. Summary and Conclusions

In this review article, we summarized and discussed the research on emotional factors, stress, cognition, and body perception in PLP. Most research on emotional factors focused on depression and anxiety. Rates of depression and anxiety are high in early stages after amputation; however, both conditions are probably not (or only weakly) associated with the occurrence of PLP but rather with problems related to the adaption to the new situation. In later stages, depression and anxiety might contribute to PLP, but these associations appear to be weaker than in other types of chronic pain. Up to now, it remains an open question why depression and anxiety might be less relevant in PLP than in other chronic pain states. One reason, which has already been suggested by Desmond and MacLachlan [36], might be that PLP less strongly interferes with everyday activity—and compared to residual limb pain even with prosthesis use—than other chronic pain syndromes. Another reason might be that, in the case of chronic back pain, emotional and cognitive variables might play a more important etiological role. For example, the fear-avoidance model of chronic pain [14] states that fear and avoidance of movement are acquired through a fear-conditioning process that might favor chronicity. Over time, avoidance of movement leads to disability and recurrent pain, which strengthens the learned association and leads to a vicious circle consisting of pain, disability, and fear. The model therefore suggests that fear conditionability might be a risk factor for chronic pain that is acquired in such a way. That chronic back pain patients show enhanced fear conditioning has been shown in several studies (e.g., [133]). The role of anxiety and negative affect in the acquisition of movement-related fear has also been shown experimentally [134, 135]. Another series of neuroimaging studies further suggest that emotional learning processes predict the transition from the acute phase to the chronic phase in back pain (for a review, see [136]). Whether these conditioning and emotional learning mechanisms are also important in PLP needs to be addressed in future studies.

Concerning stress, we showed that research, on the whole, suggests that there are bidirectional relationships between stress and PLP, probably due to interactions of the central and peripheral nervous systems. The bidirectional relationships between stress and PLP have been demonstrated both in experimental studies and more naturalistic settings. Given the relatively clear picture that can be drawn from this line of research, the utility of altering central and peripheral stress responses in clinical interventions should be explored. More recent studies also suggest that therapeutic interventions used in traumatization can be useful to treat PLP.

Little is known about the role of cognitive factors such as attention/distraction or expectation, which are commonly

discussed as mediators of the pain experience. Memory is a well-represented topic in the PLP literature. However, it has not been clearly delineated which declarative and nondeclarative components are relevant and how they relate to neuroplasticity. Research on the role of catastrophizing in PLP shows that this coping style is positively associated with PLP presence, and longitudinal studies further indicate that catastrophizing aggravates PLP. Apart from avoiding catastrophizing, little is known about effective coping with PLP. Finally, we briefly discussed the role of body representation and body perception in PLP on which there have been many studies in the recent years and which are often perceived as the most promising targets for treating PLP (for reviews, see [137–140]). We also found evidence that cortical body representations might interact with psychological variables, but that until now, only few studies have focused on connections between these topics.

Compared to other types of pain, there has been little research on the role of psychological variables in PLP. whether psychological variables are less important for PLP or whether they have merely been neglected needs to be determined in future studies that take emotional, motivational, perceptual, and cognitive variables into account.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding this paper.

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Research Article

Optimism, Positive and Negative Affect, and Goal Adjustment Strategies: Their Relationship to Activity Patterns in Patients with Chronic Musculoskeletal Pain

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Objective. Activity patterns are the product of pain and of the self-regulation of current goals in the context of pain. The aim of this study was to investigate the association between goal management strategies and activity patterns while taking into account the role of optimism/pessimism and positive/negative affect. *Methods*. Two hundred and thirty-seven patients with chronic musculoskeletal pain filled out questionnaires on optimism, positive and negative affect, pain intensity, and the activity patterns they employed in dealing with their pain. Questionnaires were also administered to assess their general goal management strategies: goal persistence, flexible goal adjustment, and disengagement and reengagement with goals. *Results*. Structural equation modelling showed that higher levels of optimism were related to persistence, flexible goal management, and commitment to new goals. These strategies were associated with higher positive affect, persistence in finishing tasks despite pain, and infrequent avoidance behaviour in the presence or anticipation of pain. *Conclusions*. The strategies used by the patients with chronic musculoskeletal pain to manage their life goals are related to their activity patterns.

1. Introduction

Patients make substantial adaptive efforts to deal with chronic pain. In their continuous attempts to manage chronic pain, they usually change the way in which they engage in daily activities. However, the goal of pain management is just one of the goals to be pursued in a context of other concomitant goals [1–5]. The specific strategies that patients use to manage these different and sometimes opposing goals may determine their behaviour when dealing with daily activities (i.e., the so-called activity patterns).

1.1. Activity Patterns in Patients with Chronic Pain. Traditionally, three activity patterns have been distinguished: avoidance, persistence, and pacing. However, more specific activity patterns have been identified in patients with chronic pain [6, 7]. Avoidance has been divided into two patterns: (a) pain avoidance, which refers to avoidance behaviour in the presence or anticipation of changes in pain (e.g., "I stop what I am doing when my pain starts to get worse"), and (b) activity avoidance, which refers to the patients' condition of being in pain rather than the fluctuating pain experience (e.g., "I have not been able to carry on with my usual level of activity"). Research has shown that activity avoidance is associated with poorer physical and psychological functioning, whereas pain avoidance is not related to patient adjustment [6, 7]. Three types of persistence have been differentiated: (a) task-contingent persistence, in which patients persist in finishing tasks or activities despite pain (e.g., "Once I start an activity I keep going until it is done"); (b) excessive persistence, referring to doing too much, not respecting one's physical limits (e.g., "I find myself rushing to get everything done before I crash");

and (c) pain-contingent persistence, in which the level of activity fluctuates with and is determined by the pain at that moment (e.g., "When my pain decreases I try to be as active as possible"). A recent study of a sample of patients with musculoskeletal pain found that all three types of persistence were positively associated with daily functioning [7]. Finally, pacing is characterized by dividing daily activities into smaller tasks. Three types of pacing have been distinguished according to the goal of the behaviour: (a) to increase activity levels (e.g., "I usually take several breaks and so I can do a lot more things"), (b) to conserve energy for valued activities (e.g., "I split activities into smaller steps so I can save energy to do other things that matter to me"), and (c) to reduce pain (e.g., "I split activities into smaller steps so that it hurts less").

1.2. Activity Patterns from a Motivational Perspective. It has been emphasized that a theoretical model is needed to explain why patients with chronic pain engage in different activity patterns (i.e., the motivational mechanisms underlying activity patterns) [8]. Chronic pain interferes with daily activities and goals, and consequently, patients may need to negotiate the competition between their goals for limited physical and cognitive resources. From this point of view, activity patterns are viewed not solely as a product of pain but also as the result of the self-regulation of current goals in the context of pain [8]. It is therefore relevant to study the relationship between the strategies that patients with chronic pain use to manage their goals and their activity patterns.

1.3. Goal Management Strategies. Three goal management models can be distinguished. Firstly, the dual process model [9] differentiates two complementary strategies: the *assimilative mode* (tenacious goal pursuit), which is directed at maintaining goals by intentional efforts that modify the actual situation in accordance with personal goals, and the *accommodative mode* (flexible goal adjustment), which is directed at adjusting goals to situational or physical constraints. Several studies in patients with a range of chronic conditions, including chronic pain, have found that the combined use of accommodative and assimilative strategies was associated with well-being [10–12].

Secondly, the goal adjustment theory [13, 14] describes possible reaction patterns when goals are no longer attainable. This theory proposes that adjustment entails both *disengaging* from unattainable goals and *reengaging* in alternative goals. This theory has been strongly supported by empirical research, showing that individual differences in the capacity to adjust to unattainable goals predict both subjective well-being and physical health.

Thirdly, the two aforementioned theories have recently been combined in the integrated model of goal management [15]. According to this model, the adaptive value of a given goal management strategy depends on the patients' situation. Goal maintenance is the preferred strategy when a person still perceives opportunities to attain a goal. Goal adjustment—understanding goal disengagement as a form of goal adjustment—is more suitable for situations in which goals are under threat. Goal reengagement appears to be an appropriate strategy at all times and can complement existing goals or replace unattainable goals. This model has been tested in a sample of patients with arthritis [15], finding that patients who reported a lower tendency to adjust their goals had higher anxiety and depression scores. Patients who reported a greater tendency to adjust their goals to changed circumstances experienced more purpose in life, more positive affect, and were more satisfied with their participation in daily life activities.

1.4. Optimism as a Facilitator of Goal Adjustment. Optimism reflects the extent to which people hold generalized favourable expectations for their future [16]. In relation to pain, recent clinical and experimental evidence suggests that positive affect and optimism are two of the most important resilient resources for successful adaptation to acute and chronic pain [17–27]. Although there is considerable evidence linking optimism and favourable outcomes, additional research is needed to better understand the mechanisms underlying the effect of optimism on health and well-being [28]. In this line, several studies have shown that optimism could promote well-being through the facilitation of goal adjustment [29]. Optimists are more inclined than pessimists to pursue goals tenaciously [30], although they also engage in flexible goal adjustment [31]. Moreover, they are more likely to reengage in new goals when their current goals are not attainable [29, 32].

1.5. Affect and Goal Adjustment. A factor that could facilitate disengagement from unattainable goals and reengagement with new goals is the perception of available alternatives, which could be promoted by positive affect. In contrast, negative affect could narrow the perception of available alternatives and consequently could be related to disengagement from unattainable goals. As the "broaden-and-build theory" postulates, positive affect broadens attention to other stimuli, thoughts, and opportunities and facilitates the ability to think creatively and flexibly [33]. This may explain the finding that, in contrast to negative affect, positive affect is related to a more diverse array of goal management strategies [12, 29, 31, 32, 34, 35]. Thus, the "broaden-and-build theory" could complement goal regulation models: given that optimism and pessimism are related to positive and negative affect, respectively, it could be postulated that affect mediates the relationship between optimism and pessimism and goal management strategies. However, affect may not only be an antecedent of goal management strategies but may also result from the specific strategy employed [10–15] and/or from the ensuing activity patterns [6, 7]. Thus, it seems relevant to study the specific role that affect may play in the relationship between optimism/pessimism, goal management strategies, and activity patterns.

Briefly, longitudinal evidence shows that disengagement is negatively related to negative affect because successful disengagement could contribute to the quality of life by avoiding the stress of repeated failures [36]. On the other hand, positive affect is positively associated with tenacious

goal pursuit, flexible goal adjustment, and goal reengagement [10–15].

1.6. Activity Patterns and Affect. Previous research has shown that positive affect is positively associated with nonpain-centred activity patterns (task-contingent persistence, pacing to increase activity levels, and pacing to conserve energy for valued activities), whereas negative affect is positively related to pain-centred activity patterns (activity avoidance, pain avoidance, pain-contingent persistence, and pacing to reduce pain) [6, 7].

1.7. Aims and Hypotheses. The aim of the present study was to investigate the association between goal management strategies and activity patterns in patients with chronic musculoskeletal pain while taking into account the role of optimism/pessimism and positive/negative affect. Three alternative models were tested. Firstly, it was postulated that affect would mediate optimism/pessimism and goal management strategies which, in turn, were hypothesized to be associated with activity patterns (Model 1). Secondly, it was postulated that there would be a direct relationship between optimism/pessimism and goal management strategies, and that affect would mediate goal management strategies and activity patterns (Model 2). Finally, it was postulated that optimism/pessimism would be related to goal management strategies, and that goal management strategies would be associated with activity patterns which, in turn, would be related to affect (Model 3). Figure 1 shows the three models. A detailed description of the postulated relationships is included in Data Analysis.

In the field of chronic pain, research based on goal management models is scarce. As far as we know, this study is the first to investigate the relationship between optimism, pessimism, positive and negative affect, goal management strategies, and activity patterns in patients with chronic musculoskeletal pain.

2. Methods

2.1. Procedure. This study formed part of a larger research project [7, 37], which was approved by the University of Málaga Ethics Committee. Participants were recruited through a physiotherapy unit and two local associations of patients with fibromyalgia and by doctors working at the Hospital Costa del Sol Pain Unit and the Hospital Quirón Rheumatology Unit in Málaga. The data were collected between March 2016 and December 2016. Individuals were considered eligible for inclusion if they met the following criteria: at the moment of participation in the study, they were experiencing musculoskeletal pain and had been experiencing pain for at least the last 6 months; they were between 18 and 65 years; they were not being treated for a malignancy, terminal illness, or psychiatric disorder; they were able to understand the Spanish language (spoken and written); and they were able to understand the instructions and questionnaires. The patients were informed of the study aims, confidentiality was assured, and written informed consent was obtained. Each participant had a semistructured interview with a psychologist to obtain demographic, social, and medical history data. Subsequently, they completed self-report questionnaires in the order described in Variables and Instruments.

Two psychologists took part in data collection. They were trained in the application of the protocol to guarantee the standardization of the assessment process and were blinded to the study design and hypotheses. The patients were always assessed in their usual health centre or in the facilities of the associations. Each session lasted approximately 1 hour.

2.2. Participants. Three hundred and eighty-eight patients were invited to take part in the study. Of these patients, 98 refused participation, 32 did not meet the inclusion criteria, and 21 were eliminated after preliminary analyses because they were outliers.

The final sample comprised 237 chronic musculoskeletal pain patients (192 women and 45 men). The average age was 52 years (SD = 9.95). At the time of the study, 71.30% were married or cohabiting. Regarding employment, 39.80% were active workers, 23.30% were retired, 20.30% were unemployed, and 15.3% were homemakers.

A total of 31.90% had completed high-school education and 39.60% had completed primary education. The median pain duration was 12.16 years (SD = 18.88), and the average pain intensity was 6.54 (SD = 1.33). The participants had musculoskeletal pain at different locations: generalized pain conditions were the most frequent (44.52%) (fibromyalgia, 28.27%; generalized osteoarthritis, 12.72%; and other conditions, 3.52%), followed by spinal pain, 26.14% (cervical, 3.53%; lower back, 6.01%; and other back sites, 16.61%), pain in the upper shoulder and upper limbs (15.19%), and pain in the lower limbs (14.13%).

2.3. Variables and Instruments

2.3.1. Dispositional Optimism. Dispositional optimism was assessed using the Spanish version of the Life Orientation Test-Revised (LOT-R) [38, 39]. The LOT-R consists of six scored items (items 1, 4, and 10 are positively worded and items 3, 7, and 9 are negatively worded) plus four filler items. The optimism and pessimism subscale scores were calculated by summing the positive and negative items, respectively. Respondents indicate the extent to which they agree with each item on a 5-point Likert-type scale ranging from 0 (strongly disagree) to 4 (strongly agree). In the present study, the LOT-R total score had Cronbach's alpha of 0.90. Cronbach's alpha for the optimism and pessimism subscales was 0.85 and 0.81, respectively. The Spanish LOT-R has shown adequate criterion validity [40].

2.3.2. Positive and Negative Affect. Positive and negative affect was assessed using the Spanish version of the Positive and Negative Affect Schedule (PANAS) [41–43], which is one of the most reliable, valid, and efficient means to measure these variables. It comprises two 10-item scales. The

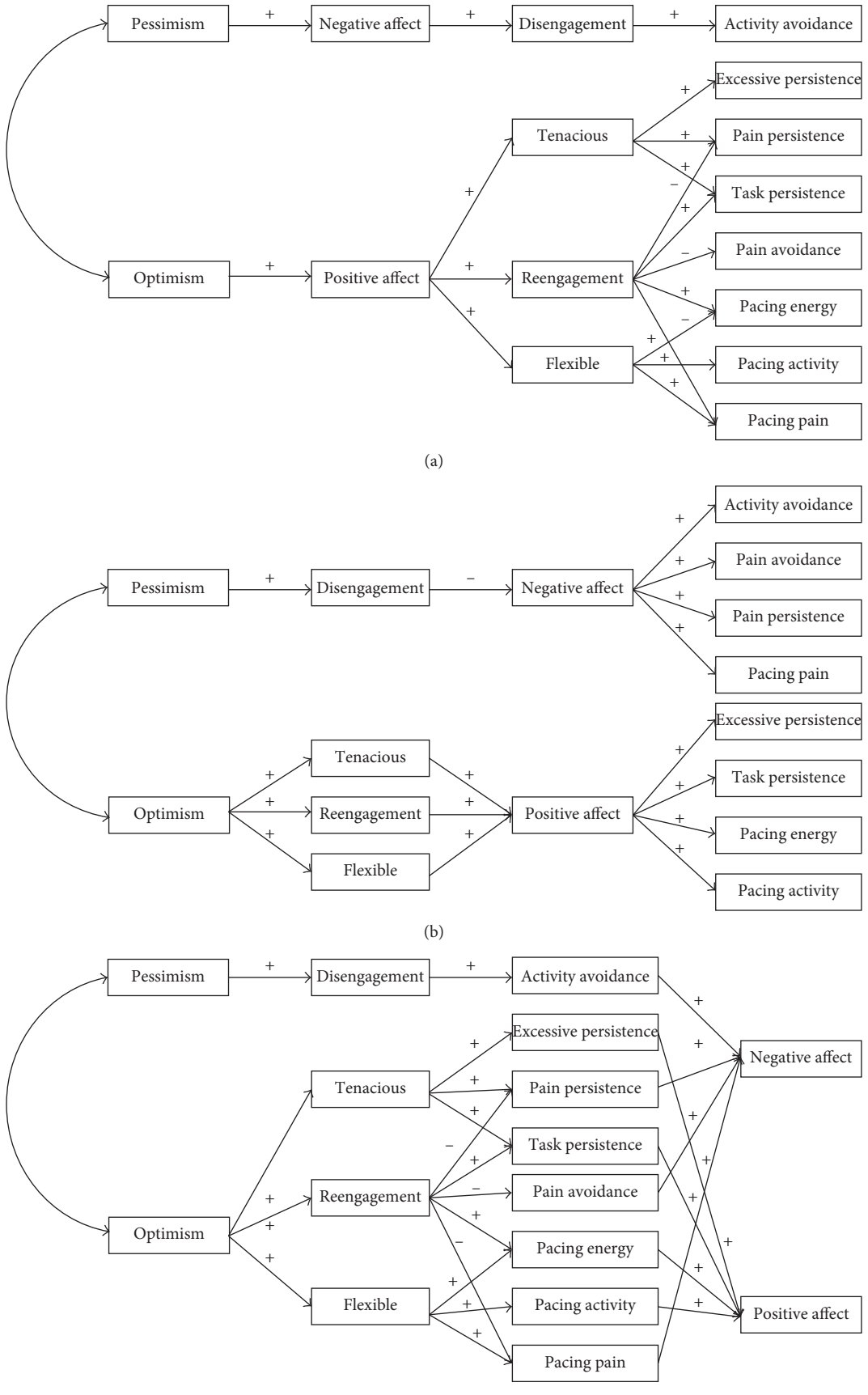

Figure 1: Hypothetical alternative models. (a) Model 1, (b) Model 2, and (c) Model 3.

instrument has demonstrated appropriate stability over a 2-month time period. The Spanish PANAS also has excellent construct and criterion validity. In this study, the positive affect and negative affect scales had Cronbach's alpha of 0.90 and 0.87, respectively.

2.3.3. Pain Intensity. Patients were asked to rate their mildest, average, and worst pain during the past 2 weeks, as well as their current pain, on a scale ranging from 0 to 10, with "0" indicating "no pain" and "10" indicating "pain as intense as you could imagine." A composite pain intensity score was calculated for each participant by calculating the average of the mildest, average, worst, and current pain [44].

2.3.4. Activity Patterns. The Activity Patterns Scale [7] consists of 24 items grouped into 8 three-item subscales: pain avoidance ($\alpha = 0.72$), activity avoidance ($\alpha = 0.82$), task-contingent persistence ($\alpha = 0.87$), excessive persistence ($\alpha = 0.80$), pain-contingent persistence ($\alpha = 0.92$), pacing to increase activity levels ($\alpha = 0.72$), pacing to conserve energy for valued activities ($\alpha = 0.81$), and pacing to reduce pain ($\alpha = 0.78$). The participants are asked to indicate to what extent the statement applies to them on a 5-point scale ranging from 0 (not at all) to 4 (always). The instrument showed adequate reliability as well as structural, convergent, and criterion validity [7].

2.3.5. Goal Management Strategies. The Goal Disengagement and Goal Reengagement Scale [14] is a 10-item instrument that measures the individual's usual reaction to having to stop pursuing an important goal. The instrument comprises a 5-point Likert-type scale ranging between 1 (almost never true) and 5 (almost always true). Four items measure an individual's tendency to disengage from unattainable goals (e.g., "It's easy for me to reduce my effort toward the goal," or "I stay committed to the goal for a long time; I can't let it go") and six items measure an individual's tendency to reengage with new goals (e.g., "I seek other meaningful goals," or "I start working on other new goals"). The Spanish version of the instrument has adequate criterion validity, internal consistency, and stability, and its factor structure is similar to the original structure [45]. In this study, the Goal Disengagement and the Goal Reengagement Scales had Cronbach's alpha of 0.70 and 0.94, respectively.

The Tenacious Goal Pursuit and Flexible Goal Adjustment Scales [9] assess two distinct modes of coping with goal disruption, respectively: tenacious goal pursuit (e.g., "The harder a goal is to achieve, the more desirable it often appears to me") and flexible goal adjustment (e.g., "In general I do not stay upset for long when I miss an opportunity"). Respondents rate the degree to which they agree with each statement on a 5-point Likert scale ranging from "fully disagree" to "fully agree." The exploratory factor analysis of the Spanish version of the scales showed the same number of factors as the original scales and was ratified by confirmatory factor analysis. Cronbach's alpha, test-retest reliability, and correlations between the scales were also similar to the original scales. The scales also demonstrated adequate criterion validity [45]. In this study, the Tenacious Goal Pursuit and the Flexible Goal Adjustment Scales had Cronbach's alpha of 0.80 and 0.81, respectively.

2.4. Data Analysis. Statistical analyses and structural equation modelling (SEM) were conducted using SPSS 15.0 software and LISREL 8.80 software, respectively [46]. Mean scores, standard deviations, and correlation coefficients for all variables were calculated.

The fit of each of the three hypothetical models (Figure 1) was tested using SEM. The data were checked prior to the analyses. Outliers were identified by cluster analysis-based outlier detection in which each record is assigned an anomaly index, which is the ratio of the group deviation index to its average over the cluster that the case belongs to [47]. Twenty-one participants were excluded from the sample because they presented anomalous values for one of the variables included in the model. We also found that some variables were not normally distributed; thus, we used maximum likelihood as the estimation method because this method is effective for any data distribution when the analyses are performed on covariance matrices, and the matrix of fourth-order moments is provided [48].

The goodness-of-fit indexes used for the overall model were Satorra-Bentler chi-square [49], the Comparative Fit Index (CFI) [49], the Normed Fit Index (NFI) [50], the root mean-square error of approximation (RMSEA), and the Akaike Information Criterion (AIC) [51]. Satorra-Bentler chi-square is a chi-square fit index that corrects the statistic under distributional violations. In order to reduce the sensitivity of chi-square to sample size, the index is divided by the degrees of freedom [49]. Ratios of 2 or smaller are indicative of an acceptable fit of the model [52]. The CFI and NFI measure the proportional improvement in fit by comparing a hypothesized model with the null model as the baseline model. The CFI and NFI range from 0 (absolute lack of fit) to 1 (perfect fit), and fit is considered to be good when the values are more than 0.90 [53]. The RMSEA is an absolute misfit index; the closer to zero, the better the fit. Values less than 0.08 indicate an adequate fit, and values less than 0.06 indicate a good fit [53, 54]. Finally, the AIC index allows alternative models to be compared by taking into account parsimony (in the sense of the number of parameters) as well as fit. This index can be used regardless of whether or not the models can be ordered in a nested sequence. In this approach, the models are ranked according to their AIC values, and the model with the smallest value is chosen [51].

Three alternative models were tested (Figure 1). Age and pain intensity were used as control variables in the three models. These variables were used as covariates in the models for the variables with which they were significantly correlated (age and goal reengagement, pain intensity and flexible goal adjustment, positive and negative affect, pain avoidance, activity avoidance, task-contingent persistence, and pacing to reduce pain). In the three models, optimism and pessimism are the exogenous variables (i.e., variables not determined by any other variable in the model; Figure 1). The remaining variables are endogenous (i.e., variables determined by one or more variables in the model). All

residual variances were assumed to be uncorrelated, and the exogenous variables were assumed to be correlated.

Causal paths were defined according to the hypothetical structural equation models shown in Figure 1. Path coefficients should not be interpreted as correlation coefficients. For example, a path coefficient of 0.80 connecting two variables (A and B) means that if A increases by one standard deviation from its mean, B would be expected to increase its own standard deviation by 0.80, while all other relevant connections remain constant. A path coefficient of −0.16 means that if A increases by one standard deviation from its mean, B would be expected to decrease its own standard deviation by 0.16, while all other relevant connections remain constant. The following paths were postulated for each of the models tested:

Model 1: (a) higher pessimism and higher optimism would be associated with higher negative effect and higher positive affect, respectively; (b) higher negative affect would be associated with the more frequent use of the disengagement goal management strategy; (c) higher positive affect would be associated with the more frequent use of tenacious goal pursuit, flexible goal adjustment, and goal reengagement strategies; (d) goal disengagement, understood as a tendency to abandon unattainable goals, would be positively associated with the activity avoidance pattern in which individuals give up doing things due to pain; (e) goal reengagement, understood as a tendency to commit to new goals, would be inversely related to activity patterns in which the patients are only centred on the goal of pain management (i.e., pain avoidance, pain-contingent persistence, and pacing to reduce pain). In contrast, goal reengagement would be positively associated with task-contingent persistence and with pacing to conserve energy for valued activities because these patterns imply that individuals are committed to goals other than pain control; (f) tenacious goal pursuit would be positively associated with task-contingent persistence, pain-contingent persistence, and excessive persistence; and (g) flexible goal adjustment would be positively associated with the three types of pacing because pacing involves adapting behaviour to the situational constraints without giving up the final goal (e.g., by flexibly alternating between rest and activity).

Model 2: (a) higher pessimism would be associated with higher disengagement; (b) higher optimism would be associated with the more frequent use of tenacious goal pursuit, flexible goal adjustment, and goal reengagement strategies; (c) higher disengagement would be related to lower negative affect; (d) higher tenacious goal pursuit, flexible goal adjustment, and goal reengagement strategies would be associated with higher positive affect; (e) higher positive affect would be related to higher task-contingent persistence, higher excessive persistence, higher pacing to increase activity levels, and higher pacing to conserve energy for valued activities; and (f) higher negative affect would be associated with higher activity avoidance, higher pain avoidance, higher pain-contingent persistence, and higher pacing to reduce pain.

Model 3: (a) higher pessimism would be associated with higher disengagement; (b) higher optimism would be associated with the more frequent use of tenacious goal pursuit, flexible goal adjustment, and goal reengagement strategies; (c) goal disengagement would be positively associated with the activity avoidance pattern; (d) goal reengagement would be inversely related to pain avoidance, pain-contingent persistence, and pacing to reduce pain and would be positively associated with task-contingent persistence and pacing to conserve energy for valued activities; (e) tenacious goal pursuit would be positively associated with task-contingent persistence, pain-contingent persistence, and excessive persistence; (f) flexible goal adjustment would be positively associated with the three types of pacing; (g) higher task-contingent persistence, higher excessive persistence, higher pacing to increase activity levels, and higher pacing to conserve energy for valued activities would be related to higher positive affect; and (h) higher activity avoidance, higher pain avoidance, higher pain-contingent persistence, and higher pacing to reduce pain would be related to higher negative affect.

3. Results

Table 1 shows mean scores, standard deviations, and correlation coefficients for all measures.

Table 2 shows all the GFIs of the 3 models tested via SEM. As can be seen, the three models meet the recommended cutoff criteria. The AIC index showed that the Model 2 had the smallest value and thus the best fit.

Thus, Model 2 was taken as the starting point for further modification. Modifications were sequentially made in line with the recommendations of the Lagrange multiplier test [48]. Firstly, we deleted all paths of the initial model that were not statistically significant. For this reason, the variables excessive persistence, pain-contingent persistence, pacing to increase activity levels, pacing to conserve energy for valued activities, and pacing to reduce pain were excluded from the model. Except for pain intensity, in relation with positive and negative affect, the remaining covariates were excluded from the final model. Secondly, a relationship suggested by the modification indexes was included: a path from positive affect to pain avoidance. Figure 2 shows the final model.

All path coefficients were statistically significant ($P < 0.05$). The goodness-of-fit indexes indicated that the estimated final model provided a good fit to the data. The Satorra–Bentler chi-square (10.67) divided by the degrees of freedom (50) was 0.21, which indicated an adequate fit of the model. The CFI (1) and NFI (1) had values higher than 0.90, which indicated an adequate fit. The RMSEA was 0.00 (values less than 0.06 indicate a good fit).

As shown in Figure 2, a high negative correlation was found between optimism and pessimism. Pessimism yielded a statistically significant positive path coefficient to

Table 1: Means, standard deviations (SD), and Pearson correlations.

Variables	Range	Mean (SD)	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Optimism	0–12	7.68 (2.99)	−0.77**	0.67**	−0.51**	0.46**	0.61**	−0.51**	0.72**	−0.27**	−0.44**	0.18**	−0.08	−0.03	0.05	0.14*	−0.02
2. Pessimism	0–12	5.18 (3.12)	—	−0.63**	0.48**	−0.56**	−0.48**	0.54**	−0.63**	0.30**	0.55**	−0.25**	0.11	0.03	−0.03	−0.08	0.09
3. Positive affect	11–45	28.99 (7.73)		—	−0.51**	0.53**	0.54**	−0.58**	0.60**	−0.38**	−0.59**	0.36**	−0.08	0.03	0.05	0.09	−0.13*
4. Negative affect	10–47	24.27 (7.63)			—	−0.33**	−0.40**	0.40**	−0.45**	0.29**	0.53**	−0.12	0.28**	0.16*	−0.02	−0.12	0.04
5. Tenacious goal pursuit	21–60	42.24 (7.95)				—	0.54**	−0.57**	0.44**	−0.27**	−0.47**	0.33**	−0.08	0.11	−0.02	0.06	−0.11
6. Flexible goal adjustment	8–35	23.77 (5.11)					—	−0.32**	0.55**	−0.17*	−0.29**	0.13**	−0.03	−0.01	0.01	0.17*	0.01
7. Goal disengagement	5–16	9.60 (2.58)						—	−0.52**	0.36**	0.51**	−0.28**	0.11	−0.07	−0.02	0.00	0.08
8. Goal reengagement	5–25	17.14 (3.85)							—	−0.27**	−0.44**	0.19*	−0.14**	−0.06	0.06	0.20**	−0.00
9. Pain avoidance	0–12	6.70 (2.64)								—	0.53**	−0.70**	−0.17*	−0.44**	0.41**	0.32**	0.51**
10. Activity avoidance	0–12	6.30 (2.76)									—	−0.48**	0.20**	−0.04	0.02	−0.05	0.25**
11. Task-contingent persistence	0–12	6.08 (2.93)										—	0.17**	0.53**	−0.43**	−0.37**	−0.57**
12. Pain-contingent persistence	0–12	6.88 (3.26)											—	0.46**	−0.11	−0.21**	−0.16*
13. Excessive persistence	0–12	5.21 (2.94)												—	−0.46**	−0.53**	−0.53**
14. Pacing to increase activity levels	0–12	6.17 (2.60)													—	0.80**	0.73**
15. Pacing to conserve energy for valued activities	0–11	6.01 (2.71)														—	0.73**
16. Pacing to reduce pain	0–12	6.70 (2.76)															—

*$P < 0.05$;** $P < 0.01$; [a]the numbers in the upper row correspond to the variables in rows 1 to 12.

Table 2: Goodness-of-fit indexes of the three models tested.

	χ^2/d.f.[a]	NFI	CFI	RMSEA	AIC
Model 1	0.47	0.99	1	0.00	157.06
Model 2	0.39	0.99	1	0.00	144.83
Model 3	0.40	0.99	1	0.00	158.65

Note. Model 1: optimism/pessimism → positive/negative affect → goal management strategies → activity patterns; Model 2: optimism/pessimism → goal management strategies → positive/negative affect → activity patterns; Model 3: optimism/pessimism → goal management strategies → activity patterns → positive/negative affect; NFI, Normed Fit Index; CFI, Comparative Fit Index; RMSEA, root mean-square error of approximation; AIC, Akaike Information Criterion; [a]χ^2/d.f.: Satorra-Bentler chi-square divided by degrees of freedom.

disengagement, disengagement yielded a statistically significant positive path coefficient to negative affect, and negative affect yielded a significant positive path coefficient to activity avoidance. Optimism yielded three statistically significant positive path coefficients to tenacious goal pursuit, flexible goal adjustment, and goal reengagement. Tenacious goal pursuit, flexible goal adjustment, and goal reengagement each yielded a statistically significant positive path coefficient to positive affect. Positive affect yielded a statistically significant positive path coefficient to task-contingent persistence and a statistically significant negative path coefficient to pain avoidance. Finally, pain intensity yielded a statistically significant positive path coefficient to negative affect and a statistically significant negative path coefficient to positive affect.

4. Discussion

The aim of the present study was to investigate the association between goal management strategies and activity patterns in patients with chronic musculoskeletal pain while taking into account the role of optimism/pessimism and positive/negative affect. Special attention was paid to the role of positive/negative affect. Three alternative models were tested in which affect was hypothesized to play different roles.

The model with the best fit was the one in which a direct relationship was postulated between optimism/pessimism and goal management strategies and in which affect was hypothesized to mediate goal management strategies and activity patterns. Specifically, in the face of unattainable goals, patients with chronic pain and higher levels of pessimism reported that they tended to abandon such goals (disengagement). This strategy was associated with higher levels of negative affect which, in turn, was related to the more frequent use of the pattern of activity avoidance (i.e., the abandonment of activities because of the pain condition). On the other hand, patients with chronic pain characterized by higher levels of optimism reported being more persistent in pursuing their goals, more able to adjust their goals to situational constraints, and in the face of unattainable goals, to more easily commit to new goals (reengagement). The more frequent use of these three strategies was associated with higher positive affect which, in turn, was related to the more frequent use of a pattern of activity characterized by persistence in finishing tasks or activities despite pain. Furthermore, positive affect was related to the more infrequent use of a pattern characterized by avoidance behaviour in the presence or anticipation of changes in pain.

4.1. Optimism/Pessimism and Goal Management Strategies. The findings of this study are in line with those of previous research showing that optimists and pessimists cope in different ways to threats to their health [29]. According to the results, patients with chronic musculoskeletal pain who have positive expectations for their future exert continuing effort when the achievement of their goals is threatened. Nevertheless, it must be taken into account that excessive persistence in the face of failure could lead to resource depletion and frustration [55]. Successful adaptation requires combining tenacity with a certain amount of flexibility; for example, chronic musculoskeletal pain sometimes demands the reformulation of the patients' current goals or a change in the strategies used to achieve such goals. The most adaptive strategy could even be to commit to new life goals. The results showed that patients with a higher level of optimism also showed higher levels of flexibility in the management of their goals and a higher level of reengagement in new goals. These findings are in line with those of previous research showing that persistence is not a sterile trait in optimistic individuals because they are also more flexible and sensitive to the contextual parameters [31, 35, 56, 57]. In addition, when optimistic individuals repeatedly fail to attain certain goals, they substitute these goals with attainable goals [29, 30, 32] and, in contrast to more pessimistic individuals, they are more likely to report more perceived progress in the pursuit of personal goals [58].

In line with the results of a previous study [29], our results showed that chronic musculoskeletal pain patients who have negative expectations for their future tend to abandon their goals when they think that such goals are unattainable. In contrast to optimism, which was associated with a wider array of strategies to manage goals, pessimism implies a certain rigidity in coping because it is associated only with giving up.

4.2. Goal Management Strategies and Affect. Model 1 predicted that affect would mediate optimism/pessimism and goal management strategies. This prediction was not confirmed by the results of this study. Based on the "broaden-and-build theory" [33], it was postulated that positive affect would favour flexible goal management, tenacious goal pursuit, and the reengagement in new goals through the perception of more available alternatives. Negative affect was hypothesized to narrow the perception of available alternatives and consequently to be related to disengagement from unattainable goals.

The findings of this study supported the predictions of Model 2 that positive/negative affect would be the result of goal management strategies. Nevertheless, contrary to the results of a previous longitudinal study using a sample of older adults [36], our results showed that the capacity to withdraw effort and commitment from unattainable goals was not associated with lower negative affect but with higher

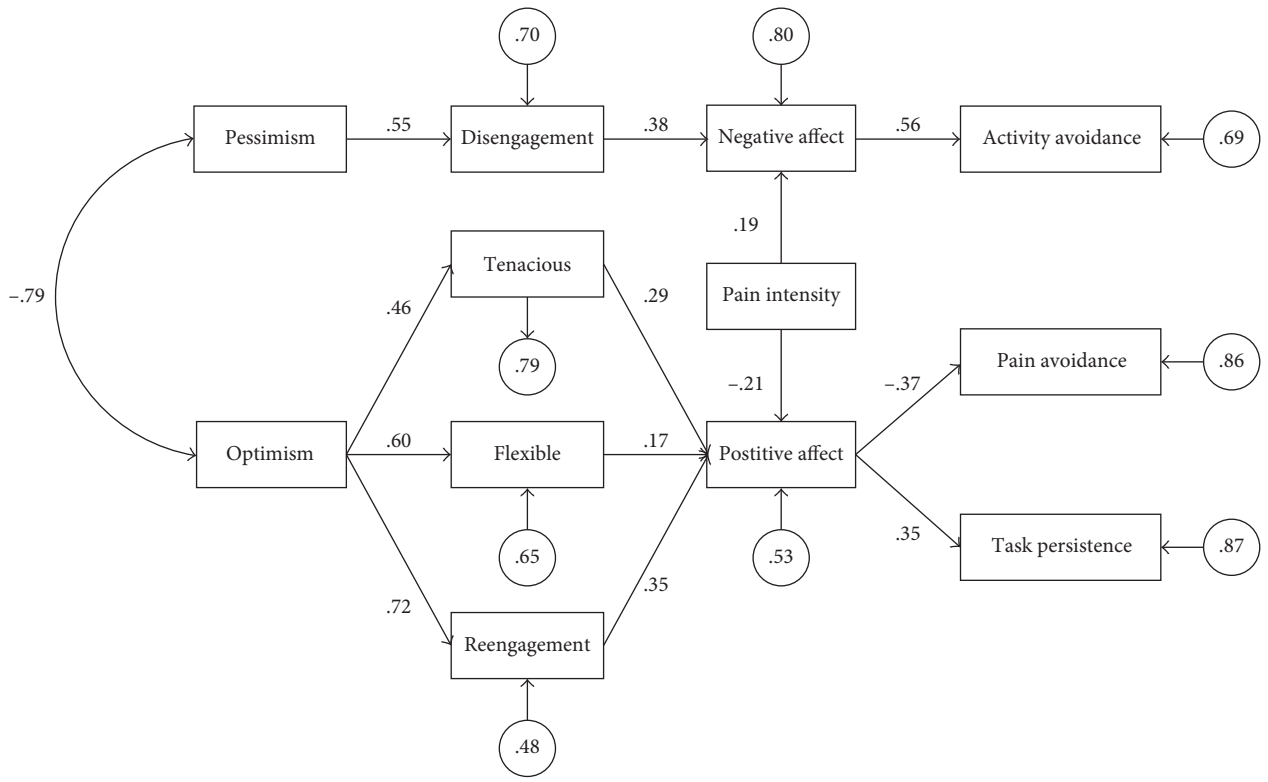

Figure 2: Final model. Rectangles represent observed (measured) variables, circles represent standardized error variances, straight lines with arrows represent presumed causal paths, values above the arrows represent standardized path coefficients, and the curved line represents the correlation between the exogenous variables.

negative affect. In patients with chronic musculoskeletal pain, the abandonment of cherished life goals may lead to frustration and distress. In contrast, our results and those of previous studies [10–15] have shown that when chronic musculoskeletal pain threatens the patients' life goals but they tenaciously continue to pursue such goals, adapt such goals to the changing circumstances, or commit to new goals, they experience greater emotional well-being.

Finally, our results show that affect did not result from activity patterns, as postulated by Model 3. It seems that positive and negative affect creates the "emotional context" in which activity avoidance and the other activity patterns are performed and negotiated in relation to concomitant life goals [59].

4.3. Affect and Activity Patterns. The results of the present study supported Model 2, which hypothesized that affect would be directly related to activity patterns. Specifically, it was found that negative affect was related to the pattern of activity avoidance in which patients give up general activities due to their condition. According to previous studies [6, 7], this activity pattern is associated with the poorest well-being. Positive affect was positively related to task-contingent persistence, which is the activity pattern with the best adaptive results [6, 7]. Task-contingent persistence means that, despite pain, patients carry on with a task or an activity until it is finished. This response suggests that patients show less protective behaviour because the value of other life goals outweighs the value of pain control. Positive affect was also related to the more infrequent use of pain avoidance in which patients interrupt specific actions because of pain.

According to previous research, several processes may explain how positive affect might influence these activity patterns. Firstly, positive affect [60] may help replenish depleted self-regulatory resources, making patients more resistant to activity avoidance. Secondly, positive affect is related to approach goals, which are goals that individuals work toward in order to gain or accomplish something positive, as opposed to goals that seek to avoid a negative outcome [61]. Finally, positive affect may make patients able to "broaden and build" [33], which refers to the act of stepping back to see the larger picture of their lives instead of a pain-centred representation of their lives. This approach would help them to persist in meaningful activities and "avoid avoidance." These three hypotheses could be the topic of systematic research.

Contrary to the postulates of Models 1 and 3, pain management strategies were not directly related to activity patterns; as mentioned, their relationship was mediated by affect. This may be because the assessment tools used in the present study measure dispositional goal adjustment capacities. There is evidence suggesting that disposition and situational adjustment capacities may operate somewhat differently from each other [62]. Therefore, future research should investigate the relationship between activity patterns and goal adjustment strategies using specific situational measures, such as vignettes, applied to the chronic pain condition. The aforementioned limitation could also account for the fact that only three activity patterns were

included in the final model. It may be the case that pain-specific goal management strategies would have shown significant relationships with more activity patterns.

On the other hand, the present approach has undeniable advantages. It emphasizes the role of dispositional variables or, to put it in another way, the role of the history of the patients. The relatively stable expectations for the future and for managing goals that may have existed before the onset of pain appear to be significantly related to activity patterns through affect. If future prospective research replicates these findings, then the assessment of optimism/pessimism and general goal management strategies will enable the early prediction of which patients will develop adaptive or dysfunctional activity patterns.

4.4. The Role of Pain Intensity. The results of the present study showed that pain intensity was positively related to negative affect, negatively related to positive affect, and related to activity patterns through these variables. The role of pain intensity in the adaptation of patients cannot be underplayed [63]. Pain and affect are inextricably linked because pain is not only an aversive physical state but also an aversive emotional state in which negative affective responses serve as a protective function motivating the individual to escape imminent threat [64].

4.5. Limitations of This Study. The present study has several limitations, and the results should be interpreted accordingly. Firstly, the only method used was self-reporting. Shared method variance may have contributed to the results. Secondly, the cross-sectional nature of the study does not allow causality to be inferred. Thirdly, twenty-one participants were excluded from the sample because they presented anomalous values for one of the variables included in the models. It has been demonstrated that, in most cases, errors of inference are significantly reduced by the removal of outliers [65]; nevertheless, it cannot be discounted with complete certainty that the removal of outliers may negatively affect the representativeness of the sample [66].

4.6. Clinical Implications. The findings of the present study demonstrate that, in order to promote adaptive activity patterns in patients with chronic musculoskeletal pain, it is not enough to aim at "fixing what is wrong": it is also essential to aim at "building what is strong" [67]. In contrast to the conceptualization of positive and negative affect being on the same continuum, research has clearly shown that they are separable affective states [64], which implies that interventions on negative affect do not guarantee improvements in positive affect. That is, patients with deficits in positive affectivity need interventions aimed at augmenting positive affect. One study [64] discussed how cognitive behavioural therapy for pain, acceptance and commitment therapy, and mindfulness-based stress reduction incorporate aspects of positive affect enhancement and encouraged the development of interventions aimed at the generation of positive affect among patients with chronic pain. A similar technique is the Best Possible Self, which aims to increase optimism [68–71]. Finally, a recent study demonstrated the clinical usefulness of an Internet-based positive psychology self-help intervention for the management of chronic pain [72].

The results of the present study suggest that cognitive behavioural intervention programs for individuals with chronic pain may benefit from the inclusion of elements aimed at promoting goal adjustment. The action phase model of goal attainment [73] has been proposed as a useful theoretical framework to integrate motivational strategies in pain intervention programs [74]. Recently, an experimental study showed that implementation intentions reduced escape-avoidance behaviour during painful tasks in healthy individuals [75]. In addition, a short goal-pursuit intervention has been developed to improve physical capacity in patients with chronic pain. This intervention includes problem-solving techniques to overcome obstacles and an implementation intention procedure [76].

4.7. Conclusion. The strategies used by patients with chronic musculoskeletal pain to manage their life goals are related to the different ways in which they engage in daily activities. This relationship is mediated by positive/negative affect. Optimism can be regarded as a protective factor that fosters the use of flexible goal management strategies.

Conflicts of Interest

The authors declare no conflicts of interest.

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Review Article

The Underestimated Significance of Conditioning in Placebo Hypoalgesia and Nocebo Hyperalgesia

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Placebo and nocebo effects are intriguing phenomena in pain perception with important implications for clinical research and practice because they can alleviate or increase pain. According to current theoretical accounts, these effects can be shaped by verbal suggestions, social observational learning, and classical conditioning and are necessarily mediated by explicit expectation. In this review, we focus on the contribution of conditioning in the induction of placebo hypoalgesia and nocebo hyperalgesia and present accumulating evidence that conditioning independent from explicit expectation can cause these effects. Especially studies using subliminal stimulus presentation and implicit conditioning (i.e., without contingency awareness) that bypass the development of explicit expectation suggest that conditioning without explicit expectation can lead to placebo and nocebo effects in pain perception. Because only few studies have investigated clinical samples, the picture seems less clear when it comes to patient populations with chronic pain. However, conditioning appears to be a promising means to optimize treatment. In order to get a better insight into the mechanisms of placebo and nocebo effects in pain and the possible benefits of conditioning compared to explicit expectation, future studies should carefully distinguish both methods of induction.

1. Introduction

Placebo and nocebo effects are prevalent topics in current research, especially in the domain of pain, where they can be investigated comparatively easily and serve as a model for other systems (e.g., immune, motor, and respiratory systems [1]). While placebo hypoalgesia refers to decreased pain sensitivity due to an inert treatment (e.g., sham procedure and inert substance), its counterpart nocebo hyperalgesia is defined as increased pain sensitivity attributable to an inert treatment [2]. Due to their capacity to improve or worsen symptoms and well-being, placebo and nocebo effects are highly relevant not only in research but also in clinical practice. They contribute to most therapeutic effects [3], occur regularly in doctor-patient interactions [4], and are assumed to play a role in the development and maintenance of chronic pain and other diseases [5, 6]. Placebo and nocebo effects also significantly influence the outcome of randomized placebo-controlled clinical trials, for example, leading to an underestimation of clinical effects of novel drugs [7–9]. Although this clinical relevance and research on placebo and nocebo effects have prospered during the past decade, many issues remain unresolved or poorly understood. One of these issues that deserve our attention concerns the causing mechanisms of placebo and nocebo effects and the significance of conditioning in this realm. Only if we understand how these effects emerge, we can systematically take advantage of placebo and avoid nocebo effects, especially in the clinical context.

After giving a brief overview over current evidence and models on the development of placebo hypoalgesia and nocebo hyperalgesia including conditioning and expectation approaches, we will turn to studies that stress the significance of conditioning and demonstrate that conditioning

effects might have been misunderstood and/or underestimated. We will highlight the need to better understand conditioned placebo and nocebo effects and propose experimental designs that allow a conclusive investigation of the specific mechanisms at work.

2. Development of Placebo and Nocebo Effects

Placebo and nocebo effects can be induced by different means. Empirical evidence shows that verbal suggestion [10], classical conditioning [11–13], and observational learning [14, 15] can lead to placebo hypoalgesia and nocebo hyperalgesia. Verbal suggestions in terms of written or spoken statements on the alleged effect of the placebo or nocebo are thought to induce an explicit expectation that directly mediates the effect [16, 17]. In contrast, direct experience of a pain-increasing or -relieving effect is essential in conditioning of placebo hypoalgesia and nocebo hyperalgesia [18]. Here, a placebo/nocebo serves as conditioned stimulus and is repeatedly coupled to a pain stimulus (unconditioned stimulus), in which the intensity is reduced or increased without the person's knowledge compared to before placebo/nocebo administration or to a simultaneous stimulation without placebo/nocebo. Subsequently, the conditioned effect is tested by retracting the surreptitious change in stimulation intensity while still administering the placebo/nocebo. Observational learning of placebo and nocebo effects has been investigated only recently. It is usually carried out by showing videos of or live models who are demonstrating reduced or increased pain sensations upon administration of a placebo/nocebo [15, 19–21]. It is assumed that the observation serves as an unconditioned stimulus [22].

Typically, conditioning and verbal suggestions are both implemented in experimental studies to increase placebo/nocebo effects in pain [23–26]. Accordingly, meta-analyses come to the conclusion that the combination of conditioning and verbal suggestion leads to larger effects than verbal suggestion alone [27, 28]. When inducing placebo hypoalgesia or nocebo hyperalgesia by verbal suggestions alone, results are inconsistent, sometimes resulting only in weak [24] or even no effects [25, 29, 30] and at other times leading to robust pain reduction [10, 31] or increase [10, 32]. Some studies indicate that learning is less important in nocebo hyperalgesia compared to placebo hypoalgesia, but direct comparisons are rare [24, 33]. Interestingly, while placebo effects induced by expectation can be antagonized by the opioid antagonist naloxone, conditioned placebo effects can be antagonized by naloxone when the pharmacological conditioning had been performed with an opioid and by cannabinoid receptor antagonists when it had been performed with ketorolac, a nonsteroidal anti-inflammatory drug [34, 35]. These findings highlight that placebo and nocebo effects in pain differ depending on whether they were induced by verbal suggestion or conditioning.

In a series of three studies, Benedetti et al. [10] showed that (a) placebo and nocebo effects in hormone secretion (growth hormone and cortisol) were affected by pharmacological conditioning, but not by verbal suggestions, (b) placebo and nocebo effects in pain were induced by pharmacological conditioning and by verbal suggestions, but pharmacologically conditioned placebo hypoalgesia was overridden by opposing verbal suggestions, and (c) motor performance in Parkinsonian patients depended on verbal suggestion after repeated deactivation of implanted stimulating electrodes. Based on these observations, the authors developed an influential model stating that conditioning can directly lead to placebo and nocebo effects in unconscious processes (e.g., hormone secretion) and that expectation can lead to placebo and nocebo effects in conscious processes (e.g., pain and motor performance) and that effects of conditioning on conscious processes are necessarily mediated by explicit expectation. Furthermore, it is assumed that expectation cannot directly affect unconscious processes [10]. Although these conclusions fit to the results of the presented studies, we assert that the model underestimates conditioned effects, as outlined below.

Previous research on the mechanisms of placebo and nocebo effects might be biased due to a number of reasons: (1) studies that investigate the effects of conditioning without verbal suggestion are scarce [30, 36, 37]. In order to estimate the contribution and investigate the mechanisms of conditioning to a given effect, it is likely not as simple as to subtract the effect size from a verbal suggestion group from that of a verbal suggestion plus conditioning group. It could well be that conditioning and verbal suggestion do not interact in an additive manner, although this seems to be assumed in most studies. (2) When investigating the effects of a conditioning procedure without verbal suggestions, oftentimes a medically connoted placebo or nocebo (e.g., ointment, pill, and sham acupuncture) is used [13, 29, 38, 39]. However, these placebos and nocebos most probably induce expectations from the outset independent of the experimental manipulation. Participants might have been preconditioned by previous experiences with similar medical devices and procedures. As a consequence, unintended additional expectations will develop that complicate disentangling expectation- and conditioning-induced effects. Evidence supporting this assumption comes from a study by Montgomery and Kirsch [39], in which a small placebo effect emerged after applying an inert tincture without giving a verbal suggestion and before conditioning. (3) Another pitfall of many studies testing conditioned effects is the implementation of the conditioning procedure itself. Due to credibility, a medically connoted placebo or nocebo, like an ointment, will only be applied once in the beginning of the study, for example, on the right arm, and then tested against a spot without ointment, for example, on the left arm [12, 13, 39–42]. In other cases, the placebo/nocebo is applied only very few times [11, 43]. Proper conditioning, however, relies on repeated pairings of the conditioned stimulus (i.e., the placebo or nocebo) and the unconditioned stimulus (i.e., reduced or increased pain) (e.g., [44]). It is known from the conditioning literature that conditioned effects are stronger when more pairings of CS and US are applied [45]. By applying a placebo/nocebo only once, it cannot be ensured that the pairing is processed as intended. To summarize, most previous studies do not allow

disentangling of placebo/nocebo effects induced by conditioning and/or explicit expectations or do not use adequate conditioning procedures to test for conditioned effects so that conditioned placebo and nocebo effects can hardly be evaluated.

3. Mediation by Expectation Hypothesis

An important aspect of the above-cited model [10] concerns the necessary mediation of conditioning effects in pain via explicit expectation. Colloca and Miller [22] developed a learning perspective on placebo responses by applying Peirce's theory of signs and refining Benedetti's model [10]. In addition to Benedetti's model, they state that signs in the form of indices (i.e., conditioned stimuli), symbols (i.e., communication), and icons (i.e., observations) are detected and processed, resulting in the formation of expectations, which thereby contribute to placebo and nocebo responses. In line with Benedetti's model, bodily functions that are consciously accessible, as pain relief, are mediated by expectation, but "an event that cannot be experienced and perceived by human cognition (e.g., growth factor secretion) appears not to be influenced by self-cognition" (p. 1865). Although the authors endorse the possibility of conditioning without awareness, and accordingly unconscious expectations, they argue that it is circumstantial in creatures with higher phylogenetic level. In the following, we will show that conditioned placebo hypoalgesia and nocebo hyperalgesia are not necessarily mediated by explicit expectations, emphasizing the assumption that the conditioned effect can exist independent of explicit expectation.

Many studies report correlations between pain and expected pain ratings [17, 39, 46, 47], sometimes on a trial-by-trial basis [26], after conducting a conditioning procedure. Using a mediation analysis, it has been shown that conditioning is highly related to expectancy and expectancy predicts the placebo effect, while the direct effect of conditioning on the placebo effect is no longer significant [38]. This result suggests that conditioning is mediated by expectation. However, the robustness of this outcome seems somewhat uncertain, as a bias-corrected bootstrap approach was not significant. A study of Montgomery and Kirsch [39] can serve as another example for mediation by expectation. They compared a conditioned group (uninformed pairing) to a group with informed pairing (i.e., participants underwent a conditioning procedure but were informed about the intensity reduction on placebo trials), and a control group that was not conditioned. The strongest placebo effect appeared in the uninformed pairing group, but when including expectancy as a covariate, group differences disappeared and expectancy was significantly related to placebo effects. Furthermore, some studies report that conditioned effects can be blocked by opposite verbal suggestions [10, 39]. However, this is not always the case, as there are studies showing conditioned effects despite opposite verbal suggestions [11, 12] or expectancy [48]. Also, conditioned effects have been shown to be mediated by expectancy only partially [49], and expectation ratings do not necessarily predict conditioned effects [37, 50] or correspond to pain ratings [29]. In a study of De Pascalis et al. [41], two placebo creams were administered with supposedly "strong" and "weaker" dosage. Subsequently, only after application of the "strong placebo," the intensity of electric pain stimuli was surreptitiously reduced. Although expected pain level varied according to the manipulation (i.e., strong placebo led to higher expectation of pain relief compared to weak placebo), pain ratings did no differ after strong and weak placebo, highlighting the dissonance between expectations and measured placebo hypoalgesia.

Studies on open-label placebo administration give another important insight into the mediating role of expectation in placebo hypoalgesia. Typically, open-label placebo studies try to boost expectation of a positive effect despite openly administering an inert substance [51, 52]. However, a highly intriguing study in healthy participants showed that conditioned placebo hypoalgesia persisted after revealing the inert nature of a placebo intervention (cream) independent of the participants' expectation. Other than in the previously mentioned open-label placebo studies, participants in this study were not encouraged to believe in a positive effect from the placebo cream. Although participants no longer expected a hypoalgesic effect, the placebo effect remained [50]. In a recent systematic review and meta-analysis on open-label placebo studies, it was hypothesized that the mechanism driving such effects is classical conditioning [53].

In an editorial, Wager [54] begs interesting questions on the role of expectation as a mediator of placebo effects. He argues that, despite the predictive value of expectation for placebo effects, a causal relationship is not necessarily implied. Besides a direct influence of expectation on pain experience, he proposes three alternative explanations for the observed effects: expectancy could affect reported pain ratings (1) directly, (2) via a kind of social contract that is initiated after giving an expectancy rating, and (3) as a consequence of the third variable that affects both expectancy and pain rating, like demand characteristics, personality traits, treatment history, or situational factors. Supporting these ideas, a study of de Jong et al. [29] can be consulted, in which three different groups were investigated: the experimental group underwent a conditioning procedure with additional verbal suggestions, control group 1 underwent the same conditioning procedure but was told that stimulus intensities would be halved during trials, in which the placebo was applied, and that an inert substance was used, and control group 2 received verbal suggestions only. Despite similar differential expectations of the experimental group and control group 2, only the experimental group showed placebo hypoalgesia. Although no placebo effect was found in control group 1, pain ratings did not differ between the experimental group and control group 1, suggesting a relative independence from verbally induced expectations. Yet, expectation was found to correlate with the placebo hypoalgesia, however, irrespective of the experimental manipulation. The authors speculate that this correlation reflects an interaction between individual traits and general characteristics of the placebo used, thus possibly serving as an example for Wager's third case.

In conclusion, mediation by expectation of conditioned placebo hypoalgesia and nocebo hyperalgesia can occur but

in many cases does not. We therefore now turn to studies that demonstrate the significance of conditioning effects independent of explicit expectation.

4. Evidence for the Significance of Classical Conditioning

Evidence of different research areas highlights the significance of conditioning of placebo hypoalgesia and nocebo hyperalgesia that is independent of explicit expectation. It has been shown that besides humans, animals, such as rodents, can develop conditioned placebo hypoalgesia and nocebo hyperalgesia [55–57]. Furthermore, a limited number of studies implemented placebo or nocebo conditioning procedures without additional verbal suggestions and used meaningless cues as conditioned stimuli (e.g., red and green lights), instead of medically connoted substances or procedures, bypassing some of the abovementioned limitations of previous studies. Results are inconsistent: while recent studies found placebo hypoalgesia and nocebo hyperalgesia after conditioning without additional verbal suggestions that were not predicted by expectancy ratings [37], or without contingency awareness [58], other studies reported no placebo hypoalgesia or nocebo hyperalgesia after conditioning without additional verbal suggestions [30, 36].

A line of research that strongly supports the existence of conditioned placebo and nocebo effects in pain that are independent of explicit expectation uses subliminal cues and implicit conditioning, that is, conditioning without contingency awareness. Some studies showed that placebo hypoalgesia and nocebo hyperalgesia that had been conditioned with supraliminally presented cues (i.e., explicit conditioning) can be activated by subliminally presented cues [21, 59]. Jensen et al. [60], for instance, conditioned healthy participants with the display of faces and activated placebo hypoalgesia and nocebo hyperalgesia by supraliminal as well as subliminal face presentation [60]. These results were replicated in a functional magnetic resonance imaging (fMRI) study of the same working group [61].

One attempt to implicitly condition placebo hypoalgesia by using a tactile cue (direction in which a placebo cream was applied to the skin) was not successful in inducing placebo hypoalgesia [43], but a recent study indicated that contingency awareness is not necessary to induce a nocebo effect in heat-pain perception [58]. So far, there is only one study that used a subliminal stimulus presentation also during the acquisition phase of a conditioning experiment in order to rule out explicit expectation in conditioning [44]. The authors assigned healthy participants to one of four groups, each including an acquisition phase and a test phase and varying subliminal and supraliminal stimulus presentations. Overall, F tests indicated that there was no difference in placebo hypoalgesia and nocebo hyperalgesia between the different types (i.e., subliminal/supraliminal) of the acquisition or test phase, strongly suggesting the presence of implicitly conditioned effects.

In order to gain more insight into the role of conditioned effects on placebo and nocebo effects in pain, research on implicit conditioning should be expanded and diversified, as previous studies mostly did not directly test for contingency awareness and typically focused on subliminal conditioning, which has some pitfalls (e.g., intra- and interindividually varying threshold for subliminal stimulus presentation). Although accumulating evidence points to an important role of conditioning of placebo and nocebo effects in pain independent of explicit expectations, most current theoretical accounts do not yet incorporate these aspects sufficiently [10, 22]. One point of criticism regarding prevalent models concerns the classification of physiological processes into being either conscious or unconscious. Evidence suggests that it is conceivable that most, if not all, bodily functions, including perception and behavior, have "unconscious" (i.e., outside a person's awareness; cf., e.g., blindsight and implicit operant conditioning [62–64]) and "conscious" (i.e., verbally represented) portions. Pain, especially, is known as a multidimensional phenomenon that incorporates sensory, affective, behavioral, and physiological levels that can all be accessed on aware and unaware levels [63–66]. An exception provides a theoretical framework of Haug [67], which, however, has not received much attention. He proposes that placebo/nocebo effects are mediated by so-called aliefs, which are subdoxastic states, that is, cognitive states "with consciously inaccessible content which is inferentially isolated from the subject's large network of beliefs (and which may directly cause behavior)" (p. 690). Aliefs can be consciously or unconsciously activated in humans and nonhumans by the internal or external environment. They are associative, automatic, arational, affect-laden, and action generating and might be a better candidate for a common final path than expectation in Colloca and Miller's [22] model because they can explain placebo and nocebo effects that have been induced by verbal suggestion as well as (implicit) conditioning.

5. Clinical Context

While the majority of studies on placebo hypoalgesia and nocebo hyperalgesia examined healthy participants, only few investigated pain patients and even less focused on clinical pain [68]. Nonetheless, the available studies give some insights into the mechanisms of placebo and nocebo effects in a clinical pain context.

Verbal suggestion of pain relief seems to be highly effective for acute procedural (large effect with Hedges' $g = 1.03$) as well as chronic pain (small effect with Hedges' $g = 0.25$ [68, 69]) even after open-label placebo administration in patients with irritable bowel syndrome (IBS [51]) and chronic low back pain [52]. Furthermore, large placebo effects (comparable to the effect of the local anesthetic Lidocain) have been induced by using verbal suggestions and application of a placebo (lubricant) during the induction of experimental pain (rectal distention) in patients with IBS [70, 71]. While explicit expectations accounted for large amounts of the variance in experimental visceral pain during placebo and Lidocain administration, it was not predictive for a cutaneous pain model despite placebo hypoalgesia being present [70]. In a similar study, expectation did predict

the placebo and Lidocain effect in the late phase of experimental visceral pain, but not in the early phase [71].

Placebo effects have also been shown in studies that combined verbal suggestion and conditioning in patients with IBS [72], knee osteoarthritis [73], atopic dermatitis [40], musculoskeletal pain [74], and chronic low back pain [69]. Results of a meta-analysis show that, in pain patients, medium-sized placebo hypoalgesia (Hedges' $g = 0.65$) was induced with a combination of verbal suggestion and conditioning; however, for this analysis, only three studies were available, and only experimental pain was investigated [68].

In a recent study, placebo effects in experimental as well as chronic pain of patients with musculoskeletal pain did not differ when induced by verbal suggestion or a combination of verbal suggestion and conditioning. Yet, larger placebo responses in chronic pain were found in responders with more negative treatment history [74], indicating that prior experience plays an important moderating role, which, however, could be mediated by expectations. Investigating patients with atopic dermatitis with experimental electric pain, placebo hypoalgesia upon administration of a placebo cream was observed after verbal suggestion, after conditioning without verbal suggestion, and after a combination of both. Without conditioning, however, the effect quickly diminished, suggesting that conditioning compared to verbal suggestion leads to longer lasting placebo hypoalgesia in patients [40]. Finally, Klinger et al. [69] tested four different groups with chronic low back pain in clinical pain, in an experimental electric pain model, in self-rated functional capacity, and in a behavioral test using time needed to perform standardized daily activities. Patients received a sham opioid solution and were either instructed that they received a placebo (PI) or a pain-reducing opioid solution (OI). Furthermore, half of the participants underwent a conditioning procedure, resulting in two more groups (PI + Cond and OI + Cond). Opioid instruction led to large placebo effects on clinical and experimental pain, to decreased time needed for the exercises (small effect), and to increased self-rated functional capacity (medium effect). The combination with conditioning (OI + Cond) led to larger effects than OI on all outcome variables. The placebo-instructed group with conditioning showed a small yet significant effect for the time needed to perform exercises. These results support the notion that conditioning incrementally contributes to placebo hypoalgesia in patients with low back pain because the effects grew larger when a combination of conditioning and verbal suggestion was used, and the behavioral outcome measure showed placebo effects even in the absence of verbal suggestions.

The available studies indicate that both verbal suggestion and conditioning are powerful determinants of placebo hypoalgesia in clinical populations. However, not enough data have been gathered yet to identify the relative significance or an independent share of conditioning compared to explicit expectation in the clinical context. From a theoretical perspective, it can be assumed that conditioning constitutes an important aspect in chronic pain [75]. Especially, extinction has shown to be deficient in patients with chronic pain [76]. Furthermore, phenomena like latent inhibition (i.e., poorer learning as an effect of ineffective preexposure) or blocking effects (i.e., ineffective responding to a second conditioned stimulus) increase the risk of negative treatment experiences. Repeated experience of therapy failures, which is common in chronic pain, might lead to weakened placebo or persistent nocebo effects potentially contributing to the maintenance of chronic pain. However, due to ethical constraints, nocebo hyperalgesia cannot be investigated as rigorously as placebo hypoalgesia in clinical samples, and most knowledge in the realm is derived from studies on the disclosure of possible adverse effects in clinical trials [77]. On the other hand, there is limited evidence that conditioned placebo effects are longer lasting compared to effects that had been induced by explicit expectation [40, 78], and this could be an opportunity for the treatment of clinical pain conditions.

6. Conclusion and Future Directions

In sum, conditioning usually leads to the development of explicit expectation or (more technically) contingency awareness. Furthermore, it is not surprising that such an expectation is able to enhance placebo hypoalgesia and nocebo hyperalgesia as numerous studies have shown when comparing the effects after verbal suggestion and conditioning with verbal suggestion, respectively [27, 28]. However, this does not exclude the existence and impact of conditioned effects that do not depend on explicit expectation. Accordingly, Amanzio and Benedetti [34] elegantly showed that placebo hypoalgesia that had been conditioned with ketorolac and enhanced by a verbal suggestion was only partly reversed by the opioid antagonist naloxone, that is, naloxone only reversed the placebo effect induced by the expectation part, as the other experimental groups indicated. It is conceivable that conditioned effects can be compensated by or at least interact with contrary explicit expectations [10, 39]. This does not mean, however, that an expectation-independent, conditioned effect does not exist. We assert that there is not only one way to elicit placebo and nocebo effects in pain that is mediation by explicit expectations. Rather, classical conditioning on its own can generate these effects, which can be substantial in size, as available evidence shows for experimental as well as clinical pain.

One possibility to avoid confounding between induction by expectation and conditioning and to advance our understanding of the mechanisms causing placebo hypoalgesia and nocebo hyperalgesia would be the implementation of implicit conditioning designs. Here, an involvement of explicit expectations is excluded, and effects purely caused by conditioning can be investigated. Compared to conditioning with subliminally presented cues, implicit conditioning has some advantages, as discussed above. Another way would be the development of experimental designs, in which contrary placebo or nocebo effects are induced by conditioning and explicit expectation, and these effects are measured on independent variables.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Review Article

Amygdala Plasticity and Pain

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The amygdala is a limbic brain region that plays a key role in emotional processing, neuropsychiatric disorders, and the emotional-affective dimension of pain. Preclinical and clinical studies have identified amygdala hyperactivity as well as impairment of cortical control mechanisms in pain states. Hyperactivity of basolateral amygdala (BLA) neurons generates enhanced feedforward inhibition and deactivation of the medial prefrontal cortex (mPFC), resulting in pain-related cognitive deficits. The mPFC sends excitatory projections to GABAergic neurons in the intercalated cell mass (ITC) in the amygdala, which project to the lateral capsular division of the central nucleus of the amygdala (CeLC; output nucleus) and serve gating functions for amygdala output. Impairment of these cortical control mechanisms allows the development of amygdala pain plasticity. Mechanisms of abnormal amygdala activity in pain with particular focus on loss of cortical control mechanisms as well as new strategies to correct pain-related amygdala dysfunction will be discussed in the present review.

1. The Amygdala and Pain

The amygdala is an almond-shaped limbic structure located in the medial temporal lobe and is well known for its role in conveying emotional significance to a sensory stimulus, emotional and affective states, and related behavioral adaptations in response to changes in the internal and external bodily environment [1–4]. The amygdala has also emerged as an important site in the brain for the emotional-affective dimension of pain and pain modulation [5–12].

A pain-related function was first suggested by the discovery of a dedicated nociceptive pathway from the spinal cord through the external lateral parabrachial (PB) nucleus to the central nucleus of the amygdala [13, 14]. Reevaluation of an historical example of reduced pain sensitivity also suggests amygdala involvement in pain processing. Patient H.M. was a man that underwent bilateral resection of the temporal lobe including the uncus, amygdala, anterior hippocampus, and parahippocampal gyrus to correct severe and intractable epilepsy [15–17]. After the surgery, H.M. did not perceive even the highest thermal stimulus intensity as painful when control groups did. It is now thought that this deficit was likely due to amygdala resection [16, 17], illustrating the importance of the amygdala in pain processing in the brain. Importantly, this deficit in pain perception occurred despite an intact nociceptive system and was not accompanied by the tissue injury characteristic of pain insensitivity disorders, indicating that protective pain functions were intact.

Since the initial discovery of nociceptive pathways to the amygdala, preclinical [5, 7, 8] and clinical [10, 11, 18, 19] studies have provided direct support for amygdala involvement in pain. Electrophysiological recordings in anesthetized rats in vivo and in rodent brain slices in vitro and molecular biological assays showed increased activity markers in response to acute noxious stimuli, including mechanical or thermal stimulation [20, 21], as well as in models of visceral pain [22–28], intraplantar formalin [29–31], acid-induced muscle pain [32], kaolin/carrageenan-induced monoarthritis [33–41], and chronic neuropathic pain [42–44].

The clinical relevance of these findings has been corroborated by human neuroimaging studies that demonstrate amygdala activation in response to experimental noxious stimuli, including mechanical compression, thermal stimulation, and capsaicin application [10], as well as increased amygdala activity in migraineurs compared to healthy controls when presented with negative but not positive or neutral emotional stimuli [45]. In addition, functional connectivity between the left amygdala and the PFC, cingulate cortex, and basal ganglia is different in patients with complex regional pain syndrome (CRPS) [46], and corticolimbic reverberating loops have been implicated in the prediction of and transitioning to chronic pain [11]. Patients with irritable bowel syndrome (IBS) had higher positive resting-state functional connectivity between the amygdala and the insula, pre- and postcentral gyri, and supplementary motor area compared to healthy controls, and this increased connectivity positively correlated to pain intensity [47]. A separate study demonstrated that IBS patients that did not have visceral hypersensitivity had decreased positive resting-state functional connectivity of the amygdala within the default mode network compared to healthy controls as well as IBS patients with visceral hypersensitivity [48]. In female twin pairs with and without chronic pelvic pain, connectivity between the right PAG and the right amygdala, connectivity between the left PAG and the right and left basolateral amygdala, and connectivity of the right basolateral amygdala to the medial orbital frontal cortex, anterior cingulate cortex (ACC), right insula, left thalamus, and hypothalamus differed between the twin with pelvic pain compared to the healthy twin before and after bladder distension by an oral water bolus [49].

2. Amygdala Pain Neurocircuitry

The amygdala receives multiple lines of input (Figure 1) relevant for pain processing, and multiple nuclei in the amygdala are involved in its pain processing functions. These include the lateral-basolateral complex (LA/BLA), the central nucleus (CeA), and the intercalated cell mass (ITC); see Figure 2 and [7–9].

The LA/BLA is predominantly composed of pyramidal glutamatergic projection neurons that receive polymodal sensory, including nociceptive, inputs from the midline and posterior nuclei of the thalamus, insular cortex, and sensory association cortices, as well as inputs from the ACC and medial prefrontal cortex (mPFC) [1, 7–9, 12]. Through associative processing, the LA/BLA attaches emotional-affective content to the sensory inputs and transmits that highly processed information to the amygdala output region in the CeA for further processing as part of amygdala fear and anxiety circuitry [3, 50, 59, 60]. This LA/BLA-CeA projection is now known to generate and modulate pain-related behaviors [7]. The BLA also projects to different cortical areas, including the infra- and prelimbic mPFC, ACC, and perirhinal and insular cortices [51, 61–67]. The BLA-mPFC projection is thought to provide emotional information for value-based executive functions [67–70] and has been implicated in pain-related cortical deactivation and cognitive control [6, 7, 11, 71].

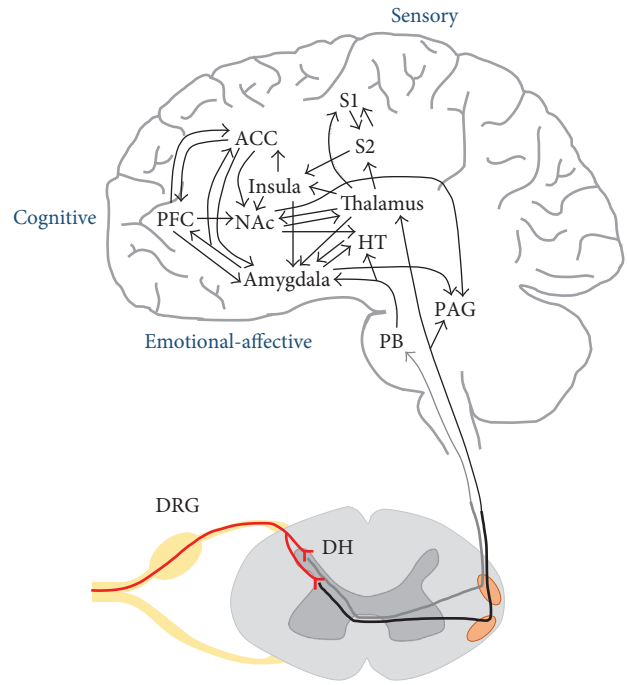

Figure 1: Pain neurocircuitry. Peripheral nociceptive afferent fibers (red lines) form synapses in the dorsal horn of the spinal cord. Axons of spinal dorsal horn neurons decussate in the anterior white commissure and travel in the ventrolateral funiculus (spinothalamic tract; black line) or the dorsolateral funiculus (spino-parabrachio-amygdaloid tract; gray line) to different targets in the brain. Sensory discriminative aspects of pain involve projections from the thalamus to somatosensory cortical areas. Cognitive aspects of pain involve integration within limbic and (prefrontal) cortical regions. Emotional-affective aspects of pain involve integrative processing in the limbic brain regions centered on the amygdala which is a key node. Circuitry is based on [6, 7, 15, 50–58]. Abbreviations: ACC, anterior cingulate cortex; DH, dorsal horn; DRG, dorsal root ganglion; HT, hypothalamus; NAc, nucleus accumbens; PAG, periaqueductal gray; PB, parabrachial nucleus; PFC, prefrontal cortex; S1/2, primary/secondary somatosensory cortex.

The CeA serves as the major output nucleus for amygdala-driven pain-related functions. The laterocapsular region of the CeA (CeLC, including both the lateral and capsular divisions) receives purely nociceptive information via the spino-parabrachio-amygdaloid tract [72] and possibly via direct projections from the spinal cord [73, 74]. The parabrachial input is characterized by its peptidergic nature and serves as the exclusive source of calcitonin gene-related peptide (CGRP) for the amygdala [75]. The CeLC contains GABAergic projection neurons that also contain peptides such as corticotropin-releasing factor (CRF); they are characterized by their nonaccommodating spike firing pattern [7, 38, 76]. Nearly half of the CRF-CeA neurons receive CGRP input from the PB [77]. This nociceptive information is integrated with polymodal sensory information from the LA/BLA to generate amygdala-mediated responses important for pain behaviors and pain modulation [1, 7–9, 12].

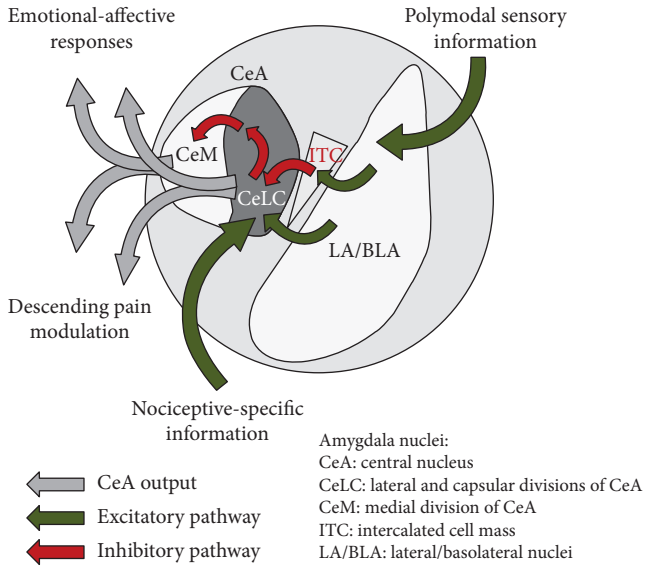

Figure 2: Amygdala pain neurocircuitry. Lateral-basolateral complex (LA/BLA), central nucleus (CeA), and intercalated cell mass (ITC) form the core circuitry involved in amygdala-dependent pain behaviors and pain modulation. The LA/BLA receives polymodal sensory information from cortical and thalamic areas and attaches emotional-affective information, which is then relayed to the CeA. This transmission includes direct excitatory projections to neurons in the lateral and capsular divisions of the CeA (CeLC) as well as feedforward inhibition of CeLC neurons through an LA/BLA projection to the ITC, a group of GABAergic interneurons between LA/BLA and CeA. ITC cells are also the target of cortical control from the mPFC. The CeLC integrates purely nociceptive information received via the spino-parabrachio-amygdaloid tract with highly processed information received from the LA/BLA to generate emotional-affective responses and contribute to top-down pain modulation via projections to the brainstem. This can be done through two types of amygdala outputs: one from CeLC projection neurons and the other from CeM neurons that can be disinhibited by CeLC neurons.

Interposed between LA/BLA and CeLC is a group of GABAergic interneurons in the intercalated cell mass (ITC). ITC cells receive excitatory inputs from the infralimbic mPFC and LA/BLA and are activated during extinction of negative emotional responses [2, 3, 50, 78–82]. Therefore, ITC cells serve a gating function for amygdala output from the CeA through feedforward inhibition that involves activation of neuropeptide S (NPS) receptors on ITC cells [39, 83, 84].

CeA output arises from medial CeA (CeM) and CRF-CeLC projection neurons. These projections target other limbic, hypothalamic, and brainstem regions including the periaqueductal gray (PAG) [3, 60, 85–87]. Projections to hypothalamus and brainstem regions such as the nucleus of the solitary tract (NTS) contribute to amygdala-driven autonomic responses. Projections to the PAG generate or modulate vocalizations and startle responses. CeA projections to other limbic structures such as the bed nucleus of the stria terminalis (BNST) and to monoaminergic regions such as locus coeruleus are thought to drive amygdala influences over anxiety and depression [3, 88, 89]. CeLC neurons can also affect output from the CeM through intra-amygdala connections involving GABAergic protein kinase C delta (PKCδ) positive and other interneurons in the lateral CeA [50, 90–92], but details of this intra-amygdalar circuitry remain to be determined.

CeA neurons expressing PKCδ (PKCδ$^+$) are inhibited by exposure to the fear-conditioned stimulus and have been termed "OFF cells,", whereas PKCδ-negative neurons are excited when presented with the conditioned stimulus, and reciprocal inhibitory connections exist between these cell types [1, 90, 91]. Inhibition of PKCδ$^+$ cells is believed to contribute to emotional responses such as freezing through disinhibition of CeM output neurons [50]. Importantly, PKCδ$^+$ neurons are distinct from CRF-containing CeLC projection neurons characterized by their nonaccommodating spike firing pattern [87, 91]. And so, it is reasonable to assume that it is the population of PKCδ-negative CRF-CeLC neurons that have been studied for their nociceptive PB input and participation in pain processing [7]. CRF-CeLC neurons are uniquely positioned to provide and regulate amygdala output through their projections to extra-amygdalar targets and through local inhibition of PKCδ$^+$ cells to disinhibit CeM output neurons [1, 3, 60, 85–87] (Figure 2).

3. Pain-Related Changes in Amygdala Neurocircuitry

Importantly, changes in the amygdala neurocircuitry have been detected in different preclinical models of pain and linked mechanistically to pain behaviors, indicating that these maladaptive neuroplastic changes are a brain mechanism of pain. In systems (whole animal) electrophysiology studies of amygdala neurons in anesthetized rats, background activity and responses to mechanical compression of peripheral tissues increased in an arthritis pain model in the CeLC [36, 37, 93–97] and BLA [71], as well as in the CeLC in a neuropathic pain model [42, 44]. These activity changes are not simply a reflection of changes along the pain pathways to the amygdala but arise from synaptic plasticity within the amygdala network. Brain slice physiology studies showed enhanced excitatory transmission at the PB-CeLC and BLA-CeLC synapses [33–35, 38, 40], decreased ITC-mediated synaptic inhibition of CeLC neurons [39, 40], and increased neuronal excitability in the CeLC [33, 34, 38], as well as enhanced excitatory transmission at the LA-BLA synapse and increased excitability of BLA neurons [71] in an arthritis pain model. Enhanced transmission at the PB-CeLC synapse and neuronal excitability [25] and increased levels of neurochemical activity markers (c-Fos and extracellular signal-regulated kinase, ERK) [22, 23, 28, 98] and CRF [24, 26] were found in the CeA in visceral pain models. Enhanced PB-CeLC and BLA-CeLC neurotransmission and excitability [43, 99] and increased expression of CRF and glucocorticoid receptors [100, 101] in the CeA were also observed in neuropathic pain models. It should be noted that not all of these neuroplastic changes have been described in all pain models. It is possible that amygdala neuroplasticity could

differ based on time course (acute versus chronic pain) or etiology (inflammatory versus neuropathic) of pain. The full scope of pain-related amygdala plasticity remains an area of active investigation.

The clinical relevance of these neuroplastic changes in preclinical pain models is supported by neuroimaging studies, indicating that amygdala activity is increased in subjects with previously diagnosed pain conditions, including osteoarthritis, IBS, and fibromyalgia compared to matched controls [10].

Interestingly, this amygdala pain-related plasticity exhibits hemispheric lateralization. Under normal conditions, nociceptive inputs into the CeLC are received by and activate both the right and left amygdala [30, 36]. No apparent difference has been detected in background activity or responses to innocuous and noxious mechanical test stimuli between neurons in the right and left amygdala (CeLC), although neurons in the left amygdala appear to have more restricted receptive fields in peripheral tissues [36]. Exogenous activators also can increase neuronal activity in the right and left CeLC [36] or induce hypersensitivity [102]. In inflammatory [36] and neuropathic [42] pain conditions, neurons in the right but not left amygdala exhibit a sustained increase in background and evoked activity irrespective of the side of injury, and the receptive field size of neurons in the right but not left amygdala is increased in an arthritis pain model [36]. In humans, differences in connectivity between the right and left amygdala have been observed in IBS patients compared to healthy controls [47], IBS patients compared to those without visceral hypersensitivity [48], and twin pairs with one twin with and one without chronic pelvic pain before and after bladder distension [49].

Mechanisms of hemispheric lateralization of amygdala plasticity and function are not yet clear. Protein kinase A (PKA) activation has been implicated in the development of central sensitization [103] and synaptic plasticity [33–35, 104] in the CeLC in an arthritis pain model, and application of a PKA inhibitor into the right but not left amygdala resulted in a reduction in neuronal activity in this pain model [36], indicating that PKA is endogenously activated in the right but not left amygdala in the pain state. ERK is also known to play an important role in amygdala plasticity and amygdala-driven behaviors in inflammatory pain models [30, 104], and activation of the metabotropic glutamate receptor 5 (mGluR5) has been shown to increase amygdala ERK activation and ERK-dependent pain behaviors [102, 105]. Application of a blocker of ERK activation [30, 31] and pharmacological blockade or conditional deletion of mGluR5 [102] prevented formalin-induced hypersensitivity when administered into the right but not left amygdala. Chemical (pituitary adenylate cyclase-activating polypeptide) or optogenetic activation of the right but not left CeA increased nociceptive visceromotor responses in a murine urinary bladder distension model, and optogenetic silencing of the left but not right CeA increased bladder distension-induced visceromotor responses [27]. In a visceral pain model cyclophosphamide-induced cystitis, optogenetic activation of the left but not right CeA inhibited abdominal mechanosensitivity, whereas activation of the right CeA further increased visceromotor responses in this model [27] These findings may suggest that while neuroplasticity in the right CeA drives pain-related behaviors, the left CeA may be linked to antinociception.

Evidence from neuroimaging studies in humans also suggests right hemispheric lateralization of amygdala responses to acute experimental pain stimuli [10], whereas in clinical pain conditions, right hemispheric deactivation [106] and left hemispheric signal increases [10] have been reported. This could be due to a compensatory increase in inhibitory transmission in the left amygdala that is not present in the right amygdala in the chronic pain state. Pain-related hemispheric lateralization may reflect a general principle of lateralized emotional processing. Right hemispheric amygdala activation has been found in response to masked fearful faces [107] and was exaggerated in veterans with posttraumatic stress disorder (PTSD) [108]. Enhanced activity of the right, but not the left, amygdala in men was related to encoding and long-term memory of films judged as arousing negative emotions compared to neutral films [109, 110]. Mechanisms and significance of pain-related amygdala lateralization remain to be determined.

4. Pain-Related Amygdala-Centered Corticolimbic Interactions

Information processing in the amygdala can be regulated by inhibitory gating mechanisms centered on ITC cells and their activation by cortical control systems (Figure 2). The mPFC influences amygdala function through feedforward inhibition of CeLC neurons via excitatory projections to ITC cells as an important mechanism of cognitive modulation of emotions such as a fear [2, 3, 50, 78, 79, 81, 82, 88, 111]. Evidence suggests that mPFC-driven feedforward inhibition of CeLC output neurons is impaired in pain [7, 112]. Electrical stimulation of the external capsule, including infralimbic mPFC inputs into the amygdala, resulted in a non-*N*-methyl-D-aspartate (non-NMDA) receptor-mediated monosynaptic excitatory synaptic response (EPSC) in dorsomedial ITC cells and non-NMDA receptor-driven synaptic inhibition (IPSC) of CeLC neurons [39]. In brain slices from arthritic rats, the monosynaptic EPSC in ITC cells and the glutamate-driven IPSP in CeLC neurons were reduced [39], suggesting pain-related impairment of mPFC-driven feedforward inhibition of amygdala output.

Decreased infralimbic mPFC activity has been implicated in extinction deficits [113–116]. Accumulating evidence points to mPFC deactivation in pain, which could explain impaired control of amygdala processing [7, 112]. Functional and structural abnormalities in the mPFC have been detected in human pain patients [117, 118] and in preclinical pain models [71, 119–121]. As a consequence, activity of output neurons in the infralimbic and prelimbic mPFC is decreased in acute [71, 122, 123] and chronic pain models [120, 124, 125]. Decreased glutamatergic drive of pyramidal cells [120] and abnormally enhanced glutamatergic activation of parvalbumin-expressing GABAergic interneurons [71, 125, 126] have been implicated in the mPFC deactivation in pain.

Hyperactivity in the BLA plays an important role in pain-related mPFC deactivation [7, 112]. The BLA sends glutamatergic projections to the pre- and infralimbic mPFC [61, 66, 67]. Importantly, while some of these BLA axon terminals make direct contact with pyramidal cells, the majority of synapses on neighboring parvalbumin and somatostatin-positive interneurons form GABAergic connections with pyramidal cells, targeting mainly the somatic and proximal axonal regions [62, 127]. This synaptic arrangement was shown to account for amygdala-driven mPFC deactivation by glutamate-driven feedforward inhibition in an arthritis pain model [71, 126]. Feedforward inhibition involves activation of GABAergic interneurons mediated by non-NMDA receptors and mGluR1 but not mGluR5 [122, 128]. It should be noted that mGluR5 in the mPFC is expressed mostly on postsynaptic elements [129] to exert excitatory effects on pyramidal cells [130–132]. In contrast, GABAergic inputs to mGluR5 expressing mPFC pyramidal cells are regulated by cannabinoid CB1 receptors under normal conditions [131, 133]. In brain slices from arthritic rats, IPSCs evoked by electrical or optogenetic activation of BLA axon terminals in pre- and infralimbic mPFC pyramidal cells were increased; IPSCs could be blocked with non-NMDA glutamate receptor and $GABA_A$ receptor antagonists [71, 126]. Systems electrophysiology studies in anesthetized rats showed that pain-related decreases in background and evoked activity of prelimbic mPFC pyramidal-like neurons were reversed by a $GABA_A$ receptor antagonist and attenuated by an mGluR1 but not mGluR5 antagonist [122]. The decrease in mPFC pyramidal cell activity was causally linked to increased BLA neuronal activity in the arthritis pain model because restoring BLA activity with a CRF1 antagonist increased background and evoked activity of prelimbic mPFC neurons [71].

5. Pharmacological Strategies Targeting Amygdala Pain Neurocircuitry

Interventions that increase amygdala output, even in the absence of acute injury, elicit pain behaviors [27, 30, 102, 134, 135], whereas those that decrease amygdala activity generally inhibit pain behaviors (see [7] for review). Therefore, controlling amygdala activity is a desirable therapeutic strategy for chronic pain. Interventions that were found to have some beneficial effect in preclinical studies include non-NMDA and NMDA receptor antagonists, mGluR1 and mGluR5 antagonists, agonists for group II mGluR2/3 and group III mGluR, including mGluR8, antagonists for CGRP1 and CRF1 receptors, neuropeptide S activating NPS receptors, and inhibitors of ERK and PKA (reviewed in [7]). Here, we will discuss strategies to control amygdala activity by restoring cortical control as well as interventions targeting the amygdala that have emerged from recent studies.

5.1. Strategies Targeting Pain-Related Corticoamygdala Dysfunction. There is good evidence to suggest that mPFC deactivation in pain results in loss of amygdala control (see the Pain-Related Amygdala-Centered Corticolimbic Interactions section). A *CRF1 receptor antagonist* (NBI27914) inhibited the pain-related increase in synaptic excitation and background and evoked activity of BLA neurons in arthritic rats and increased the background and evoked activity of mPFC neurons that was decreased in the pain model [71]. This intervention also inhibited increased mechanosensitivity (spinal withdrawal reflexes), averse affective responses (audible and ultrasonic vocalizations), and anxiety-like behaviors (measured in the elevated plus maze) and restored normal decision-making on a rodent gambling task in arthritic rats [71].

Another strategy to restore mPFC output used a *group II mGluR antagonist* (LY341495) to increase synaptically evoked spiking of mPFC pyramidal cells in brain slices from normal and arthritic rats [136]. Effects of a group II agonist (LY379268) showed that these receptors act on glutamatergic synapses from BLA to inhibit direct excitatory transmission and feedforward inhibition onto pyramidal cells, but their net effect is decreased pyramidal cell output, possibly because the effect on EPSCs preceded that on IPSCs. Facilitatory effects of the antagonist suggest that the system may be tonically active to control pyramidal output.

Activation of mGluR5 was tested because of its location on mPFC pyramidal cells (see the Pain-Related Amygdala-Centered Corticolimbic Interactions section). A *positive allosteric modulator (PAM) of mGluR5* (VU0360172) increased synaptically evoked spiking in mPFC pyramidal cells using electrical and optogenetic stimulation of BLA inputs [126, 131]. This facilitatory effect on mPFC output involved inhibition of synaptic inhibition by engaging endocannabinoid signaling because CB1 antagonists (AM251 and AM281) and an intracellular inhibitor of diacylglycerol lipase DAGL (tetrahydrolipstatin, THL) blocked the effect of VU0360172 [126, 131]. While this strategy worked under normal conditions, the facilitatory effect of VU0360172 was lost in the arthritis pain model due to a breakdown of mGluR5-driven endocannabinoid signaling in the mPFC resulting in a lack of 2-arachidonoylglycerol (2-AG) [126]. The facilitatory effect of mGluR5 activation on mPFC output was restored with inhibitors of the postsynaptic 2-AG hydrolyzing enzyme ABHD6 (intracellular WWL70) and the monoacylglycerol lipase MGL (JZL184) to increase availability of 2-AG in the postsynaptic cell or with a $GABA_A$ receptor blocker (intracellular picrotoxin) [126]. Coapplication of *a CB1 receptor agonist (ACEA) with the mGluR5 PAM* also increased synaptically evoked spiking of mPFC pyramidal cell neurons in brain slices from arthritic rats by decreasing abnormally enhanced feedforward inhibition from the BLA through depolarization-induced suppression of synaptic inhibition [126]. Systems electrophysiology studies in anesthetized rats with arthritis showed that coadministration of VU0360172 and ACEA into the mPFC increased background and evoked activity of pyramidal-like cells in the mPFC and inhibited the pain-related increase of background and evoked activity in amygdala (CeLC) neurons [123]. This combination strategy also inhibited increased mechanosensitivity (spinal withdrawal reflexes) and audible and ultrasonic vocalizations and mitigated cognitive deficits in the reward-based decision-making in a rodent

gambling task in the arthritis pain model [126]. The data further confirm the inverse link between mPFC and amygdala activity and that restoring mPFC output with a combination strategy of mGluR5-CB1 activation can engage cortical control of abnormally enhanced amygdala output to inhibit pain behaviors.

Neuropeptide S (NPS) binds to the G_q/G_s-coupled NPS receptor (NPSR), which is expressed in several brain regions including the dorsomedial ITC cell cluster in the amygdala, and produces anxiolytic effects [84, 137–141]. NPS increased mPFC-driven feedforward inhibition of CeLC neurons by activating ITC cell drive and output in brain slices from arthritic rats through a PKA-dependent mechanism [39]. Intra-ITC as well as nasal application of NPS resulted in decreased background and evoked activity of CeLC neurons in anesthetized rats with arthritis pain, and this effect was blocked by stereotaxic administration of an NPSR antagonist ([D-Cys(^{t}Bu)^5]NPS or SHA68) into the ITC area [142]. Intra-ITC or nasal application of NPS also inhibited pain-related increases in audible and ultrasonic vocalizations as well as anxiety-like behaviors on the elevated plus maze but had no effect on mechanosensitivity; the inhibitory effects were blocked by stereotaxic administration of [D-Cys(^{t}Bu)^5] NPS or SHA68 [39, 142].

These studies provide strong evidence for the concept that engaging mPFC control of amygdala processing may be a useful therapeutic strategy for pain management. This concept is supported by studies in humans that have implicated corticolimbic loops, including mPFC-amygdala interactions, in the prediction of and transitioning to chronic pain [11, 143].

5.2. Therapeutic Strategies Targeting Pain-Related Amygdala Hyperactivity. Pharmacological interventions targeting glutamate receptors and neuropeptide systems in the amygdala have been reviewed recently [7]. Here, additional strategies involving the *serotonergic system and potassium channels* will be discussed.

Serotonergic descending pathways are involved in endogenous antinociceptive signaling from the brain to the spinal cord [52, 144, 145]. However, serotonin (5-HT) actions can be excitatory or inhibitory depending on the specific receptor subtype and its associated neurotransmitter [52]. It is therefore not surprising that selective serotonin reuptake inhibitors (SSRIs) have shown inconsistent efficacy for neuropathic pain treatment [146–148]. One of the at least 14 5-HT receptors, the $G_{q/11}$-coupled 5-HT_{2C} receptor, has been implicated in adverse and inconsistent effects of SSRIs for neuropathic pain [149, 150] and, specifically in the BLA, in the generation of anxiogenic behaviors [151–153].

In a rat model of neuropathic pain, viral vector-mediated *5-HT_{2C} receptor knockdown* in the BLA inhibited mechanical hypersensitivity, aversive affective pain behaviors (vocalizations), anxiety-like behaviors, and depression-like behaviors [44]. Pharmacological blockade of 5-HT_{2C} receptors (SB242084) in the BLA conveyed efficacy to a systemically applied SSRI (fluvoxamine) for inhibition of emotional responses (vocalizations) and anxiety-like pain behaviors but not mechanical hypersensitivity [154]. The beneficial behavioral effects of 5-HT_{2C} receptor knockdown in the BLA involved inhibition of irregular and burst firing and evoked activity of CeLC neurons in neuropathic rats [44]. At the synaptic level, 5-HT_{2C} receptor knockdown in the BLA blocked the increase in excitatory transmission at the BLA-CeLC synapse in brain slices from neuropathic rats but had similar inhibitory effects on feedforward inhibition under control conditions and in the neuropathic pain model. 5-HT_{2C} receptor is predominantly expressed in GABAergic neurons, but increased expression in non-GABAergic BLA cells was detected in the neuropathic pain state. The underlying mechanisms of this switch remain to be determined.

Another recent strategy to mitigate pain-related amygdala hyperactivity is *activation of small-conductance calcium-activated potassium (SK) channels* in the CeA. SK channels are calcium-sensitive, voltage-insensitive potassium channels that are expressed in somatic and dendritic regions of the neuron in a brain region-specific manner [155–158]. Somatically expressed SK channels regulate neuronal excitability by mediating the medium after-hyperpolarization (mAHP) to decrease action potential firing rate [155]. In the amygdala, SK channels regulate action potential firing of neurons in the lateral CeA [159] but not LA [160]. SK channels also regulate dendritic excitability to modulate synaptic transmission and plasticity. In the amygdala, activation of synaptic SK channels in the LA acts as a postsynaptic shunt to reduce excitatory synaptic transmission [161], whereas removal of SK channels from the postsynaptic membrane of LA neurons by a PKA-dependent mechanism facilitates excitatory transmission and synaptic plasticity [162].

A clinically available compound that can inhibit SK channels is *riluzole*, an FDA approved drug for the treatment of amyotrophic lateral sclerosis (ALS) that easily crosses the blood-brain barrier [163, 164]. It should be noted that other actions of riluzole include inhibition of voltage-gated calcium channels, rapidly inactivating voltage-gated and persistent sodium channels, and glutamate receptor currents [165–167]. Systemically applied riluzole had antinociceptive effects in the formalin test [168–170], in the carrageenan model of hindpaw inflammation [171], and in neuropathic pain models [172–175]. Riluzole also produced pain relief in patients with irritable bowel syndrome [176]. The site and mechanism of pain-related riluzole effects were not identified in these studies. Systemic application of riluzole inhibited emotional responses (audible and ultrasonic vocalizations), but not mechanosensitivity (spinal withdrawal reflexes), in a rodent model of arthritic pain, and these inhibitory effects were reversed by stereotaxic (intra-CeA) administration of a blocker of SK channels (apamin) but not of large-conductance calcium-activated potassium BK channels (charybdotoxin) [177].

An interesting observation is that not every intervention targeting the amygdala to inhibit emotional-affective responses to pain affects mechanosensitivity. This is true for

riluzole [177] as well as for NPS [142], an mGluR5 antagonist [178], and an SSRI [154], and may suggest differential roles of neurochemically distinct intra-amygdala circuits.

8. Conclusions

The amygdala is a key node in the interaction of emotional-affective factors with sensory and cognitive aspects of pain. The synaptic and cellular analysis of amygdala function and plasticity as the neurobiological basis of certain pain behaviors has provided a model system for the study of brain mechanisms of pain. The better understanding of relevant intra- and extra-amygdalar circuits and their neurochemical and molecular signatures should yield novel targets for therapeutic interventions because amygdala activity is causally linked to pain behaviors, and therefore, controlling abnormally enhanced amygdala activity is a desirable goal for pain management.

Abbreviations

2-AG: 2-arachidonoylglycerol
5-HT: Serotonin
ACC: Anterior cingulate cortex
CeA: Central nucleus of the amygdala
CeLC: Laterocapsular division of the CeA
CeM: Medial division of the CeA
CGRP: Calcitonin gene-related peptide
CRF: Corticotropin-releasing factor
EPSC: Excitatory postsynaptic current
ERK: Extracellular signal-regulated kinase
HT: Hypothalamus
IBS: Irritable bowel syndrome
IPSP/C: Inhibitory postsynaptic potential/current
ITC: Intercalated cell mass of the amygdala
LA/BLA: Lateral/basolateral amygdala nuclei
mGluR: Metabotropic glutamate receptor
mPFC: Medial prefrontal cortex
NMDA: *N*-methyl-D-aspartate
NPS: Neuropeptide S
NPSR: NPS receptor
PAG: Periaqueductal gray
PAM: Positive allosteric modulator
PB: Parabrachial nucleus
PKA: Protein kinase A
PKCδ: Protein kinase C delta
SK: Small-conductance calcium-activated potassium channel
SSRI: Selective serotonin reuptake inhibitor.

Conflicts of Interest

There are no conflicts of interest.

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Research Article

Disentangling the Sleep-Pain Relationship in Pediatric Chronic Pain: The Mediating Role of Internalizing Mental Health Symptoms

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Background. Pediatric chronic pain often emerges in adolescence and cooccurs with internalizing mental health issues and sleep impairments. Emerging evidence suggests that sleep problems may precede the onset of chronic pain as well as anxiety and depression. Studies conducted in pediatric populations with pain-related chronic illnesses suggest that internalizing mental health symptoms may mediate the sleep-pain relationship; however, this has not been examined in youth with primary pain disorders. *Objective*. To examine whether anxiety and depressive symptoms mediated relationships between sleep quality and pain outcomes among youth with chronic pain. *Methods*. Participants included 147 youth (66.7% female) aged 8–18 years who were referred to a tertiary-level chronic pain program. At intake, the youth completed psychometrically sound measures of sleep quality, pain intensity, pain interference, and anxiety and depressive symptoms. *Results*. As hypothesized, poor sleep quality was associated with increased pain intensity and pain interference, and anxiety and depressive symptoms mediated these sleep-pain relationships. *Discussion*. For youth with chronic pain, poor sleep quality may worsen pain through alterations in mood and anxiety; however, prospective research using objective measures is needed. Future research should examine whether targeting sleep and internalizing mental health symptoms in treatments improve pain outcomes in these youth.

1. Introduction

Pediatric chronic pain (i.e., pain lasting for three months or longer) tends to emerge in late childhood (recurrent abdominal pain [1]) and early adolescence (musculoskeletal pain [2] and headaches [3]). Prevalence rates of chronic pain are rising (median prevalence rates ranging from 11% to 38%) [4], and longitudinal research suggests that up to 64% of youth with chronic pain will continue to have pain problems into adulthood [5]. Pediatric chronic pain is integrally linked to internalizing mental health symptoms, such as elevated anxiety and depression symptoms (for review, see [6]). Moreover, even when pain resolves by adulthood, its initial occurrence confers risk for lifetime diagnoses of depression and anxiety [7, 8].

In addition to the persistent subjective suffering, sleep impairments are also associated with chronic pain across the lifespan [9], and this cooccurrence is linked to greater functional disability and reduced quality of life [10]. While the sleep-pain relationship was initially posited to be bidirectional [11], a review by Finan and colleagues came to a different conclusion. The majority of reviewed studies were longitudinal and experimental sleep deprivation studies that included adult samples, with three studies investigating the sleep-pain relationship in youth [9]. Overall, Finan et al. found that sleep impairments are a stronger and more reliable predictor of pain than vice versa [9].

Emerging research utilizing microlongitudinal data (i.e., daily assessments of mood and pain) among pediatric pain populations supports this. In youth recovering after

a major surgery, poor sleep quality was predictive of higher next-day pain intensity, suggesting that sleep impairments may contribute to persistent postsurgical pain [12]. A similar pattern was found among youth with juvenile idiopathic arthritis (JIA), whose daily reports of worse sleep quality were associated with higher levels of next-day pain intensity [13]. Further, in a sample of youth with chronic pain, longer sleep duration and more minutes awake after sleep onset (i.e., less restorative sleep) were predictive of higher levels of next-day pain intensity [14].

Similar relationships have been reported in epidemiological studies. Sleep problems in childhood (age 10-11 years; [15]) and young adulthood (age 19 years; [16]) were associated with a higher risk of developing pain problems two to three years later [15, 16]. Few studies have empirically examined the mechanisms underlying the sleep-pain relationship in youth; however, negative affect [17] and depressive symptoms [18] have been proposed as potential mechanisms underlying the association between sleep impairments and increased pain intensity. In a sample of youth with chronic pain, lower positive affect and increased negative affect were shown to mediate the relationship between self-reported poor sleep quality and increased functional disability [17]. Further, negative, but not positive, affect mediated the relationship between youth reported poor sleep quality and increased pain intensity [17].

Research suggests that elevated depressive and anxiety symptoms often cooccur with both sleep impairments and chronic pain in youth. Moreover, the earlier that sleep problems emerge in development, the more likely children are to experience symptoms of anxiety and depression by mid-adolescence [19]. Additionally, insomnia at 4.5 years of age that continues to be present by the age of 9 years predicted clinically significant levels of anxiety into early adulthood [20]. Relatedly, depressive symptoms cooccurring with sleep impairments at the age of 5 years were found to be associated with an increased risk of depressive symptoms at the age of 34 [21]. The high cooccurrence of internalizing mental health symptoms and chronic pain in youth has been established (for review, see Vinall et al. [6]), and to account for this high cooccurrence, conceptual models [22] have pointed to sleep impairments (e.g., hyperarousal) as a key mutually maintaining factor. Enhanced understanding of the mechanisms underlying these overlapping, commonly cooccurring difficulties could inform targeted interventions to improve outcomes in these vulnerable youth.

Several conceptual models have been proposed to explain the relationship between sleep and pain in children and adolescents. Lewin and Dahl [11] posit a bidirectional relationship between sleep and pain, where pain is associated with fewer hours of sleep. Decreased sleep duration is related to a range of negative affective and behavioral responses (e.g., decreased attentional control and higher levels of irritability). These consequences, in turn, are associated with increased perception of pain [11]. Valrie et al. [23] extend and complement Lewin and Dahl's conceptual model. Potential mechanisms (e.g., biological factors) contributing to the association between sleep and pain are added as well as functional outcomes (e.g., quality of life). Moreover, this is the first model to propose that negative mood may mediate this relationship [23]. That is, negative mood along with positive emotions, developmental stage, sex, ethnic-cultural, and sociocontextual factors may explain the complex association between pain and sleep in youth. Further, the interplay of these factors influences functional outcomes (e.g., health care use and quality of life) in children and adolescents [23]. A similar conceptual model explains the influence of pediatric chronic fatigue syndrome on sleep impairment [24]. Specifically, an interplay between child's physiological (e.g., hormonal fluctuations), developmental (e.g., developmental stage), sociocultural (e.g., family structure and cultural beliefs), psychological and behavioral (e.g., temperament), and disease-related (e.g., levels of pain and fatigue) factors are thought to influence quality and quantity of sleep [24].

However, the empirical support is limited to pediatric samples of youth with JIA [13], sickle cell disease (SCD) [25], and cancer [18]. Moreover, anxiety symptoms that are common in youth with chronic pain [26] and that are heightened by poor sleep [27] were not included in the model [23] or the recent empirical studies [17]. The current study is the first to examine the mediating roles of anxiety and depressive symptoms in the relationship between sleep quality and pain outcomes, that is, pain intensity and interference in youth with primary pain disorders. We hypothesized that higher anxiety and depressive symptoms would mediate the relationships between poorer sleep quality and worse pain outcomes.

2. Materials and Methods

2.1. Participants and Setting. 159 youth and one of their parents and/or caregivers participated in the current study. They were invited to participate in the study by email or phone prior to their first appointment at a tertiary-level chronic pain program in a pediatric hospital in Canada. Youth aged 8 to 18 years were eligible to participate if they were referred to one of the chronic pain programs for assessment and/or treatment. Youth diagnosed with a developmental disability and/or who did not speak English were excluded from the study.

Data from 147 youth (66.7% female, 13.32 years old ($SD = 2.59$, range 8–18)) who completed at least 80% of the questionnaires were included in the analyses. Youth had been referred to either the abdominal pain (1.4%), complex pain (36.1%), or headache (62.6%) clinic. Sociodemographic information of the sample (i.e., age, sex, ethnicity, and income) is presented in Table 1. Descriptive statistics of the key variables are presented in Table 2. Reported average pain intensity was 5.07/10 ($SD = 2.34$), and average pain interference was 56.52 (T-score; $SD = 9.76$). Overall, 43.5% of the youth reported pain to be "always present (intensity varies/the same intensity)." Pain in multiple locations was reported by 62.6% of the youth. On average, pain has been present for 35.17 months ($SD = 33.98$).

2.2. Procedure. One to three weeks prior to the first clinical appointment, potential participants were informed about

Table 1: Sociodemographic characteristics of the sample.

Sociodemographics	$N = 147$
Child's age (*M* years, *SD*)	13.32 (2.59)
Child's sex (% female)	66.7
Parent's sex (% female)	92.5
Relationship to the child (%)	
Biological parent	97.9
Adoptive parent	1.4
Legal guardian	0.7
Child's ethnicity (%)	
White (Caucasian)	81.4
Two or more ethnicities	9.0
Latin American	3.5
Arab/West Asian	1.4
Other	2.8
Do not want to answer	0.7
Household income (%)	
<$10,000–$29,999	4.3
$30,000–$59,999	9.3
$60,000–$89,999	9.3
More than $90,000	54.3
Do not want to answer	22.9
Pain locations (%)	
Multiple locations	62.6
Single location	37.4
Head	18.4
Limb	8.8
No location reported	4.8
Abdomen	2.7
Face	0.7
Chest	0.7
Groin	0.7
Hip	0.7

Table 2: Descriptive statistics for key variables.

Variable	*M* (*SD*)
Sleep quality (rASWS), total	3.40 (0.80)
Anxiety symptoms (PROMIS), *T*-score	49.05 (11.86)
Depressive symptoms (PROMIS), *T*-score	49.72 (11.12)
Pain intensity (PROMIS), total	5.07 (2.34)
Pain interference (PROMIS), *T*-score	56.52 (9.76)

Note. rASWS = revised Adolescent Sleep-Wake Scale; PROMIS = Patient-Reported Outcomes Measurement Information System. Means of prorated total scores are displayed for the rASWS. Means of *T*-scores are displayed for pain interference and depressive and anxiety symptoms.

the study over the phone. If they were eligible and interested to participate, online consent forms were sent to youth and one of their parents. Upon providing consent, the youth completed psychometrically sound self-report measures of pain characteristics, pain interference, sleep quality, and anxiety and depressive symptoms using REDCap, a secure online data collection application [28]. Parents reported sociodemographic information. A standard protocol of prompting families to complete the questionnaires up to four times over the course of four weeks was used. The institutional Research Ethics Board (REB) approved the study.

2.3. Measures

2.3.1. Demographics. Parents reported on their child's age, sex, and ethnicity, their relationship to the child, and household income.

2.3.2. Pain Characteristics. Youth completed the valid and reliable pain questionnaire [29]. Youth reported their pain location using a validated body map [30] (Table 1). They also reported the duration of their pain problem (in months) and pain frequency using a 5-point Likert scale ranging from "rarely present pain (occurs every few days or weeks)" to "always present (always the same intensity)."

2.3.3. Sleep Quality. The revised Adolescent Sleep-Wake Scale (rASWS) was administered to assess sleep quality in the past seven days on a 6-point Likert scale (anchors: 1 = "never" and 6 = "always") [31]. Ten empirically derived items of the original ASWS [32] were averaged to yield three subscale scores, that is, Falling Asleep and Reinitiating Sleep, Returning to Wakefulness, and Going to Bed. A total score (i.e., a mean of three subscales) indicated the overall quality of sleep, with higher scores representing better sleep quality. The rASWS has been validated for use in youth with a variety of health conditions, including youth with chronic pain [31].

2.3.4. Pain Outcomes—Intensity and Interference. Youth completed the Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Profile-25 that is a part of the NIH assessment toolbox [33]. The PROMIS instruments have been rigorously developed to assess mental and physical health in youth and adults and have been validated for use in pediatric samples with chronic pain [34]. Item response theory and the associated calibration of the individual items allowed for creation of brief, sensitive-to-change forms with a smaller standard error of measurement [34]. The Pain Interference subscale assessed how much pain interfered with youth's everyday activities in the past seven days using a 5-point Likert scale (anchors: 0 = "never" and 4 = "almost always") (e.g., "It was hard for me to walk when I had pain"). This scale is composed of four items that yield a standardized *T*-score used in the analyses. Average pain intensity in the past 7 days was reported using an 11-point Numeric Rating Scale item from the PROMIS Pediatric Profile-25 (anchors: 0 = "no pain" and 10 = "worst pain you can think of"). The PROMIS measures demonstrated good construct validity (intercept and slope ≥ 0.98 [34]) and internal consistency (pain interference, 4 items $\alpha = 0.85$) in a sample of youth with chronic pain.

2.3.5. Anxiety and Depressive Symptoms. Anxiety and depressive symptoms were assessed using the PROMIS

Pediatric Profile-25 Anxiety and Depression subscales [33]. Participants reported if they experienced any of the symptoms (e.g., "I felt everything in my life went wrong" and "I felt like something awful might happen") in the past 7 days using a 5-point Likert scale (anchors: 0 = "never" and 4 = "almost always"). The summed scores of each subscale were transformed into standardized *T*-scores for the analyses. The subscales have demonstrated good construct validity (intercept and slope ≥ 0.93 [34]) and excellent internal consistency (depressive symptoms, 4 items, $\alpha = 0.91$; anxiety symptoms, 4 items, $\alpha = 0.90$). The subscales have been validated in youth with chronic pain [34]. Their brevity reduces participant burden in real clinical settings while still providing psychometrically sound self-report assessment of core constructs in chronic pain [34].

2.4. Statistical Analyses. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 24. Prorated scores were used for missing data (less than 20% within each subscale) [35]. Participants who completed less than 80% on each subscale ($n = 12$) were excluded. Demographic characteristics of the sample were reported using descriptive statistics. Frequency statistics were used for categorical variables (youth's sex, household income, and pain location and frequency). Means and standard deviations were reported for all key continuous variables. *T*-tests were used to examine differences in key variables as a function of main sociodemographic variables, that is, youth's age and sex. Bivariate correlations between key variables were conducted to justify inclusion in the mediation models. Specifically, to be included in the analyses, sleep quality had to be significantly correlated with anxiety and/or depressive symptoms. The latter, in turn, had to be significantly associated with pain outcomes, that is, intensity and interference. The relationship between sleep quality and pain outcomes did not have to be significant, but it was tested. Mediation analyses were conducted using the Preacher and Hayes' PROCESS macro for SPSS [36].

Based on the correlational analyses, four mediation models (Figure 1) were tested to examine the associations between youth sleep quality and pain outcomes, that is, pain intensity and pain interference. In the first two models, anxiety symptoms were included as a mediator. In the remaining two models, depressive symptoms were included as a mediator. The total effect of sleep quality on pain outcomes (weight *c*) consisted of a direct effect of sleep quality on pain outcomes (weight c') and an indirect effect of sleep quality on pain outcomes through the mediator, anxiety, or depressive symptoms (weight *ab*). In Figure 1, weight *a* denotes the effect of sleep quality on anxiety or depressive symptoms, weight *b* denotes the effect of anxiety or depressive symptoms on pain outcomes.

The main indication of mediation is the presence of an indirect effect, that is, a significant contribution of the mediator to the relationship between the independent and dependent variables. Confidence intervals that do not contain zero suggest with 95% confidence that the indirect effect is not zero [37]. Mediation is established if the confidence interval does not contain zero. To maximize robustness of the results, bootstrapping with 10,000 samples, a preferable method of testing indirect effects of mediation [36], was used in testing the mediation models.

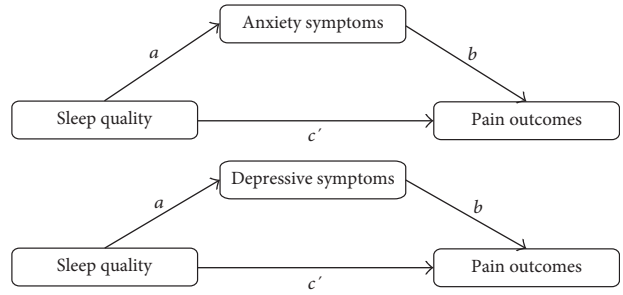

Figure 1: Proposed mediation models.

3. Results

3.1. Descriptive Statistics. On average, youth sleep quality was 3.40/6.00 ($SD = 0.80$). Internalizing symptoms averaged 49.05 for anxiety symptoms ($SD = 11.86$) and 49.72 for depressive symptoms ($SD = 11.12$). Girls reported higher levels of anxiety symptoms ($t(142) = 2.19$, $p = 0.030$), pain interference ($t(75) = 3.11$, $p = 0.003$), and worse quality of sleep ($t(145) = -2.22$, $p = 0.028$), as compared to boys. Age was significantly correlated with depressive symptoms with older youth reporting significantly higher levels of depressive symptoms ($r = 0.29$, $p < 0.001$). Therefore, age and sex were entered as covariates in all tested mediation models.

3.2. Correlational Analyses. Bivariate correlations between key variables and outcomes are presented in Table 3. Poor sleep quality was associated with higher levels of anxiety ($r = -0.40$, $p < 0.001$) and depressive ($r = -0.39$, $p < 0.001$) symptoms as well as higher pain intensity ($r = -0.20$, $p = 0.016$) and pain interference ($r = -0.43$, $p < 0.001$). Higher anxiety and depressive symptoms were correlated with higher pain intensity ($r = 0.27$, $p = 0.001$; $r = 0.22$, $p = 0.008$) and interference ($r = 0.48$, $p < 0.001$; $r = 0.41$, $p < 0.001$).

3.3. Mediation Analyses

3.3.1. Anxiety Symptoms as a Mediator in the Relationship between Sleep Quality and Pain Outcomes. Two separate models were tested to investigate whether anxiety symptoms mediated the effect of sleep quality on pain outcomes (i.e., pain interference and pain intensity). Youth's age and sex were included as covariates (Table 4 for regression coefficients and indirect effects). As hypothesized, anxiety symptoms were a partial mediator of the relationships between sleep quality and pain interference as well as sleep quality and pain intensity, over and beyond the influences of child age and sex (anxiety symptoms and pain intensity:

Table 3: Correlations among key variables.

Variable	1	2	3	4	5
(1) rASWS, total	1	−0.40***	−0.39***	−0.20*	−0.43***
(2) PROMIS—anxiety symptoms, *T*-score	—	1	0.71***	0.27**	0.48***
(3) PROMIS—depressive symptoms, *T*-score	—	—	1	0.22**	0.41***
(4) PROMIS—pain intensity, *T*-score	—	—	—	1	0.54***
(5) PROMIS—pain interference, *T*-score	—	—	—	—	1

Note. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ two-tailed test. rASWS = revised Adolescent Sleep-Wake Scale; PROMIS = Patient-Reported Outcomes Measurement Information System.

Table 4: Unstandardized coefficients and indirect effect sizes.

Model	*b*	*SE*	*t*	*p*	CI_{BCa} (LL)	CI_{BCa} (UL)
Pain intensity						
Sleep quality → anxiety symptoms (*a*)	−5.60	1.16	−4.84	<0.001	−7.89	−3.32
Anxiety symptoms → pain intensity (*b*)	0.04	0.02	2.48	0.014	0.01	0.08
Sleep quality → pain intensity (*c*′)	−0.30	0.26	−1.15	0.254	−0.82	0.22
Sleep quality → anxiety symptoms → pain intensity (a ∗ b)	−0.25	0.11	—	—	−0.52	−0.07
Pain interference						
Sleep quality → anxiety symptoms (*a*)	−5.73	1.16	−4.94	<0.001	−8.02	−3.44
Anxiety symptoms → pain interference (*b*)	0.28	0.06	4.28	<0.001	0.15	0.40
Sleep quality → pain interference (*c*′)	−3.20	0.95	−3.37	0.001	−5.09	−1.33
Sleep quality → anxiety symptoms → pain interference (a ∗ b)	−1.58	0.49	—	—	−2.75	−0.77
Pain intensity						
Sleep quality → depressive symptoms (*a*)	−5.37	1.04	−5.15	<0.001	−7.44	−3.31
Depressive symptoms → pain intensity (*b*)	0.04	0.02	2.08	0.040	0.002	0.08
Sleep quality → pain intensity (*c*′)	−0.32	0.26	−1.21	0.228	−0.84	0.20
Sleep quality → depressive symptoms → pain intensity (a ∗ b)	−0.22	0.11	—	—	−0.46	−0.02
Pain interference						
Sleep quality → depressive symptoms (*a*)	−5.40	1.05	−5.13	<0.001	−7.48	−3.32
Depressive symptoms → Pain interference (*b*)	0.25	0.07	3.50	0.001	0.11	0.39
Sleep quality → pain interference (*c*′)	−3.49	0.96	−3.63	0.0004	−5.39	−1.59
Sleep quality → depressive symptoms → pain interference (a ∗ b)	−1.33	0.46	—	—	−2.40	−0.57

Note. *N* for analyses is 144 cases for pain intensity-anxiety symptoms, 142 cases for pain interference-anxiety symptoms, 147 cases for pain intensity-depressive symptoms, and 145 cases for pain interference-depressive symptoms models. Sleep quality (rASWS, total score) is the independent variable (IV) in all models. Anxiety or depressive symptoms (PROMIS Anxiety and Depression subscales, *T*-scores; M); pain intensity (NRS; DV1); and pain interference (PROMIS Pain Interference subscale, *T*-score; DV2) are the outcome variables. CI_{BCa} (LL) = lower limit of a 95% confidence interval; CI_{BCa} (UL) = upper limit. Analyses are controlling for youth's age and sex.

$n = 144$, $PE = -0.25$, $SE = 0.11$ ($CI_{BCa} = -0.52$ to -0.07); anxiety symptoms and pain interference: $n = 142$, $PE = -1.58$, $SE = 0.49$ ($CI_{BCa} = -2.75$ to -0.77)).

3.3.2. Depressive Symptoms as a Mediator in the Relationship between Sleep Quality and Pain Outcomes. Similarly, two separate models were tested to examine whether depressive symptoms mediated the effect of sleep quality on pain intensity and pain interference. Consistent with hypotheses, depressive symptoms partially mediated the associations between sleep quality and pain intensity as well as sleep quality and pain interference, over and beyond the influences of child age and sex (depressive symptoms and pain intensity: $n = 147$, $PE = -0.22$, $SE = 0.11$ ($CI_{BCa} = -0.46$ to -0.02); depressive symptoms and pain interference: $n = 145$, $PE = -1.33$, $SE = 0.46$ ($CI_{BCa} = -2.40$ to -0.57)).

4. Discussion

The current study is the first to examine anxiety and depressive symptoms as mediators in the relationship between sleep quality and pain outcomes (intensity and interference) in youth with primary pain disorders. As hypothesized, both anxiety and depressive symptoms partially mediated these relationships. This suggests that internalizing mental health symptoms may be a mechanism or a process underlying the relationship between sleep quality and chronic pain outcomes in youth and should be considered both theoretically and clinically.

Our findings support and complement Valrie et al.'s theoretical model that hypothesized mood as one of the factors influencing the sleep-pain relationship in pediatric populations with pain-related chronic illness (juvenile idiopathic arthritis and sickle cell disease) and primary pain

disorders [23]. The model assumes a bidirectional relationship between sleep and pain perception, which, in turn, affects health-related quality of life, functional disability, and health care utilization [23]. In addition to mood alterations, physiological and biological factors were also posited to influence the sleep-pain relationship. The current findings are also consistent with the existing research in pediatric populations with pain-related chronic illness (e.g., JIA, oncology/hematology-related illness, and SCD) [13, 18, 25]. Moreover, our findings extend this previous work by providing evidence that depressive symptoms mediate the sleep-pain relationship in a pediatric sample with primary pain disorders. The mediating role of depressive symptoms in sleep quality-pain outcomes relationship is also in line with the recent research showing that negative affect mediated the relationship between poor sleep and functional disability and pain intensity in youth with chronic pain [17]. In the current study, anxiety symptoms were also found to mediate the association between sleep quality and pain outcomes. Thus, anxiety symptoms could be added to future revisions of Valrie et al.'s conceptual model [23] as an additional mechanism that in part explains why sleep impairments and pain problems cooccur in youth.

The current findings also support the conceptual model of pediatric sleep and pain proposed by Lewin and Dahl [11]. Specifically, their model suggests that acute and chronic pain is associated with decreased sleep duration in children and adolescents. Sleep impairments, in turn, are thought to result in higher levels of fatigue, irritability and affective disturbance, as well as decreases in attentional control and positive coping behaviours [11]. These consequences of sleep impairments were posited to heighten pain perception, thus creating a vicious, self-maintaining sleep-pain cycle. Depressive and anxiety symptoms may independently contribute to this sleep-pain cycle through a range of cognitive and affective mechanisms. For example, elevations in anxiety symptoms are linked to higher presleep arousal, which may delay sleep onset and is associated with poorer sleep quality [38]. Moreover, elevated anxiety symptoms may also increase hypervigilance [39] and attentional biases (e.g., increased tendency to selectively attend to pain) which, in turn, disturb sleep [11]. The proposed sequelae of sleep impairments (e.g., increased irritability and alterations in emotion [11]) overlap with depressive symptoms (anhedonia and irritability) and may, in part, explain the contribution of negative mood to the sleep-pain relationship. The findings of experimental studies examining sleep deprivation in adult clinical samples converge to suggest that sleep impairments may lead to both altered pain perception (e.g., hyperalgesia [40] and elevated pain sensitivity [41]) and higher levels of depressed mood [42].

Beyond internalizing mental health symptoms, it is important to consider other potential factors contributing to the sleep-pain relationship. Neurobiological mechanisms are likely to play a key role. For example, sleep architecture may explain the association between sleep impairments and pain. Disrupted slow wave sleep (SWS) has been linked to lower pain thresholds in experimental pain studies with healthy adults (for review see [43]). Reductions in SWS have also been demonstrated in adults with chronic pain [44] and children with pain-related chronic illness (JIA) [45]. Moreover, brain structures that regulate sleep (e.g., reticular nucleus of thalamus and midbrain periaqueductal gray) are also involved in pain modulation [43] and chronic pain maintenance (e.g., recurrent migraines [46]). Another potential pathway could involve neurotransmitter networks. Finan et al. [9] summarized literature supporting the role of the mesolimbic dopamine system in influencing linkages between insomnia, chronic pain, and depression. Overall, existing research exploring neurobiological mechanisms of sleep-pain relationship is limited to adult populations. Given rapid changes in the developing brain and neurocircuitry during the period of adolescence, future research should examine the neurobiological pathways underlying the sleep-pain relationship in pediatric populations.

In addition to internalizing mental health symptoms, future research should also examine the role of *positive* affect on the relationship between sleep impairments and chronic pain outcomes in youth. In a recent study, positive affect was found to mediate the association between sleep quality and functional disability (but not pain intensity) in a sample of youth with chronic pain [17]. Positive affect may facilitate engagement in positive coping behaviours (e.g., attending away from pain sensations), which could lead to attenuation of sleep-pain cycle. To date, the few studies examining positive affect [17, 47] have used the Positive and Negative Affect Schedule (PANAS), an instrument targeted to measure subjective distress or absence thereof (negative affect) and pleasurable engagement with the environment (positive affect) [48]. Moreover, while it is crucial to examine the role of positive affect, it would be beneficial to consider other resilience factors implicated in the chronic pain experience (e.g., optimism [49]) as they may also serve to buffer the impact of poor sleep on pain and functioning.

The findings of our study should be viewed in light of limitations that may be addressed in future research. First, the cross-sectional nature of the current study prevents inferences about the directionality of the relationships between our variables. Mediation analyses are ideally used in longitudinal research designs as it allows a more rigorous investigation of underlying mechanisms [50]. Given that our study is cross-sectional in nature, this is a methodological limitation and future longitudinal work is needed. However, accumulating basic and clinical investigations provide compelling evidence that sleep problems more strongly drive increases in pain [9] and internalizing mental health conditions [51], than vice versa. Longitudinal studies assessing mood, anxiety, sleep, and pain on a daily basis are needed to examine fluctuations and dynamic relationships between these factors in more ecologically valid settings over time. Existing microlongitudinal studies have captured daily relationships between mood and pain [52] or pain levels and sleep [14]; however, our results suggest that investigations integrating all three factors/processes are needed.

Second, the current study assessed anxiety and depression at a global symptom, rather than a diagnostic, level; therefore, the applicability of findings to youth with clinical diagnoses of anxiety and depression or particular types of

anxiety (e.g., social and generalized) is not known. Nevertheless, given that this relationship was present among youth with subclinical symptom presentations, it is plausible that these relationships would be even stronger in the context of clinically diagnosed anxiety and/or depressive disorders. Third, we did not assess positive affect, a construct that is independent of depressive symptoms and that has been shown to buffer the negative associations between sleep impairments and pain outcomes [9, 13]. Future studies should include measures of positive affect to examine its unique contributions to the sleep-pain associations in youth with chronic pain. Finally, the sample was mostly white with a reported annual income greater than $90,000, thereby limiting the generalizability to more diverse populations of youth with chronic pain.

Our findings emphasize the importance of addressing internalizing mental health symptoms and sleep impairments in the treatment of pediatric chronic pain given their negative influence on pain outcomes. Although sleep hygiene is sometimes included in cognitive-behaviour therapy (CBT) interventions for chronic pain [53], mental health issues are often not formally addressed. Improving sleep and internalizing mental health symptoms in more integrated chronic pain interventions could improve treatment outcomes in these youth. Cognitive-behaviour therapy for insomnia (CBT-I) has been used in adult [51] and pediatric populations [54] with a variety of comorbid mental health conditions to improve sleep and comorbid psychiatric or pain conditions. Core elements of these treatments include sleep restriction, stimulus control, and sleep hygiene [55]. Preliminary results of a trial of a 4-session CBT-I intervention for youth with insomnia and a comorbid psychological (e.g., depression) or physical (e.g., asthma, chronic pain) diagnosis demonstrated improvements in sleep quality as well as in health-related quality of life [54]. Some trials of CBT-I in adult populations with pain-related chronic illnesses (e.g., osteoarthritis) have shown improvements in pain [56], whereas others have not [57]. Limited evidence supports efficacy of CBT with sleep-specific components for pain outcomes in pediatric populations with pain-related chronic conditions (e.g., fibromyalgia [53]). The evidence for the influence of CBT-I interventions on improving mental health outcomes is relatively stronger. Given that poor sleep has been reported to impede the progress of CBT treatments for both chronic pain and depression in children and adolescents [58, 59], the findings of the present study provide additional rationale for addressing sleep issues to potentially reduce elevations in internalizing mental health symptoms and improve pain and functioning. In the context of chronic pain, it is likely that approaches that integrate targeting mental health, sleep, and pain will be most effective.

In conclusion, this study was the first to demonstrate that elevated anxiety and depressive symptoms partially mediate the relationship between poor sleep quality and higher levels of pain intensity and pain interference among youth with primary pain disorders. The findings point to potential affective mechanisms underlying the highly comorbid relationship between pediatric chronic pain and sleep problems and provide support for, and extend, existing conceptual models of sleep and pain in youth. The study also highlights a critical need for addressing internalizing mental health symptoms and sleep within the context of pediatric chronic pain. Future longitudinal studies are needed to further investigate these proposed mechanisms.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Review Article

School Anxiety in Children and Adolescents with Chronic Pain

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Anxiety is highly prevalent in pediatric chronic pain. This comorbidity has been explained by the presence of shared mechanisms underlying the development and maintenance of chronic pain and anxiety. Accumulating evidence demonstrates that school is a significant source of anxiety among youth with chronic pain and that anxiety contributes to school-related functional impairment in this population. This article reviews the cooccurrence of pediatric chronic pain and anxiety, identifies unique sources of heightened school anxiety among youth with chronic pain, and describes current approaches for assessing anxiety in pediatric pain settings. Highlighted by this review is the absence of a comprehensive evidence-based approach for assessing school anxiety in pediatric chronic pain. Given the psychometric limitations inherent to gathering data from a single source, recommendations for advancing measurement methods are provided. Novel approaches may be needed to shed more light on the way in which school anxiety is experienced in pediatric chronic pain.

1. Introduction

Emerging evidence has shown that anxiety is an important factor in pediatric chronic pain [1]. Anxiety is significantly more common in youth with chronic pain than in the general population [2–4]. This comorbidity is a critically important health problem. It is associated with poorer response to pain-focused cognitive-behavioral interventions [5] and increased risk for both chronic pain [6] and anxiety disorders in adulthood [7].

School can be a significant source of anxiety among pediatric chronic pain patients. School anxiety comprises several domains of academic and interpersonal distress, such as fears pertaining to academic performance, negative teacher evaluations, and peer relationships [8]. School anxiety is a significant concern among health care professionals as it is often linked with school avoidance behavior [9–12]. Though related, school anxiety and school avoidance (a term often used interchangeably with school refusal [13]) are distinct constructs. (Of note, though the terms school refusal and school avoidance have been used interchangeably, the term school *avoidance* has predominantly been used in the pediatric chronic pain literature [12]. School *refusal* is the more common term in the child anxiety literature [11] and has been applied more broadly to include youth exhibiting a variety of internalizing and externalizing (e.g., aggression, truancy) behaviors [13]. School avoidance, on the other hand, is primarily linked to internalizing (e.g., anxiety) rather than externalizing problems in the school environment [12].) Although anxiety is characterized by disruptions in multiple domains (e.g., cognitive, affective, and behavioral), the term *school anxiety* is typically used to describe the cognitive-affective (e.g., fear, worry) domain, whereas *school avoidance* is viewed as a behavioral manifestation of anxiety [11, 12] or a serious behavioral complication accompanying anxiety disorders in youth [14]. In other words, school avoidance is a pattern in which a child experiences severe anxiety related to school and thus avoids it, fostering frequent absenteeism as well as heightened anxiety [15]. School anxiety is not a recognized diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), at this time [16]. However, evidence of significant anxiety in the context of school warrants further diagnostic clarification, as it may be associated with a number of different DSM-5 clinical disorders (e.g., separation anxiety disorder, social anxiety disorder, or generalized anxiety disorder) [14, 17].

Despite overwhelming evidence of school anxiety among pediatric pain patients [18–20], research focused specifically

on the measurement of school anxiety symptoms remains largely undeveloped. There is a need for more tailored assessment strategies targeting school anxiety in pediatric chronic pain [20–23] as clarifying the nature and extent of school anxiety in pediatric chronic pain has important implications for theory, assessment, and intervention.

This paper reviews the (i) comorbidity between pediatric chronic pain and anxiety, (ii) sources of heightened school anxiety, in particular, among youth with chronic pain, and (iii) existing approaches for assessing school anxiety. To guide future research on this understudied topic, suggestions for advancing the measurement of school anxiety are provided. This discussion includes a consideration of both traditional self-report methods as well as the potential role of novel, implicit assessment strategies toward improving our understanding of school anxiety.

2. Comorbidity between Chronic Pain and Anxiety

Anxiety symptoms are prevalent in pediatric chronic pain [3, 20] with upwards of 80% of chronic pain patients meeting criteria for an anxiety disorder based on structured diagnostic interviews [24, 25]. This has led to the call for routine screening for anxiety disorders in youth with functional abdominal pain [26] and in other pediatric pain populations [20].

Given that pain and anxiety are both associated with physiological arousal (e.g., accelerated heart rate, increased respiration rate, and muscular tension), it may be assumed that the high prevalence of anxiety symptoms in pediatric chronic pain is solely attributable to overlapping somatic symptoms (e.g., dizziness, difficulty breathing). However, this is not the case. Youth with chronic pain experience a wide range of anxiety disorder symptoms, including separation anxiety and social anxiety, which have fewer physiological symptoms included within the diagnostic criteria [20, 22]. For example, Tran and colleagues [20] found that 46% of pediatric chronic pain patients reported clinical elevations on at least one anxiety subscale on the Screen for Child Anxiety-Related Emotional Disorders (SCARED). Notably, the most common clinical elevations were on the school phobia, separation anxiety, and social anxiety subscales.

2.1. Shared Mechanisms of Pediatric Chronic Pain and Anxiety. The shared vulnerability model [27] posits that there is a similar underlying diathesis for chronic pain and anxiety. Specifically, the shared vulnerability model applies a diathesis-stress framework, postulating that individuals who are at increased risk for the development of chronic pain and/or an anxiety disorder share predisposing vulnerabilities, including anxiety sensitivity and reduced threshold for alarm, which give rise to particular negative emotional responses—namely, fear and anxiety—in the face of stressful events. Consequences of fear and anxiety, including attentional biases, avoidance behavior, and autonomic nervous system arousal, further contribute to the development of chronic pain, anxiety disorders, and their cooccurrence.

Though originally developed to explain the cooccurrence of posttraumatic stress disorder (PTSD) and chronic pain in adults, aspects of the shared vulnerability model have been well supported by research in pediatric populations. For example, anxiety sensitivity (i.e., fear of fear) has been shown to increase the risk for pain-related avoidance and disability in youth with chronic pain [28, 29]. In research with healthy children, anxious symptomatology is directly related to pain sensitivity; and anxiety sensitivity impacts pain intensity indirectly via its effects on pain-related anticipatory anxiety (e.g., [30]). Children with recurrent abdominal pain and children with anxiety disorders show indistinguishable laboratory stress responsivity [31, 32]. Notably, children with recurrent abdominal pain may be less likely to endorse trait anxiety and anxiety symptoms on *self-report* measures, despite demonstrating similar levels of state anxiety and physiological arousal in response to laboratory stressors [31].

Also included in the shared vulnerability model is avoidance behavior, as a characteristic of both anxious populations and chronic pain patients. The fear avoidance model is often used to explain avoidance in the context of pediatric chronic pain [33]. For instance, Simons and Kaczynski [33] describe similarities between youth with anxiety and pediatric patients with chronic pain, such that both groups tend to struggle with social (e.g., socializing with friends) and academic (e.g., attending school) developmental tasks. This often results in activity avoidance and, for many, significant disruptions in social and academic domains of functioning [3, 18, 34].

Finally, longitudinal research suggests that pain in childhood predicts anxiety in adulthood, even when pain symptoms have abated [7]. This is consistent with the shared vulnerability model such that common predisposing factors (e.g., anxiety sensitivity) and maintenance factors (e.g., avoidance behavior [35], attentional biases [36]) that are central to both conditions may connote heightened risk for the development and continuation of pain and/or anxiety across the lifespan.

3. School-Related Anxiety and Impairment in Pediatric Chronic Pain

Chronic pain in children and adolescents is associated with impaired school functioning in multiple domains [2, 3, 34, 35, 37–42]. In fact, school absence rates in pediatric chronic pain possibly exceed rates of absenteeism due to other chronic health conditions [34]. Youth with chronic pain who frequently experience periods of missed school often fall behind academically as a result of their pain symptoms [18, 23, 35, 37, 38]. Chronic pain patients also report lower grades and other maladaptive school-related behaviors following the onset of pain [37, 39].

Anxiety appears to be a key driving force behind the school disability and avoidant behavior that often characterizes youth with chronic pain [33, 40]. About one-third of youth with chronic pain exhibit anxiety-related school avoidance [23]. Anxiety is also a robust predictor of difficulties with keeping up academically and concentrating at school [12, 23, 35]. Anxiety has been shown to be a stronger predictor of functional disability than pain severity [23]. Further, in the

context of high levels of anxiety and worry, pain is unrelated to school functioning [40] or overall functional disability [33]. Thus, research suggests that anxiety plays a central role in maintaining school disability by driving school avoidant behavior, thus perpetuating a cycle of avoidance that, in turn, further heightens anxiety [39]. It is not surprising that the coupling of anxiety and pediatric chronic pain creates an especially high risk for school-related disability [22].

Several studies have demonstrated seasonal patterns of pain and anxiety complaints, indicating that these difficulties frequently cooccur, may influence each other, and fluctuate corresponding to the school year [43–46]. For example, Saps and colleagues [46] found that consultations for anxiety and complaints about abdominal pain were most common in the winter months, declining throughout the summer months and steadily rising again in the fall. They speculated that the winter dominance of pain-related and psychiatric complaints in children is attributable to school-related anxiety and stress. Showing a very similar pattern—and drawing the same conclusion—a recent study found that the volume of parent phone calls made to a pediatric pain clinic pertaining to headache and abdominal pain was approximately three times higher during the winter [47].

4. Specific Sources of School Anxiety among Chronic Pain Patients

School is a source of anxiety among youth with chronic pain, supported by the aforementioned evidence of high rates of anxiety and school avoidance exhibited in this population. School anxiety plays an important role in both getting to school and functioning while at school [23, 35]. For example, school anxiety frequently peaks on school day mornings—manifesting in a variety of anxious and somatic symptoms—resulting in parents deciding to let their child stay home from school [12]. When at school, youth with chronic pain may worry about whether pain symptoms will negatively influence their test-taking performance or bother them while trying to participate in other academic or social activities.

Though chronic pain patients understandably have a heightened sensitivity to experiencing physical symptoms when at school (e.g., what if my stomach starts to hurt after I eat my lunch?), school represents a myriad of other sources of anxiety as well. As is to be expected during childhood and adolescence, some pediatric chronic pain patients likely experience some degree of anxiety regarding their grades, performance on standardized tests, and other aspects of their academic performance. Not surprisingly, youth with chronic pain often report feeling as though pain has negatively impacted their school success [39]. It makes sense then that youth with chronic pain, who not only need to grapple with the typical test-related performance stress, also have the additional burden of worrying about the degree to which pain symptoms may distract them during important academic situations. To date, there is no published data establishing the degree to which youth with chronic pain struggle with specific types of academic anxiety, such as test anxiety or performance-related anxiety (e.g., giving speeches in front of class).

The social aspects of school likely also give rise to anxiety. Research suggests that approximately 20 to 25% of youth with chronic pain report elevated social anxiety scores [20]. Likewise, given the high prevalence of public speaking anxiety in childhood [48] it is probable that a good number of chronic pain patients experience heightened fear of speaking in front of others at school—which may occur in the context of class presentations, but also in subtler forms such as raising one's hand during class to ask the teacher a question. Finally, youth with chronic pain may also worry about teachers' perceptions, perhaps sensing that teachers are unsupportive or misunderstand the pain problem. Such concerns are not unwarranted, as teachers have been shown to lack a biopsychosocial framework for understanding chronic pain in childhood [49]. This is concerning given how common it is for chronic pain patients to need to initiate conversations with one or more teachers in regard to classroom accommodations (e.g., requesting permission to leave class to go to the nurse's office), assignment accommodations (e.g., requesting deadline extensions), or school absences.

Social-evaluative concerns are developmentally appropriate during childhood and adolescence. However, chronic pain patients may face additional challenges, such as feeling different than peers due to having a pain condition or finding it challenging to explain their pain condition or reasons for school absences to peers. Children and adolescents with chronic pain may have fewer friends, be more socially isolated, and experience higher rates of peer victimization compared to youth without pain [50]. To the degree that youth with chronic pain perceive social situations at school as threatening, over time, they may develop fear-related avoidance behavior toward school [33].

Forgeron et al. [51] found social information processing differences between youth with chronic pain and healthy controls. Specifically, adolescents with chronic pain showed heightened sensitivity to vignettes depicting potentially nonsupportive social situations. When asked to envision themselves as a healthy friend in vignettes, adolescents with chronic pain indicated that they would have enacted more supportive behaviors toward a chronic pain vignette character. The authors suggested that youth with chronic pain may expect more supportive behaviors from their friends and when they perceive friends at school as being unsupportive may distance themselves socially and avoid particular social situations [51].

In a recent study examining adolescents' interpretation biases, it was found that those who reported greater pain catastrophizing and more recent pain complaints endorsed more negative interpretations (and rejected more benign interpretations) of ambiguous situations regarding pain and bodily threat [52]. Interestingly, these adolescents showed the same pattern for ambiguous *social situations*, suggesting a generalized rather than pain-specific interpretation pattern—and a pattern that would be expected of those experiencing anxiety in general or social anxiety specifically. Though speculative, it may be that youth who are vulnerable to interpreting ambiguous situations as threatening tend to

apply such interpretations broadly. This would be consistent with the shared vulnerability model of chronic pain and anxiety [27, 53], as well as research suggesting that youth with chronic pain have more difficulty attending to and interpreting social cues [54]. In other words, youth at increased risk for developing negative bodily threat interpretations—a risk factor for the development of chronic pain—may exhibit similar cognitive biases that increase their risk for the development and/or maintenance of anxiety disorder symptoms.

Parent influences are also important to consider. Robust evidence demonstrates that parental protectiveness in response to pain confers risk for school impairment in youth with chronic pain [55] and has been shown to mediate the relationship between parental pain catastrophizing and child school attendance rates and general school impairment [56]. Furthermore, there is evidence to suggest that parental distress operates, at least in part, through amplification of child anxiety. For example, etiological studies suggest that parental anxiety is a crucial factor in the development of childhood anxiety [57, 58] and has been shown to predict children's physiological reactivity following stress [59]. These findings underscore the importance of evaluating parental anxiety and parental responses to children's school anxiety symptoms, as both are likely important contributors to the child's affective and behavioral responses to stressors occurring in the school environment.

In summary, school represents a context in which youth with chronic pain experience significant anxiety and school-related functional disability. There are many unique sources of school-related anxiety, such as fear of academic failure or inability to keep up with demands, fear of negative peer evaluation, and fear of experiencing physical symptoms at school. Knowing that youth with chronic pain generally experience elevated school anxiety is not specific enough to guide intervention efforts. Thus, all potential sources of school anxiety should be assessed because each one may be a unique treatment target [22, 23].

5. Assessment of School Anxiety: Current Practice and Limitations

The primary measurement issue stalling efforts to understand school anxiety in pediatric pain is simple—there are no instruments designed for this particular purpose. A measure specifically focused on school anxiety has yet to be developed or normed for use in pediatric pain settings. Thus, despite growing recognition of the importance of evaluating school anxiety in pediatric chronic pain [20, 22], clinicians and researchers lack a comprehensive evidence-based approach for doing so.

Current methods for assessing anxiety among pediatric pain patients consist of using either broadband measures of psychopathology symptoms that include one or more anxiety-related subscales, or narrow-band anxiety measures, such as the Multidimensional Anxiety Scale for Children (MASC) [60], Revised Children's Manifest Anxiety Scale (RCMAS) [61], or the Screen for Child Anxiety-Related Emotional Disorders (SCARED) [62]. One key concern regarding this practice is that although these anxiety measures have demonstrated strong psychometric properties in the general population or in treatment-seeking psychiatric samples, few have been validated for use in pediatric settings [63]. This calls into question whether current measures of anxiety—regardless of their psychometric properties in other samples—are appropriate for youth with pediatric chronic pain.

Existing anxiety measures also lack adequate content validity for the assessment of *school* anxiety specifically. For example, the MASC contains only two items that explicitly mention school as a context for anxiety symptoms ("I worry about being called on in class" and "I try hard to obey my parents and teachers"). Other MASC items may apply to how the child feels at school but do not specifically refer to school situations or school peers (e.g., "I worry about what other people think of me"). Similarly, though the SCARED has shown good evidence of internal consistency and construct validity when used in a treatment-seeking pediatric chronic pain sample [22], the primary caveat for its usage is its lack of an appropriate school anxiety subscale. The SCARED School Phobia subscale showed poor internal consistency—likely due to problems with content validity, in terms of both item content and scope. Specifically, the School Phobia subscale comprises only four items; thus it lacks the necessary breadth to adequately measure a multifaceted construct like school anxiety. When used in pediatric pain settings, the fact that some School Phobia items also mention specific pain symptoms is especially problematic [22].

6. Future Directions in the Assessment of School Anxiety

Current assessment approaches limit our understanding of the precise fears of youth with chronic pain. This has led to a call for more research to address gaps in the assessment of school anxiety [20–22]. Given the limitations of using broad anxiety measures to gauge school anxiety, one possibility would be to expand the school-related content of existing self-report anxiety measures, such as the SCARED. An arguably better solution would be to develop a new, multifaceted school anxiety measure—one that includes items assessing fears pertaining to academic performance, such as test anxiety and falling behind on assignments, negative teacher evaluations, and peer relationships—that could be validated for use in pediatric chronic pain.

Because anxiety in pediatric chronic pain may manifest itself in ways that existing instruments were not developed to evaluate, it would be advantageous to gather input from pain patients to ensure that item content is relevant to and representative of the way in which school anxiety is experienced. For example, though not typically included in measures of school anxiety in nonmedical populations, it may be clinically relevant to include content pertaining to fears about pain symptoms interfering with academic performance or concerns about having to ask the teacher to go the nurse's office. This focus on content validity would help determine the most relevant content to include, the irrelevant content

to exclude, and how to best achieve content balance (i.e., avoiding excessive over- or underemphasis of some aspects of social anxiety) [64]. These are important issues regardless of whether an existing anxiety self-report measure is modified or a completely new instrument is developed.

Existing measures of related constructs, such as school refusal, may also be relevant for capturing behavioral complications associated with school anxiety in pediatric chronic pain. The School Refusal Assessment Scale-Revised (SRAS-R) [65] measures four hypothesized functions of school refusal, including avoidance of stimuli that provoke negative affect and escape from aversive social situations. Similarly, the School Refusal section of the Anxiety Disorders Interview Schedule (ADIS-IV) [14] assesses whether a child has difficulty going to or staying at school and, if so, queries potential reasons for school refusal. Given that these measures have not been validated for use with pediatric pain patients, or more broadly, for youth with cooccurring anxiety and chronic medical conditions, items will likely need to be tailored. For instance, the SRAS-R may require the modification and/or addition of content that more clearly distinguishes school avoidance due to pain symptoms versus other (nonpain) factors. Some youth with chronic pain may report that school avoidance occurs exclusively in response to pain symptoms, whereas others may be able to identify academic and social factors that also keep them from going to school (e.g., they feel as though they do not have many friends at school; they are afraid of tests or riding the school bus).

It may also prove useful to explore other measures that have been developed particularly for pediatric chronic pain that may capture some aspects or correlates of school anxiety. Measures of pain anxiety, pain catastrophizing, and fear of pain, while not focused on school situations specifically, may be helpful when developing school anxiety measures in this population. Such measures would make it possible to distinguish youth whose fear and avoidance are limited to the school context from those who manifest a more generalized pattern of pain avoidance. This would strengthen the discriminant validity of school anxiety measurement.

Given the psychometric issues inherent to gathering data from a single source [66], it is imperative to include multiple perspectives. Teachers and other key school personnel are uniquely positioned to provide insights based on their direct observations of the child's behavior at school, including how the child functions in the classroom and in his or her interactions with peers. Parent-proxy reports are valuable in discerning the child's school-related anxiety symptoms at home, such as heightened anxiety on school day mornings compared to weekends, distress about upcoming tests, and difficulty keeping up with homework assignments.

Novel measurement approaches may also be needed due to the numerous challenges inherent to assessing school-related fears in pediatric chronic pain with self-report methodology. For instance, youth with chronic pain often underreport anxiety [21, 33, 38]. Logan and colleagues [21] found that 31% of their pain sample likely minimized anxiety on a self-report measure by responding in a socially desirable manner. As mentioned previously, children with chronic pain have shown to be less likely to *self-report* anxiety but responded to a threatening stressor with the same degree of anxiety and physiological stress reactivity as children with anxiety disorders [31]. Moreover, youth often verbally report wanting to attend school and experiencing minimal anxiety, despite exhibiting school avoidance behavior [35]. It has been argued that some youth with chronic pain who experience school anxiety may have difficulty identifying or articulating specific precipitating stresses. Other youth may be unaware of the extent of their school anxiety, identifying pain symptoms as the *sole* reason for not being able to attend school [12].

6.1. Potential Utility of Novel Implicit Measures. Multiple methods are needed to evaluate different facets of any problem. Given the limitations of self-report measures of school anxiety in the context of pediatric pain, novel *implicit* measures may represent an important assessment tool to circumvent youths' difficulty with overtly discussing school-related fears and reason(s) for school avoidance. Implicit measures, in conjunction with subjective self-reports, have the potential to shed new light on the way in which school anxiety is experienced in pediatric chronic pain.

Evaluation of implicit school-related *attentional biases* may be a useful approach in discerning the most salient facets of school anxiety. Attentional biases involve implicit, preferential tendencies to orient attention to particular threatening stimuli [67]. Various cognitive theories (e.g., attentional control theory) assert that anxiety is characterized by an attentional bias toward personally relevant, threatening stimuli [68]. Attentional biases have been implicated in both the development and maintenance of anxiety disorders [69–71]. In other words, attentional biases have been shown to be associated with current anxiety symptoms and also confer risk for the development of anxiety [72]. Though extant theories make different assumptions about the precise role that attentional biases play in anxiety (e.g., whether they play a causal role or not), available evidence suggests that attentional biases and anxiety are mutually maintaining [73].

Attentional biases represent a potential mechanism underlying the cooccurrence of chronic pain and anxiety [27, 53]. Attentional biases in the context of school, though implicit, may influence school functioning even when a particular behavior (e.g., school avoidance; [12]) stands in opposition to long-term goals (resuming or maintaining adaptive school functioning). To date, only *pain*-related attentional biases have been examined in pediatric chronic pain [54, 74, 75]. There remains a dearth of research considering other types of attentional biases that may be relevant to pediatric chronic pain patients. When considering *school* as a source of threat in the lives of youth who experience chronic pain, attentional biases for stimuli that become associated with pain and anxiety, such as school-related triggers, may become risk factors for the perpetuation of school anxiety *and* chronic pain symptoms over time [36, 76].

Studies characterizing the mechanism(s) underlying school-related attentional biases exhibited by youth with chronic pain may be important. Eye-tracking methods—which are able to continuously and directly measure attention—are able to assess various patterns of attention. For example, school anxious youth may demonstrate an

attentional bias driven by an *initial orienting bias* that involves a constant visual search of the environment for school-related threat, such that the child's attention is more quickly captured by school-related threatening stimuli relative to other stimuli. Here, the child shows hypervigilance to school threat stimuli. An attentional bias may also be driven by an *attention maintenance bias* involving difficulty disengaging from school-related threat, wherein, after the child fixates upon a school-related stimulus, he/she is unable to shift attention away from the threatening stimulus. This pattern suggests excessive cognitive processing of threat. Finally, an attentional bias may be characterized by a *vigilance-avoidance* pattern that involves an orienting bias toward school-related threat (momentary fixation upon a stimulus) followed by avoidance of the stimulus. Here, the child scans the environment for a threat stimulus, and once they find it, they actively avoid it.

Notably, all three patterns have been identified in the literature. While the above hypothetical scenarios share many facets of cognitive processing, they are distinct enough to warrant scientific inquiry so as to advance our understanding of the specific pattern(s) of school-related attentional biases (e.g., hypervigilance or vigilance-avoidance) that may exist in pediatric chronic pain. It is possible that particular patterns of school-related attentional biases connote a higher risk for school anxiety. For example, based on recent work in test anxiety [77], it is plausible that youth with chronic pain who show a pattern of early attentional engagement followed by avoidance of school-related threat are at particular risk for school anxiety.

7. Conclusion

Both chronic pain and school anxiety in childhood are associated with concurrent and long-term impairment [41, 78–80]. An evidence-based approach for assessing school anxiety in pediatric chronic pain is needed, as existing measures fail to adequately capture this specific form of anxiety [20, 22, 81]. More research is needed to improve upon or develop new self-report measures of school anxiety. Implicit measures, in conjunction with subjective self-reports, may have the potential to shed new light on the way in which school anxiety is experienced in pediatric chronic pain.

Conflicts of Interest

The author reports no conflicts of interest.

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