BABEŞ-BOLYAI UNIVERSITY
FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES
DOCTORAL SCHOOL "EVIDENCE-BASED ASSESMENT AND PSYCHOLOGICAL INTERVENTIONS"

Ph.D. THESIS

A TRANSDIAGNOSTIC APPROACH FOR PAIN AND EMOTIONAL DISTRESS. THE ROLE OF PAIN CATASTROPHIZING

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-Summary-

CLUJ-NAPOCA
2019

Table of Contents

Key words: The Transdiagnostic Model; Pain; Emotional Distress; Cognitive-Behavioral Therapy; Virtual Reality

CHAPTER I. THEORETICAL BACKGROUND

1.1. Introduction and Research Topic

Pain was traditionally defined as a response to stimulation of specific noxious receptors, a sensory experience which might occur after physical injury or from progressive disease (Asmundson, Wright, & Stein, 2004). As literature noticed, this perspective assumed that the relationship between nociceptor activity and pain experience is invariant; therefore, nociceptive input will always conduct to pain (Asmundson & Katz, 2009). However, since a number of emotional consequences were studied in association with pain, research indicated that pain experience has two co-occurring components, specifically an affective and a sensorial dimension (Meesters, Vancleef, & Peters, 2019). It is now understood and widely accepted that pain is not a consequence of the intensity of nociceptive stimulation, but is a complex perceptual experience (Rhudy, Williams, McCabe, Rambo, & Russell, 2006; Wang, Jackson, & Cai, 2016). Contemporary models of pain assume that it is determined by sensory, as well as psychological and social influences (Asmundson & Katz, 2009; Meesters, Vancleef, & Peters, 2019).

It is well documented in the literature that pain, especially when it becomes chronic, is a complex and multifaceted phenomenon. Prevention of chronic pain would be attained by understanding the processes involved in the transition from acute to chronic pain (Lavand'homme, 2011). Research underlined that besides poor regenerative capacity of nerves, 33% of patients who developed chronic pain share a common psychological profile, defined by catastrophic thinking, dysfunctional emotions, and low levels of pain tolerance (Lavand'homme, 2011; Nicholls et al., 2018).

Given that pain relief is the ultimate objective, multiple treatments were developed in order to increase patient's well-being (Reid et al., 2011). Pharmacological, psychological, and social factors are frequently employed in pain management, as international guidelines recommend (NICE, 2018). Among the psychological interventions, multicomponent programs appear to be more useful in the management of both mental illnesses and chronic medical symptoms and conditions, such as depression, migraine, headache, chronic pain, and inflammatory bowel disease (Prince et al., 2007). Namely, treatments within the cognitive behavioral therapy framework (CBT; Beck, 1979) have shown the strongest empirical support for a broad range of psychopathology and pain conditions (Butler, Chapman, Forman, & Beck, 2006) and it proved to be particularly effective in cases where psychopathology and pain co-occur (Jia & Jackson, 2016; Asmundson & Katz, 2009). Nevertheless, the field of psychological treatment for pain and distress received considerable benefits from the development of information and communication technologies. For example, virtual reality (VR) interventions are being used in the treatment of psychological disorders and pain, improving the effectiveness of some specific components of treatment (Herrera, Jordan, & Vera, 2006).

1.2. Relevance of Research Topic

Pain is a common symptom in a broad category of malignant or non-malignant disorders (Svendsen et al., 2005). In the first years after oncological treatment, it is considered a side effect of treatment, or if it became chronic, a consequence of multiple factors (Glare et al., 2014). Longitudinal data show that approximately 5% to 10% of cancer survivors have chronic severe

pain that affects functioning and the approach to pain management in these patients is mainly based on pharmacotherapy (Glare et al., 2014). However, the efficacy of pharmacotherapy is limited for cases where psychopathology co-occur, while CBT has significant results (Asmundson & Katz, 2009).

Also, research data based on 46 000 subjects found that 19% of individuals included in the study had chronic pain (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006) and it was estimated that by 2030 almost 171 million Americans will be living with multiple chronic medical conditions (LeRoy et al., 2014), while 10% to 20% will have major depressive or anxiety disorders as comorbidities (Evans et al., 2005). As previously mentioned in the literature, the understanding of particular risk factors and the need for interventions that target pain and psychopathology as comorbidity is particularly challenging and strongly important for healthcare community (Gatchel, 2004; Reis et al., 2019).

Psychological interventions are useful for patients with acute pain, who follow painful medical procedures, or for patients who developed chronic pain in reducing the associated distress (Gatchel et al., 2018). Anxiety and depression symptoms were the main emotional difficulties associated with chronic pain (Tsang et al., 2008). Comorbidity of medical illnesses and emotional disorders negatively affects symptom distress, quality of life, overall function, and it will lead to higher healthcare expenses (Dindo, Van Liew, & Arch, 2017). It is known that previous severity of pain and emotional distress episodes represent a risk factor for future pain and distress (Tunks, Crook, & Weir, 2008).

1.2.1. The Transdiagnostic Perspective

For the advance in the field and for a better understanding of the theoretical model explaining the generation of pain and emotion, research should focus on the features that would sustain a greater understanding of the processes involved in both conditions (Linton, 2013). The transdiagnostic approach for pain and emotion assume that development and maintenance of specific observed symptoms are predicted by cognitive factors (Linton, 2013; Mansel, Harvey, Watkins, & Shafran, 2009). Moreover, this perspective suggest that common psychological processes might explain both pain and emotion (Le Borgne, Boudoukha, Petit, & Roquelaure, 2017). Since pain and emotional distress appear to be strongly connected processes, a transdiagnostic approach would offer many advantages in terms of research and practice, such as the flexibility in delivery of psychotherapeutic interventions, by focusing on the identification and development of intervention techniques, and by integrating of psychotherapeutic services in different health care settings (Dindo, Van Liew, & Arch, 2017). As a consequence, from a cognitive approach, pain catastrophizing has been found as a possible shared predictor that may explain pain and the associated distress variance across different populations (Crombez et al., 2012; Reis et al., 2019).

Moreover, the practical and theoretical implications of transdiagnostic perspective on pain and emotion consist in improved knowledge regarding the common processes involved, with important benefits for clinical interventions (Linton, 2013; Le Borgne et al., 2017). This approach is similar with the concept of crossover treatments (Kwekkeboom et al., 2010). As Kwekkeboom et al. (2010) noted, crossover interventions describes treatments that were efficacious "for more than one of the cluster component symptoms and may be beneficial in treating the symptom cluster as a whole, with a broad spectrum of effects on other symptoms in the cluster" (p. 2). Where there is a large spectrum of effects on other symptoms in the cluster, Kwekkeboom (2010) noted that

"the symptoms may share a common etiology, diminishing one symptom may prevent exacerbation of the others, and a single intervention may be indicated for more than one symptom" (p. 2). Kwekkeboom (2016) also suggested that the generation of crossover treatments has the possible benefit of using a single intervention to simplify intervention, which may reduce costs. The transdiagnostic model offers the possibility to address some other critical factors associated with pain, such as anxiety and depression, which may complicate and increase the risk for future pain and psychopathology (Allen, Tsao, Seidman, Ehrenreich-May, & Zeltzer, 2012).

1.3. Current Status of the Field

1.3.1. Transition from Acute to Chronic Pain: Pain Catastrophizing

Pain catastrophizing is one of the most studied cognitive feature that was found to explain the transition from acute to chronic pain (Nicholls et al., 2018; Sullivan, Rodgers, & Kirsch, 2001; Vlaeyen & Linton, 2012). It is a component of almost any CBT interventions for pain population (Jensen, Turner & Romano, 2001; Turner & Aaron, 2001). Pain catastrophizing may be considered a risk factor, highly predictive of psychopathology (Le Borgne et al., 2017). Based on cognitive behavioral therapy (Beck, 1979), literature defines pain catastrophizing as a dysfunctional pain-related cognition, or as a negative thinking pattern which might be activated during a painful event or when pain is anticipated (Sullivan, Rodgers, & Kirsch, 2001). It is measured by Pain Catastrophizing Scale, as a unitary construct (PCS; Sullivan, Bishop, & Pivik, 1995). It contains three different dimensions: magnification, rumination, and helplessness (Sullivan, Bishop, & Pivik, 1995). Also, it is one out of the four irrational processes. According to Ellis (1994) there are two types of beliefs relevant for mental health: irrational beliefs and rational beliefs. More specifically, Ellis (1994) highlighted four irrational and four rational thinking patterns: demandingness vs. preferential thinking; awfulizing/ catastrophizing vs. nuanced evaluation of badness; frustration intolerance vs. frustration tolerance; and global evaluation of self, others, life vs. unconditional acceptance of self, others, life (see for details David, 2003; David, Szentagotai, Lupu, & Cosman, 2008; Dryden, David, & Ellis, 2010).

1.3.2. Pain Catastrophizing as a Core Feature of Cognitive Behavioral Therapy for Pain and Distress

Cognitive behavioral therapy is based on the concept of rational and irrational beliefs (Ellis, 1994) and states that one's emotions related to certain activating life events are significantly mediated by the beliefs that one holds about these events (David, 2003; David, Szentagotai, Lupu, & Cosman, 2008; Dryden, David, & Ellis, 2010). CBT is described as a system of psychotherapy with a powerful theoretical and empirical support, efficacious either alone or as an adjunct to medication, and provides a prophylaxis against relapse and recurrence (Beck & Dozois, 2011). It is organized around the ABC trans-diagnostic model (David et al., 2008; Ellis, 1964).

Given the multiple benefits that a unifying approach may bring to the field, in terms of research and clinical practice, pain catastrophizing has been investigated as a potential core mechanism of CBT interventions for pain, while in numerous correlational and predictive designs is having a significant impact in both pain and emotional distress, but with a high heterogeneity of results (Nicholls et al., 2018; Vlaeyen & Linton, 2003). Based on the positive results from clinical studies, cognitive behavioral therapy became the most dominant empirically supported treatment

for a broad category of emotional disorders (David, Cristea, & Hoffman, 2018; Morley, 2011).

Catastrophizing has been treated recently as an important treatment target in different disorders: panic, phobia, health anxiety, obsessive–compulsive disorder, posttraumatic stress disorder, and traumatic brain injury (Gellatly & Beck, 2016). Given the need to focus on specific common cognitive factors (Mehl et al., 2015), it is important to add more data that highlight its role in prevention and psychotherapeutic interventions for population who suffers from pain and emotional distress in more complex designs, to investigate its impact on both the sensorial and the emotional components of pain, and to emphasize whether it is an important feature to target for increasing treatment effectiveness for pain and emotional comorbidities across different types of pain (Hanscom et al., 2015).

1.3.3. Virtual Reality in the Study of Pain and Distress Reduction

As previously noted, CBT focused on cognitive change, behavioral modification/ physical therapy, exposure or acceptance may significantly impact on pain and pain-related outcomes (Nicholls et al., 2018; Asmundson & Katz, 2009; Majeed & Sudak, 2017). Although significant, CBT for pain is often criticized for its low to moderate effect sizes (Majeed & Sudak, 2017). Research suggests that a possible solution to improve treatment efficacy lays on the new development of technology, such as virtual reality tools (VR; David, Matu, & David, 2013). The use technology in the field of psychological interventions has rapidly developed in recent years (David, Matu, & David, 2013). Virtual reality tools may help health professionals to attain different objectives. Generally, it was used mainly to decrease pain, unpleasantness, and anxiety associated with common painful cancer procedures and treatments, or to decrease symptom distress, to reduce general distress, and to reduce the perceived time spent during oncological treatment procedures (Li et al., 2011). Recent data indicate that relaxation in VR could be a potential new treatment for persistent pain (Chirico et al., 2016). Specifically, natural scenes may have a strong impact, given that they provide relaxation both objectively and subjectively in a stressful experience, improving emotional well-being and quality of life in patients (Anderson et al., 2017). These are important results, since negative emotions are a barrier in achieving therapeutic goals, causing low motivation and low self-efficacy (Herrero, Garcia-Palacios, Castilla, Molinari, & Botella, 2014).

CHAPTER II. OBJECTIVES AND GENERAL METHODOLOGY

This thesis presents a theoretical framework of the transdiagnostic approach, integrating the research on pain and emotional comorbidities, and extends on investigating whether similar predictors might be related to co-occurring pain and emotional distress. We also aimed to analyze the relationship between pain and emotional distress (anxiety and depression) in oncological patients, as well as integrating new tools for pain and distress reduction, such as virtual reality, for patients who suffer from cervical cancer. A number of studies have been designed to attain the goals outlined below.

1) Our first objective is to highlight the impact of pain catastrophizing on pain intensity and general distress for patients who suffer from different types of pain, and to investigate the possible moderators of these associations (Study 1).

2) Also, we aim to make a step further to the transdiagnostic perspective for pain and emotion, by emphasizing systematic similar associations of pain catastrophizing with pain and distress (Study 1 and Study 2).

3) Our third objective is to test the link between pain catastrophizing and relevant pain-related outcomes. A randomized experimental study was employed to attain this objective, analyzing the impact of pain catastrophizing and state anxiety on targeted outcomes (Study 2), and a longitudinal study on a clinical sample, investigating the impact of pain catastrophizing, coping strategies, and initial psychopathology level on targeted outcomes (Study 3).

4) Also, we aim to expand on the paths that explain pain tolerance and pain-related anxiety, by exploring pain catastrophizing and state anxiety as possible predictors. Drawing on the previous findings, response expectancies and their impact on pain intensity were tested as potential mechanisms (Study 2).

5) The fifth objective aims to explore pain catastrophizing, specific coping strategies, baseline anxiety, and baseline depression in predicting adjustment prospectively from the point shortly following breast surgery through the first year. We aim to investigate adjustment in time in terms of anxiety, depression, quality of life, pain intensity, and pain tolerance (Study 3).

6) Another goal of this thesis aims to test whether pain catastrophizing predicts pain-related outcomes when psychopathology and coping style are taken into consideration (problem-focused, emotion-focused, dysfunctional coping) (Study 3).

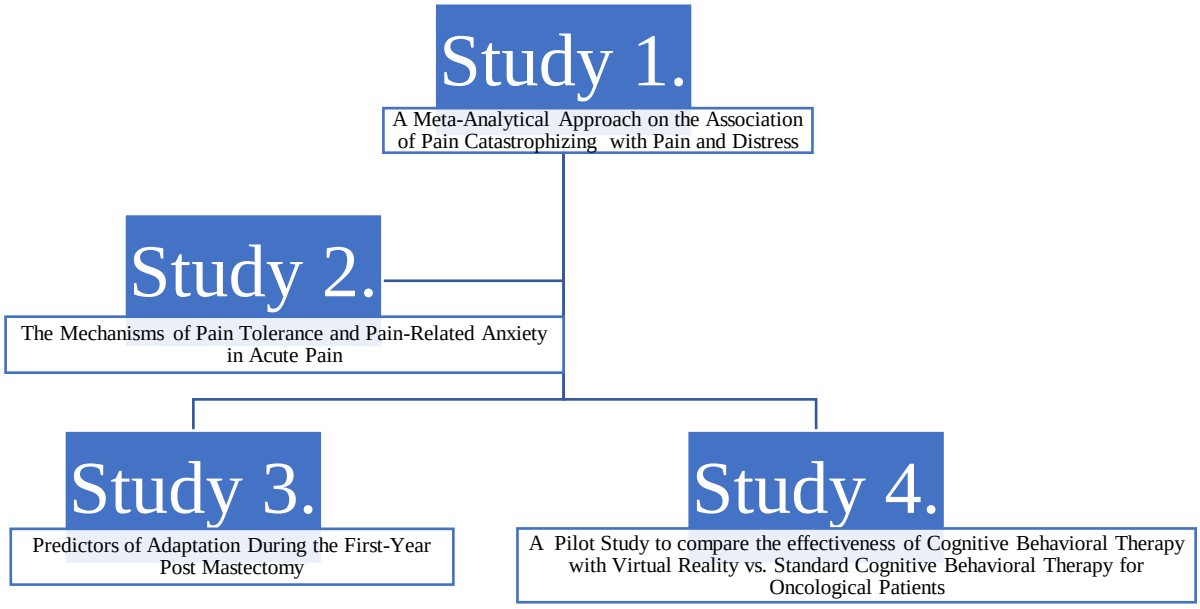
7) Also, we aim to integrate a new method of relaxation within the CBT protocol and to compare its effectiveness with standard CBT. We compared CBT VR with CBT Standard, targeting anxiety, depression, quality of life, pain intensity, and pain tolerance in hospitalized cervical cancer patients (Study 4).

Specific hypotheses were formulated for a number of specific aims of this thesis. Also, given the relatively new perspective on pain catastrophizing as a transdiagnostic predictor for pain and emotion, some exploratory analyses were conducted.

In order to meet the first two objectives of the theses, our first study was a meta-analysis, which included samples of adults with acute and chronic pain, and experimental studies conducted on healthy samples. We responded to the second, third, and forth objectives by developing an experimental design on healthy adults. Anxiety was manipulated and pain was induced in order to emphasize the impact of pain catastrophizing in the presence of a perceived threat. The last objectives of this thesis were attained by developing the third and fourth study on clinical population. Namely, hospitalized oncological patients were assessed on the cognitive and emotional variables of interest (anxiety, depression, quality of life, pain intensity, and pain tolerance) for our research. Specifically, the third study was developed to predict adjustment in time after mastectomy. Also, we investigated the variance added by pain catastrophizing in predicting the targeted outcomes. The fourth study tested a CBT intervention for changing the supposed mechanism identified by our previous studies, and the introduction of a new tool for relaxation in clinical patients. Comparative analyses were conducted to investigate whether superior results may be found when VR is added to standard CBT for oncological patients. Considering the transdiagnostic perspective of pain and related emotions (Linton et al., 2013), this methodology is expected to generate results that would also be of relevance for the clinical practice and to inform future research. Thus, the general methodology was developed assuming pain catastrophizing as a predictor for both pain and emotion, with similar paths and interconnected

symptoms. This perspective challenges the assumption that pain catastrophizing is of interest mainly for the sensorial dimension of pain, namely pain intensity, and provides support for the transdiagnostic model. All the participant included in this thesis signed an informed consent and all the studies meet the ethical guidelines of the hospital where the data were collected.

The Schematic Structure of the Project.



CHAPTER III. ORIGINAL RESEARCH

STUDY I. A meta-Analytical Approach on the Association of Pain Catastrophizing with Pain and Distress

3.1.1. Introduction

Studies highlights that pain catastrophizing is associated with pain intensity, psychological distress, and reduced functioning (Gellatly & Beck, 2016). Specifically, moderate associations were observed between pain catastrophizing and dysfunctional emotions, such as anxiety (Granot & Ferber, 2005; Pinto, McIntyre, Almeida, & Araújo-Soares, 2011), fear of pain (Vlaeyen & Linton, 2012), depression (Sullivan, Neale, & Kendler, 2000), and other negative mood indices (Sullivan, Rodgers, & Kirsch, 2001). Because the transdiagnostic approach has not been used to explain pain and the associated emotions (Linton, 2013), literature emphasized the need for focusing on the similar associations of pain and emotional distress with a common underlying feature (Harvey, Watkins, Mansell, & Shafran, 2004). Focusing on similarities, rather than on differences among these factors, should facilitate a step toward simplifying treatments for pain and distress (Harvey et al., 2004).

The present study

Given the high inconsistence of the association strength of pain catastrophizing with a series of pain related outcomes across different types of pain, we decided to summarize the data with the meta-analytic procedure in order to highlight a possible shared mechanism for pain and emotional distress. Identifying the pain catastrophizing as a common mechanism would facilitate a step forward to a transdiagnostic perspective. Since catastrophizing has been treated recently as a core predictor in different disorders, such as pain, panic, phobia, health anxiety, obsessive–compulsive disorder, posttraumatic stress disorder, and traumatic brain injury (Gellatly & Beck, 2016), it is important to highlight its role for prevention and psychotherapeutic interventions also in the case of population who suffers from pain. Therefore, we focus on the impact of pain catastrophizing for patients who suffer from different types of pain. Moreover, there is no recent meta-analytic study to summarize the results of correlational studies on different contexts, such as acute pain, chronic pain, and experimental pain on healthy participants.

3.1.2. Methods

Literature search

Relevant studies were selected through a systematic search on PsycInfo, PubMed, Scopus, and Web of Science, using the following search terms: catastroph* OR awful*, maladaptive cognitions*, distress AND pain. The computer identification algorithm was set to find articles between 1990 and March, 2017.

Selection of studies

We included in the meta-analysis only studies that meet the following inclusion criteria: a) investigate the relation of catastrophizing with pain intensity and general distress; b) English language publications; c) utilize a self-report measure of pain catastrophizing, emotional distress, and pain intensity; d) are conducted on adult population; d) have sufficient data to compute the

effect size. There were 63 studies which satisfied the inclusion criteria and were selected in this meta-analysis.

Given the high heterogeneity, we grouped the outcomes in two categories: *general distress* and *pain intensity.* In the first category, general distress was coded on several outcomes: anxiety (health anxiety, anticipatory anxiety, state/trait anxiety, and pain anxiety), depression (depression, and depressive mood), fear of pain, and emotional distress (negative affectivity, negative mood, and general distress). In the second category, pain intensity was referred as reported pain, sensorial pain, and pain severity. Pain intensity was measure by self-report scales.

We coded as moderators several aspects: type of pain (chronic pain, acute pain, and experimental pain on healthy participants), due to the significant differences underlined by the literature (Grichnik & Ferrante, 1991); the instrument used to measure the predictor; the instrument used to measure the outcome; sample size; percentage of unemployed participants; and percentage of women.

Procedure

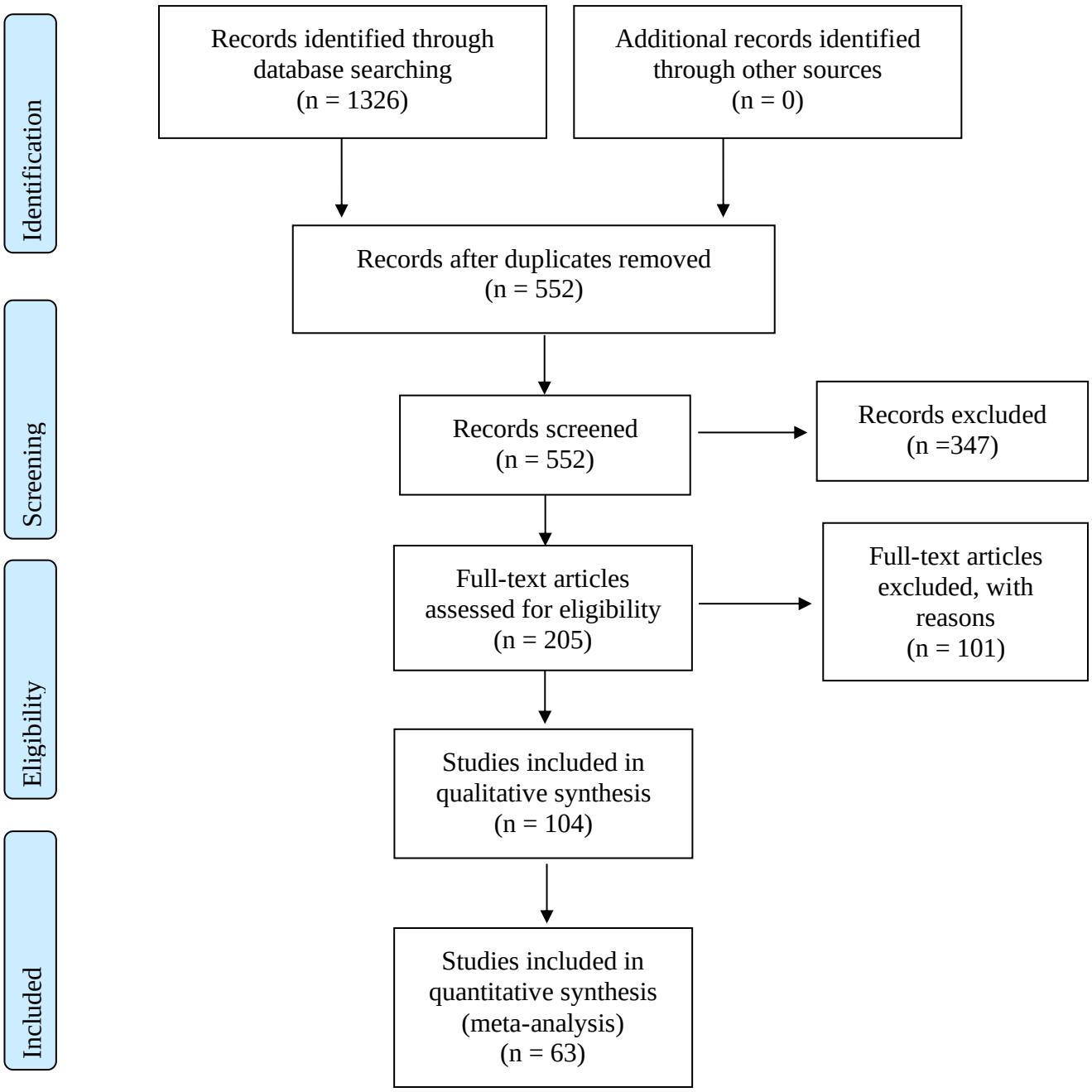
The computations were conducted by using Comprehensive Meta-Analysis Software (Borenstein, Hedges, Higgins, & Rothstein, 2013). Bivariate correlations (*r*) were computed to emphasize the effect sizes of included studies. Fisher`s Z transformations were used for all effect size computations. Preliminary analysis for effect sizes were conducted. Effect sizes were examined for outliers. As Hunter & Schmidt (2004) concluded, extreme values can cause artificial within-group heterogeneity of individual effect sizes. Also, we conducted publication bias analyses to investigate whether small effect sizes or studies with no significant results had a lower chance of getting published. For this objective, we used Trim and fill method and funnel plot investigation. The lack of publication bias is represented by a symmetrical funnel plot. Trim and fill analysis assume that studies with small effect size are less likely to be published.

Given the high heterogeneity observed in the literature, random effects model was used to calculate the mean effect sizes. We calculated the I^2 statistic to assess the homogeneity of effect sizes.

Categorical moderators, namely type of pain (acute pain, chronic pain, experimental pain on healthy participants), instrument used to measure the predictor (PCS vs. CSQ), and the instrument used to measure the outcome, were evaluated with Cochran's Q values with effect sizes based on correlation coefficient. Meta regression was used to examine the continuous moderator variables: percentage of women, sample size, and percentage of unemployed participants. Also, *r* values and an associated *p* were reported for each of the variables analyzed.

3.1.3. Results

Figure 1.
PRISMA Chart



The PRISMA Group, 2009.

The search procedure lead to 1326 studies (see Figure 1). After duplicates were removed, we investigated whether a study is relevant based on the abstract. Following our exclusion criteria

of irrelevant studies (e.g. the screened abstracts indicated reviews on the topic/conference abstract; the study was conducted on children or adolescents; were not English language publications; did not measure both pain intensity and emotional distress; or did not report sufficient data to compute the effect size), 104 studies were analyzed for relevance based of their full text. A total of 63 studies were included in the final meta-analysis.

Main effect size

Overall general distress: The mean effect size of the relation between pain catastrophizing and overall distress was $r = 0.47$ (95% CI 0.41-0.52) for 46 studies. Heterogeneity was high ($I^2 = 87.27\%$) and highly significant. Removal of one outlier lead to an effect size $r = 0.49$ (95% CI 0.44-0.54) and high heterogeneity ($I^2 = 82.29\%$).

Anxiety: The mean effect size of the relation between pain catastrophizing and anxiety was $r = 0.48$ (95% CI 0.37-0.58) for 20 studies. Heterogeneity was high ($I^2 = 90.08\%$) and highly significant.

Depression: The mean effect size of the relation between pain catastrophizing and depression was $r = 0.51$ (95% CI 0.41 - 0.59) for 23 studies. Heterogeneity was high ($I^2 = 91.10\%$) and highly significant.

Fear of pain: The mean effect size of the relation between pain catastrophizing and fear of pain was $r = 0.57$ (95% CI 0.36 - 0.73) for 8 studies. Heterogeneity was high ($I^2 = 95.76\%$) and highly significant.

Emotional distress: The mean effect size of the relation between pain catastrophizing and emotional distress was $r = 0.45$ (95% CI 0.37-0.53) for 24 studies. Heterogeneity was high ($I^2 = 88.61\%$) and highly significant.

Pain intensity: The mean effect size of the relation between pain catastrophizing and pain intensity was $r = 0.41$ (95% CI 0.34-0.46) for 48 studies. Heterogeneity was high ($I^2 = 86.92\%$) and highly significant. Removal of one outliner lead to an effect size $r = 0.42$ (95% CI 0.36 - 0.46) and heterogeneity ($I^2 = 86.31\%$) (Table 1).

Table 1.
Main effects

Outcome	R	C.I	No. of studies	I
General distress	0,49	0.44-0.54	45	0,82
Anxiety	0,48	0.37-0.58	20	0,9
Depression	0,51	0.41-0.59	23	0,91
Fear of pain	0,57	0.36-0.73	8	0,95
Emotional distress	0,45	0.37-0.53	24	0,88

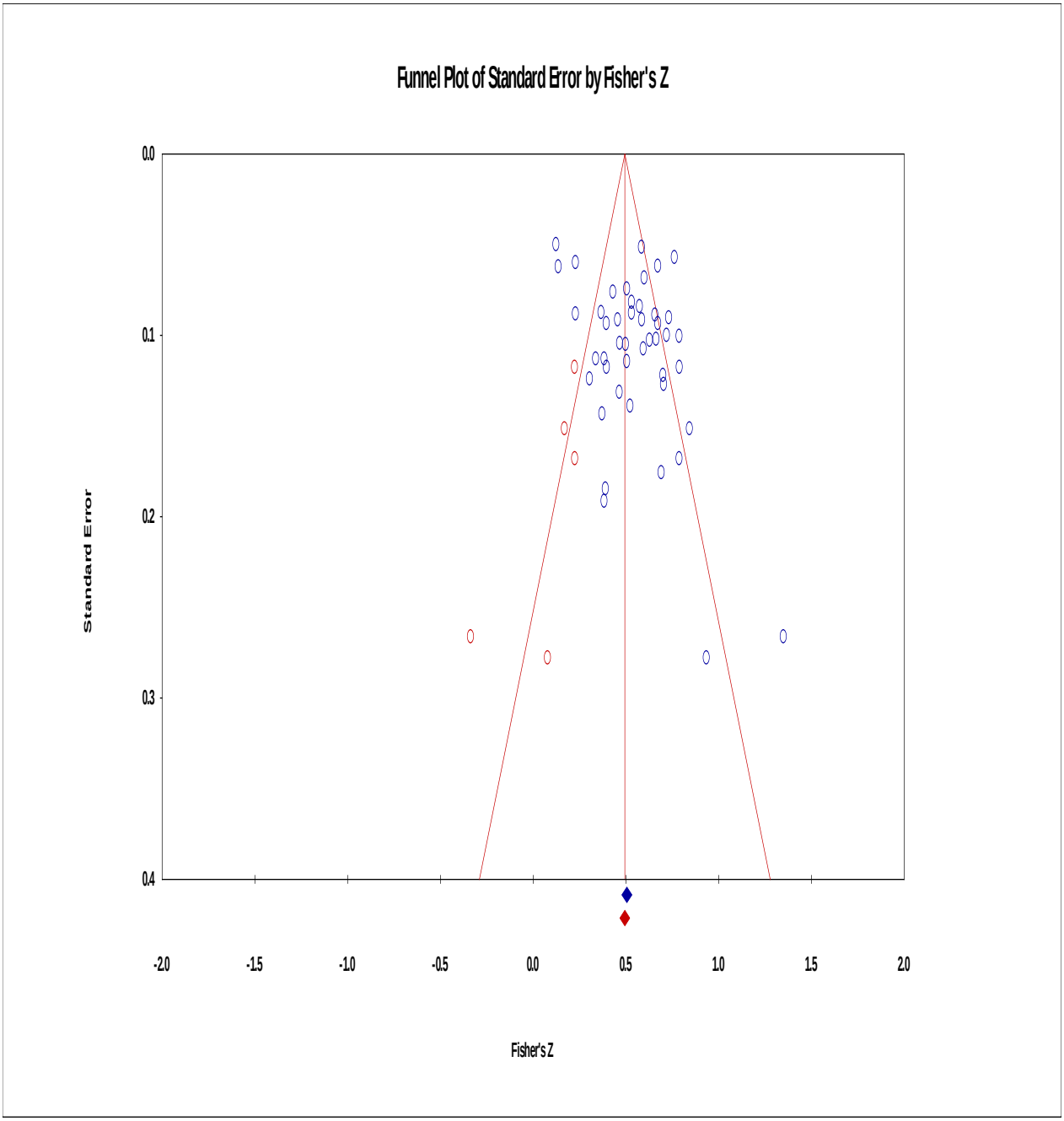
Pain intensity	0,41	0.34-0.46	48	0,86

Publication bias for overall general distress

Inspection of the funnel plot and the Duval and Tweedie trim and fill procedure indicated significant publication bias for overall general distress. There were 5 imputed values which changed the effect size from $r = 0.45$ to $r = 0.44$ (95% CI 0.42 - 0.44), Q = 278.341. Eggar's test was also significant (intercept 2.29, 95% CI 0.30 – 2.29, $p = 0.02$). For anxiety, there were 1 imputed value, which did not change the effect size, $r = 0.35$ (95% CI 0.31 - 0.38), Q = 191.691. Eggar`s test was also significant (intercept 5.32, 95% CI 2.76 – 7.88, $p = 0.00$). For depression, there were 6 imputed values, which changed the effect size from $r = 0.43$ to $r = 0.39$ (95% CI 0.36-0.42), Q = 298.395. Eggar`s test was also significant (intercept 4.08, 95% CI 0.65 – 7.52, $p = 0.02$). For fear of pain, there were no imputed values, the effect size was $r = 0.51$ (95% CI 0.46 - 0.55), Q = 143.324. Eggar`s test was not significant (intercept 5.07, 95% CI -6.19 – 16.35, $p = 0.31$). For emotional distress, there was 1 imputed value, the effect size was $r = 0.41$ (95% CI 0.38 - 0.44), Q = 212.618. Eggar`s test was significant (intercept 3.01, 95% CI -0.65 – 6.69, $p = 0.10$) (Figure.2).

Figure 2.

Funnel plot of publication bias. Funnel plot of publication bias for the effect size of the association of pain catastrophizing with general distress

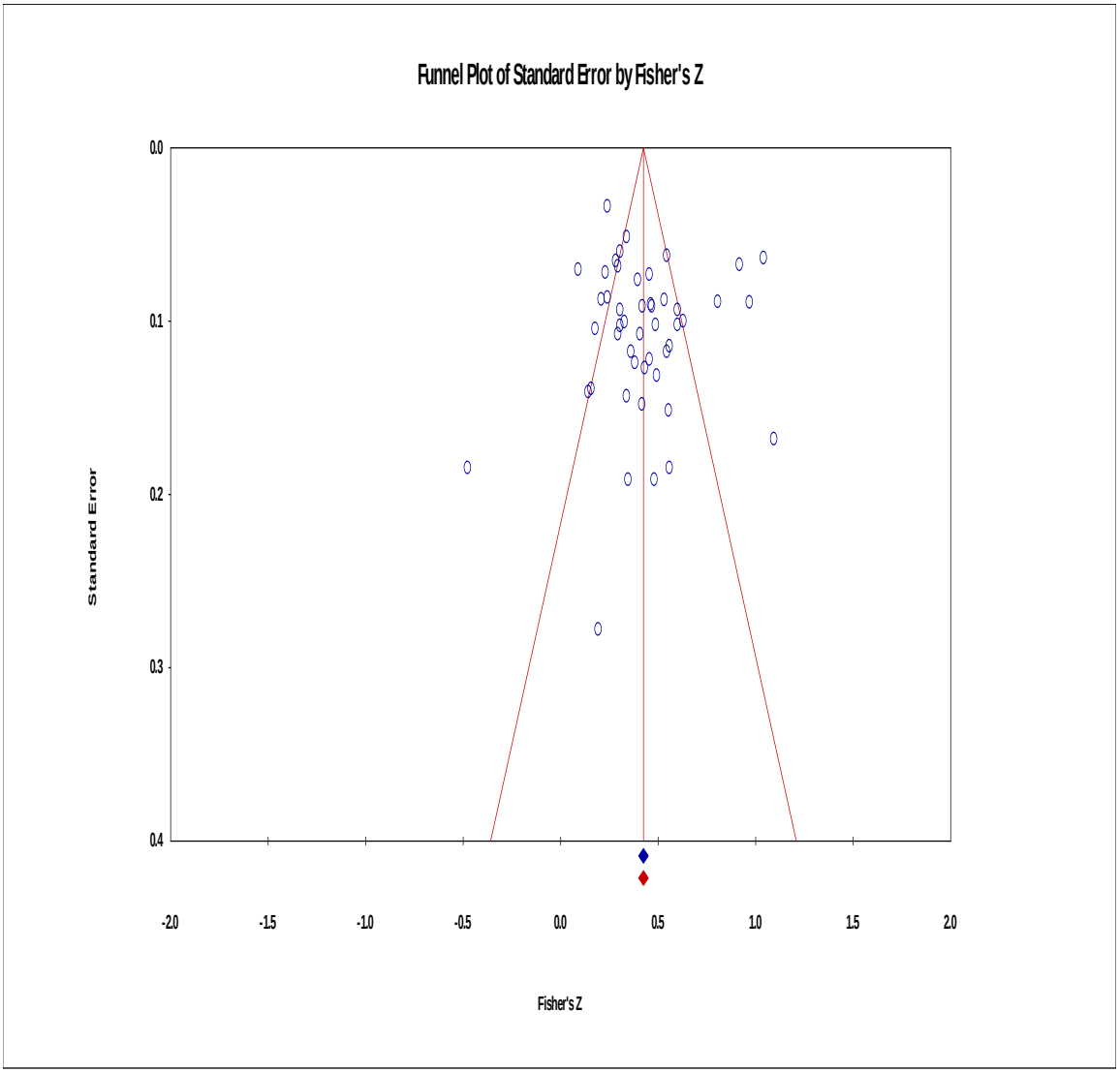


Publication bias for pain intensity

Inspection of the funnel plot and the Duval and Tweedie trim and fill procedure indicated no significant publication bias for pain intensity. There were no imputed values and the effect size was r = 0.40 (95% CI 0.37 - 0.42), Q = 359.462. Eggar`s test was not significant (intercept 0.69, 95% CI -1.44 - 2.82, p = 0.51) (Figure 3).

Figure 3.

Funnel plot of publication bias. Funnel plot of publication bias for the effect size of the association of pain catastrophizing with pain intensity



Moderation analysis

We performed moderation analysis for overall general distress, for the subcategories of distress (anxiety, depression, fear of pain, emotional distress), and for pain intensity. The categorical moderators tested were: type of pain (chronic, acute, and experimental), which was also analyzed 2x2; the instrument used for measuring the predictor and also the instrument used for measuring the outcome. Continuous moderators tested were: percentage of women, sample size, and percentage of unemployed participants.

Type of pain

On 2 x 2 analysis, we found a significant moderation effect between studies conducted on chronic pain vs. experimental pain on healthy participants for anxiety. Specifically, studies on chronic pain population show a stronger association of the relation between pain catastrophizing

and anxiety, compared to experimental studies. Also, it moderated the relation between pain catastrophizing and depression. On 2x2 analysis, we found that studies conducted on acute/chronic pain vs. experimental studies show a stronger association between pain catastrophizing and depression. Regarding emotional distress, we found studies that were evaluating this outcome only on participants with chronic or experimental pain and our results showed that type of pain is not a significant moderator. For pain intensity and also for general distress, type of pain was not a significant moderator.

The instrument used to measure the pain catastrophizing (PCS vs. CSQ) and the instrument used to measure the outcome.

We did not find significant differences on the association strength between studies in which pain catastrophizing was measured by PCS and those which used CSQ. The instrument used to measure the outcome significantly moderated the relation between pain catastrophizing and pain intensity. Our results indicate that studies which used multidimensional scales (McGill, BPI) showed a stronger association between pain catastrophizing and pain intensity, compared to studies that used unidimensional scales (VAS, NRS).

Gender

Regression analysis highlighted a moderation effect for anxiety, indicating that the higher the percentage of women, and the stronger the association of pain catastrophizing with anxiety and depression. Regression analysis showed a moderation effect for emotional distress, which means that the higher the percentage of women is, the weaker the association between pain catastrophizing and emotional distress will be. Gender was not a significant moderator for fear of pain, nor for pain intensity or general distress.

Employment

Our results showed that there is a significant moderation effect for anxiety, which suggest that the higher the percentage of unemployed participants, the stronger the association between pain catastrophizing and anxiety.

Sample size

Our regression analysis showed that there is a moderation effect for anxiety. It means that the higher the sample size is, the weaker will be the association investigated. Also, the higher the sample size, the weaker the association of pain catastrophizing with depression. Also, it was a significant moderator for general distress. In other words, the higher the sample size, the weaker the association between pain catastrophizing and general distress. Sample size was not a significant moderator for emotional distress, nor for pain intensity (Table 2 and Table 3).

Table 2.
Categorical moderators

Outcome	Moderator	No. of studies	No. of participants	Effect size	C. I		Q	p
General distress	type of pain (acute, chronic, experimental)	41	4494	0,45	0,403	0,503	1,72	0,42
	acute x chronic	35	4536	0,48	0,417	0,541	0	0,96
	acute x experimental	16	1894	0,42	0,333	0,504	0,59	0,41
	chronic x experimental	31	3358	0,45	0,397	0,508	1,61	0,21
Anxiety	type of pain (acute, chronic, experimental)	57	7392	0,38	0,337	0,439	0,04	0,84
	acute x chronic	50	6914	0,42	0,363	0,484	6,3	0,09
	acute x experimental	22	2455	0,34	0,263	0,424	1,12	0,28
	chronic x experimental	43	5521	0,38	0,329	0,439	6,17	0,04
	predictor scale (PCS vs. CSQ-C)	18	2102	0,48	0,354	0,592	0,53	0,46
	outcome scale (HADS-A vs. STAI-S)	6	903	0,49	0,306	0,647	1,56	0,21
Depression	type of pain (acute, chronic, experimental)	22	2986	0,43	0,364	0,507	12,27	0
	acute x chronic	19	2335	0,54	0,483	0,605	0,01	0,89
	acute x experimental	6	1031	0,43	0,358	0,506	11,35	0
	chronic x experimental	17	1728	0,44	0,364	0,511	12,32	0
	predictor scale (PCS vs. CSQ-C)	22	2593	0,51	0,444	0,574	0,39	0,52
	outcome scale (BDI vs. HADS-D)	7	894	0,55	0,408	0,675	0,7	0,4
Fear of pain	type of pain (acute, chronic, experimental)	8	1161	0,58	0,37	0,744	0,04	0,97
	acute x chronic	4	834	0,58	0,293	0,781	0,04	0,83
	acute x experimental	6	676	0,59	0,361	0,759	0,005	0,94

	chronic x experimental	6	812	0,57	0,264	0,778	0,02	0,86
Emotional distress	type of pain (acute, chronic, experimental)	22	3070	0,48	0,39	0,55	2,49	0,28
	acute x chronic	18	2721	0,48	0,4	0,56	2,06	0,15
	acute x experimental	6	905	0,52	0,385	0,64	1,79	0,18
	chronic x experimental	20	2514	0,44	0,35	0,53	0,14	0,7
	predictor scale (PCS vs. CSQ-C)	22	2989	0,47	0,39	0,54	1,3	0,25
	outcome scale (PANAS, SF-36-MH, VAS	8	1049	0,3	0,2	0,4	2,11	0,34
Pain intensity	type of pain (acute, chronic, experimental)	48	5968	0,38	0,332	0,439	4,38	0,22
	acute x chronic	42	4686	0,41	0,343	0,477	0	1
	acute x experimental	18	1806	0,36	0,28	0,442	0,57	0,45
	chronic x experimental	37	4654	0,38	0,326	0,436	4,23	0,12
	predictor scale (PCS vs. CSQ-C)	41	4945	0,41	0,361	0,473	0,6	0,43
	outcome scale (unidimensional vs. multidimensional)	43	5968	0,38	0,335	0,439	6,77	0,03

Table 3.
Continuous moderators

Outcome	**Moderator**	**Slope**	**p**	**Q model**	**df model**	**p model**	**Q residual**	**df residual**	**P residual**
General distress	% woman	0	0,62	0,23	1	0,62	27,53	35	0,81
	% unemployed	0,002	0,44	0,59	1	0,44	5,82	9	0,75
	sample size	-0,0008	0,006	7,81	1	0,006	29,37	41	0,91
Anxiety	% woman	0,06	0,04	4,07	1	0,04	17,96	19	0,52
	% unemployed	0,009	0,009	2,85	1	0,09	1,77	2	0,41
	sample size	-0,001	0	14,62	1	0	17,55	15	0,28
Depression	% woman	0,003	0,07	3,15	1	0,07	14,4	19	0,56
	% unemployed	0	0,98	0	1	0,98	2,05	2	0,35
	sample size	-0,01	0,05	3,79	1	0,05	12,12	19	0,88
Emotional distress	% woman	-0,002	0,02	5,1	1	0,02	130,69	17	0
	% unemployed	-0,004	0,21	1,5	1	0,21	2,8	3	0,42
	sample size	-0,001	0,36	0,82	1	0,36	5,53	6	0,47
Pain intensity	% woman	-0,001	0,34	0,89	1	0,34	32,18	40	0,8
	% unemployed	0,003	0,42	0,63	1	0,42	9,37	10	0,49
	sample size	0	0,56	0,33	1	0,56	43,36	44	0,49
Fear of pain	% woman	-0,009	0,76	0,08	1	0,76	4,16	5	0,52
	sample size	-0,001	0,26	0,82	1	0,36	5,53	6	0,47

3.1.4. Discussion

Our results support the importance of catastrophizing as a significant feature of pain experience in terms of emotional distress and pain intensity. Also, the identification of a potentially shared mechanism that drive both problems could facilitate a better understanding of the processes involved. As a consequence, better interventions for people who suffer from pain may be developed. The present meta-analysis investigates the association magnitude of pain catastrophizing with general distress (anxiety, depression, fear of pain, emotional distress), and with pain intensity. We analyzed the possible moderators of these associations, relevant to pain related research or psychotherapeutic interventions. We included 63 studies which offered sufficient data to compute the effect size. Overall, we highlighted a moderate effect size for general distress and for pain intensity. Excluding one outlier and adjusting for publication bias did not reduced significantly the effect size. Also, anxiety, depression, fear of pain, and emotional distress was moderately associated with pain catastrophizing.

Practical and theoretical implications of the moderation analysis

The moderation analysis highlights important features which might influence the relation strength of pain catastrophizing with general distress and pain intensity.

Type of pain moderated the relation of pain catastrophizing with anxiety and depression. It was not a significant moderator for general distress. Therefore, our data sustain that pain catastrophizing is a trait dimension, related with distress and pain intensity regardless of pain characteristics (Sturgeon & Zautra, 2013; Severijins et al., 2001). Also, it is in line with the literature which emphasizes that emotional distress is strongly influenced by dysfunctional cognitive evaluations (David et al., 2001; Dryden, 2005). Overall, general distress was moderated by sample size. In other words, the higher the sample size is, the weaker the association. It is known in the literature that a higher sample size may show weaker associations due to the reduced standard deviations and reductions in the mean effect sizes (Slavin & Smith, 2008). It is important to note that this moderator highlights a more reliable effect size, as a concequence of an larger sample size. As Slavin & Smith (2008) noted, as sample size increases, effect sizes become more reliable and less likely to be artefacts.

Our results highlight differences between studies conducted on acute/ chronic pain vs. experimental studies on healthy participants. In other words, studies on acute or chronic pain populations showed a stronger association of the relation between pain catastrophizing and depression. One explanation of this results is that in acute or chronic pain studies participants were usually patients with medical diagnoses, which might indicate that the presence of an actual or inferred negative activating event, such as a specific illness, will activate maladaptive beliefs and conduct to dysfunctional emotions (Dryden, 2005), compared to experimental studies, conducted in laboratory environments, on healthy subjects. While it might activate dysfunctional beliefs, the literature suggests that the context of a noxious stimulus is strongly relevant for pain related outcomes (Merskey & Bogduk, 1994). Also, our results suggest that pain catastrophizing may contribute to anxiety and depression in chronic pain samples. Gender moderated the association between pain catastrophizing and emotional distress. In other words, the lower the percentage of women was, the stronger the association between pain catastrophizing and emotional distress. This result might be due to a lower level of distress in women, which supports the recent findings in the literature which state that women might experience lower levels of emotional distress because they ask more for psychological support in confrontation with a threatening condition (Faller et al., 2016). Also, our results on emotional outcomes must cautiously be interpreted, considering that publication bias was high for the emotional outcomes. It is indicating that studies which reported significant associations between pain catastrophizing and an emotional outcome had higher chances of getting published, therefore most of the studies included in this meta-analysis emphasized medium-high associations, with few exceptions. For pain intensity, our results show that the instrument

used to measure pain intensity is the only significant moderator. In other words, multidimensional scales might highlight a stronger association due to thehigher complexity of the assesment tool (Doctor, Slater, & Atkinson, 1995).

Clinical implications of the study

This is the first quantitative study to summarize the associations of pain catstrophizing with senzorial and emotional dimensions of pain. Our results add more empirical support to CBT approach for pain patients by showing the association of an important dysfunctional belief with clinical relevant aspects. Our study shown that pain catastrophizing might be a common factor for pain and psychopathology, which often co-occur. It is important to underline these results, since literature stated that unified treatment principles would increase the efficiency of treatments (Hanscom et al., 2015; Wilamowska et al., 2010). By showing similar associations of pain catastrophizing with pain and distress, the findings of the present research contribute to the transdiagnostic model and facilitate theoretical advances of the literature on pain and related emotions. The consequences of this perspective, as they were clearly addressed previously, may be relevant to the processes involved in predisposing an individual to develop a disorder, in the processes involved in the etiology of a disorder, as well as in the processes of maintaining a disorder (Harvey et al., 2004).

Our moderation analysis indicates specific factors to be considered in assessment and intervention (Mehl et al., 2015).

Limitations of the study

Pain and emotional distress are significantly related. Catastrophizing is an important common factor between them, yet other psychological, physiological and social factors are also known to have a significant role. It is possible that the shared variance between the two to have an impact on our results. Further, we assumed that studies included in the meta-analysis have made a careful distinction between pain intensity and its emotional dimension, although research states that it is difficult to clearly differentiate pain as sensation from emotions that co-occur. Another limit of our study lays on the fact that we included only studies which assessed state pain catastrophizing. This measure is used following a painful stimulation, whether it is experimentally induced on healthy population, or it is clinical pain due to a medical procedure. Therefore, it is difficult to generalize the magnitude of the relationship between pain catastrophizing and the outcomes investigated in this research for trait pain catastrophizing, which is an important question for research. Lastly, dysfunctional beliefs, such as pain catastrophizing, are considered latent constructs that require a negative life event, real or expected, to produce dysfunctional consequences (Edwards et al., 2008). We assumed that the included studies have activated state pain catastrophizing to the same extent, irrespectively by the type of pain (cold pressor pain vs. pain due to a medical condition). Another limitation of this study is the inclusion of correlational studies exclusively. Our conclusions regarding the transdiagnostic model are aware that finding correlations of the similar magnitudes across the board is not an enough support for this claim. The future studies should look into causal mechanisms. Our meta-analysis represents a step further to this aim, but there is still a strong need for more data in order to sustain this perspective for pain and distress.

STUDY II. The Mechanisms of Pain Tolerance and Pain-Related Anxiety in Acute Pain

3.2.1. Introduction

Pain catastrophizing and anxiety may have a significant impact on response expectancies, which can be explained by the history of high levels of pain in different contexts,

of individuals who catastrophize (Sullivan, Rodgers, & Kirsch, 2001). These patients develop expectancies of future pain experiences or may develop negative beliefs regarding the aversiveness associated with pain-related contexts (Locher et al., 2019; Sullivan et al, 2001). Previous painful experience, or the associated beliefs about pain-related contexts, will influence individuals who catastrophize to expect that future pain provoking contexts will be related with a high level of pain and low level of pain tolerance (Baker & Kirsch, 1991) and distress (Sullivan et al., 2001). The research shown that response expectancies are very good predictors of both positive (relaxation) and negative (e.g., pain intensity or distress) non-volitional outcomes in clinical and non-clinical samples (David, Montgomery, & DiLorenzo, 2006). They impact pain intensity, while pain intensity influence pain tolerance (Kirsch, 1985).

The present study

The roles of anxiety and pain catastrophizing have been investigated in separate models, which limits the control for shared variance between the two (Benore et al., 2015; Eccleston et al., 2005). Therefore, we need to investigate the relationships between these constructs in a single model, by analyzing whether these constructs are statistically distinct, and analyze the paths through which they impact the pain-related outcomes (see Tran et al., 2015). Although the relationships between pain catastrophizing/ state anxiety and pain tolerance/ pain-related anxiety have been extensively investigated in the literature, but the mechanisms behind these associations remain poorly understood.

Therefore, the present study aims to expand on the pathways that explain pain tolerance and pain-related anxiety by exploring pain catastrophizing and state anxiety as possible predictors. Drawing on the previous findings, response expectancies for pain tolerance and their impact on pain intensity were investigated as potential mechanisms. By identifying the paths that may explain both pain tolerance and pain-related anxiety, we will take a step towards a transdiagnostic perspective for pain and anxiety în acute pain (Linton, Flink, Schrooten, & Wiksell, 2016).

3.2.2. Methods

Participants

A number of 78 undergraduate students were included in the study. The mean age of participants was 21.74 (ranged from 19 to 33 years). Individuals who suffered from medical conditions associated with pain (migraine, headache, and back pain) and participants with other conditions that might be negatively interacting with our procedure of pain induction (cardiovascular problems, previous episodes of frostbite, etc.) were not included in the study. All participants signed a written informed consent.

Procedure

Experimental manipulation of anxiety

Participants were randomly allocated to one of two experimental conditions: (1) the

[1] This study has been accepted for publication.
Cimpean, A., & David, D. (2019). The mechanisms of pain tolerance and pain-related anxiety in acute pain. Health Psychology Open, DOI 10.1177?2055102919865161.

aversive condition (n = 41) and (2) the neutral condition (n = 37). Written information regarding the task was given. Participants were told that important information about the task will be given and they were told to read carefully before signing the informed consent. Participants from the aversive condition received written information which informed them that in some extreme cases, the cold pressor task could be dangerous and might result in a serious degeneration of the immersed hand, while those in the neutral condition were told that the task was very similar to searching for a drink in a freezer, and that it would not result in any physical injury. After signing the informed consent, participants followed the assessment phase and then they were instructed to place their hand into the water and to keep it immersed for as long as they could tolerate.

Measures

Pain catastrophizing

The Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) is a 13-item self-report measure of pain catastrophizing. The scale evaluates dysfunctional thoughts associated with pain. The PCS instrument has three subscales that measure rumination, magnification, and helplessness. Participants are asked to rate their feelings of pain on a five-point Likert scale (where 0 is "not at all", and 4 is "all the time"). The scores range from 0 to 52, where higher scores indicate more pain catastrophizing.

State anxiety

The State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a measure of trait and state anxiety. It can be used in clinical and experimental settings to diagnose anxiety. The total scale has 40 items, 20 for evaluating trait anxiety and 20 for state anxiety. We used the items from state anxiety subscale.

Response expectancies

We asked participants to rate the level of pain they expected to tolerate during the cold pressor task by marking a line between 0 (no pain tolerance) and 100 (extreme pain tolerance).

Example of item: Please rate how much pain tolerance you are expecting to have during cold pressor test.

Pain-related anxiety

A visual analogue scale (VAS) was given to the participants after cold pressor procedure. Participants provided reports of the anxiety they experienced by marking a line between 0 (no anxiety) and 100 (extreme anxiety).

Pain measures

Pain tolerance was the total time, in seconds, that the participant had his hand immersed into the water, minus pain threshold time.

Pain threshold was determined by asking participants to report the moment when they began to feel pain or discomfort. The time, in seconds, between the start of the immersion and the reporting of the pain was recorded as the pain threshold.

Pain intensity was the pain experienced during the cold pressor task, measured using a VAS, which ranged from 0 (no pain) to 100 (extreme pain). Participants were asked to mark a line between 0 and 100 to suggest the intensity of pain. Example of item: Please rate the level of pain intensity you experienced during experimental procedure.

Apparatus

A cold pressor device was used to induce pain. Specifically, it is a refrigeration unit that is cooling constantly circulating water in an insulated container measuring 30 cm × 40 cm × 30 cm. The water temperature was maintained at 5°C. We used water at room temperature

in order to standardize the temperature of the hand before immersion in the cold water. The apparatus was a Refrigerated Bath Circulator, Model JSRC-13C.

Statistical analyses

Student's t-test was used to evaluate how the experimental manipulation influenced state anxiety before pain induction. Path analysis was used to identify the model that was most predictive for pain tolerance and pain-related anxiety. We found one model that fit the data well. This was tested for each experimental condition, considering pain tolerance and pain-related anxiety as separate outcomes. In this study, the hypothesized model was tested in an exploratory manner, based on the contributing variables, namely pain tolerance and anxiety. Following the recommendations of Weston & Gore (2006), model-data fit was examined using several fit indices, including the comparative fit index (CFI), the non-normed fit index or Tucker-Lewis index (TLI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). Statistical significance of the path coefficients was also analyzed. We used R (R Core Team, 2012) and Lavaan Package to perform these analyses.

3.2.3. Results

Descriptive analyses

We had 41 participants in the aversive condition and 37 participants in the neutral condition. Means and standard deviations were calculated for each measure (See Table 1).

Table 1.
Descriptive statistics

Condition	Measures	N	M	SD
Aversive group	Pain catastrophizing	41	20,46	12,36
	State anxiety	41	36,86	18,74
	Response expectancies for pain tolerance	41	33,7	20,07
	Pain intensity	41	41,95	27,2
	Pain tolerance	41	62,5	13,25
	Pain related anxiety	41	41,83	17,82
	Pain catastrophizing	37	19,94	13,41
	State anxiety	37	25,42	17,72
	Response expectancies for pain tolerance	37	28,13	18,54

Neutral group	Pain intensity	37	34,56	26,4
	Pain tolerance	37	118,68	23,2
	Pain related anxiety	37	40,42	12,31

Manipulation check

Our results showed that the experimental manipulation was effective. There were significant differences between conditions on state anxiety level (t = 2.04, $p < .05$) (See Table 2).

Table 2.
Manipulation check

	Aversive group *m*	**Neutral group *m***	***t Test***	***p***
State Anxiety	36,86	25,42	2,04	0,004

The path model for predicting pain tolerance

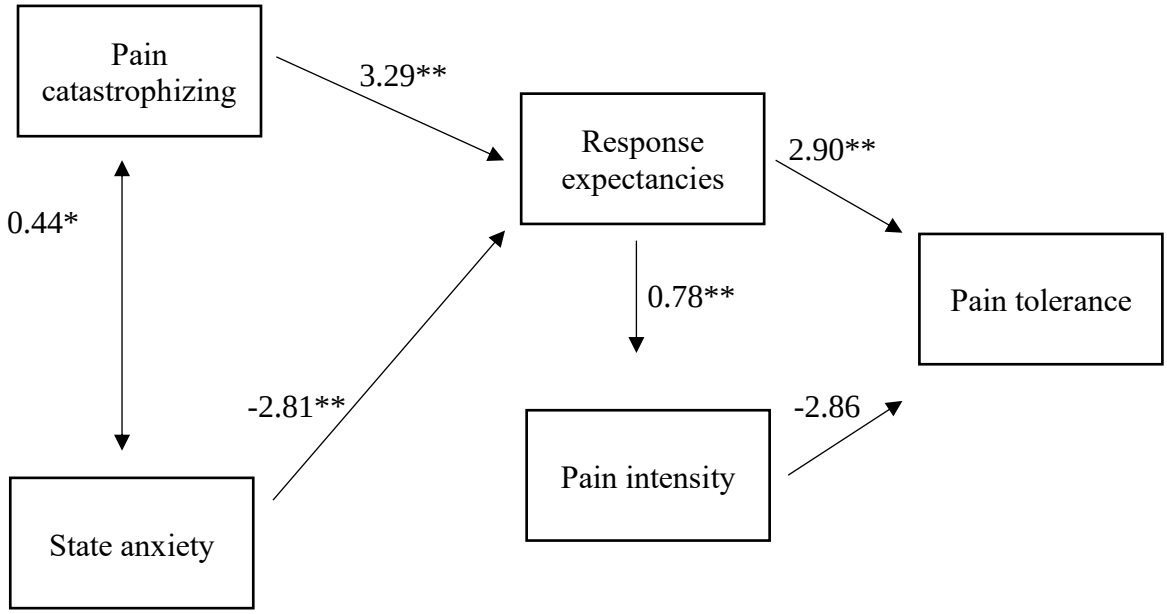
Various fit indices were used to assess the adequacy of the path models. The goodness-of-fit index (GFI) of 0.993 indicated an excellent fit. The root mean square residual (RMSEA) of 0.024 was within the expected range of unaccounted variance (<0.05) and represented a high level of closeness of fit for the model. The Tucker-Lewis coefficient and comparative fit index were 1 for both aversive and neutral conditions, also indicating a good fit.

Table 3.
Direct and indirect paths for predicting pain tolerance

	Aversive condition		**Neutral condition**	
	Estimate 95%CI	*p*	Estimate 95%CI	*p*
Direct effects				
Pain catastrophizing → Response expectancies	3,29	0,005	-0,62	0,377

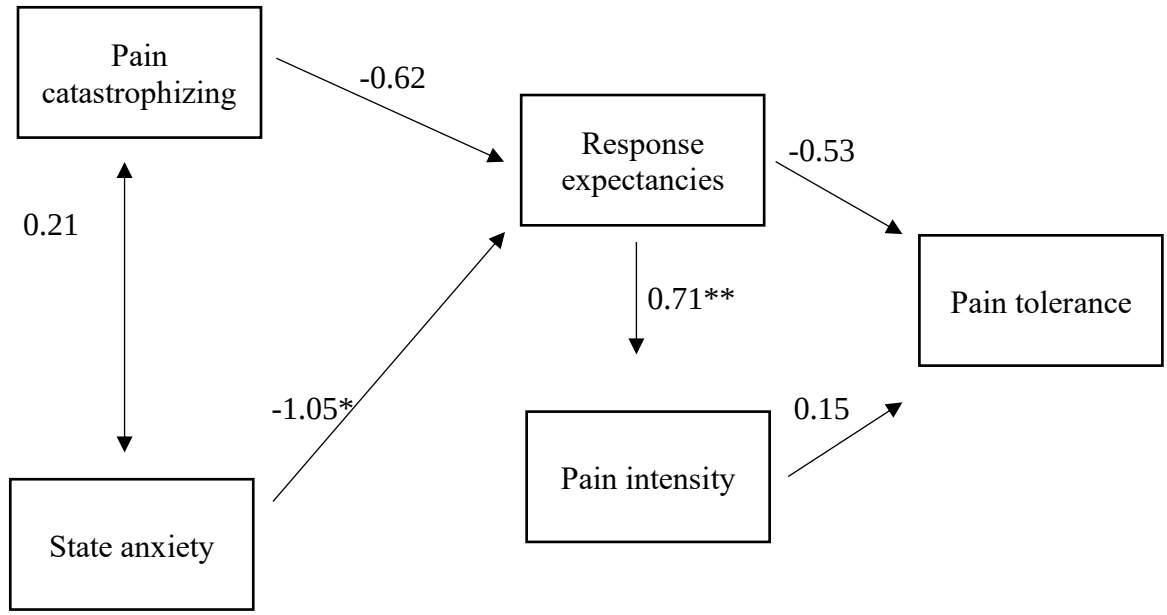
State anxiety → Response expectancies	-2,81	0,001	-1,05	-0,032
Response expectancies → Pain intensity	0,78	0	0,71	0
Pain Intensity → Pain tolerance	-2,86	0,68	0,15	0,731
Response expectancies → Pain tolerance	2,9	0,009	-0,53	0,275
Indirect effects				
Pain Catastrophizing → Response Expectancies → Pain tolerance	0,25	0,057	-0,03	0,742
State anxiety → Response expectancies → Pain tolerance	-0,91	0,003	0,04	0,735
Response Expectancies → Pain Intensity → Pain tolerance	-2,25	0,004	0,11	0,731
Pain catastrophizing → Response expectancies → Pain intensity → Pain tolerance	-7,34	0,04	-0,07	0,721
State anxiety → Response expectancies → Pain intensity → Pain tolerance	6,27	0,041	-0,11	0,731

Figure 3.
Graphic representation of paths predicting pain tolerance in aversive condition



Note: *p<.05; **p<.01

Figure 4.
Graphic representation of paths predicting pain tolerance in neutral condition



Note: *p<.05; **p<.01

The path model for predicting pain-related anxiety

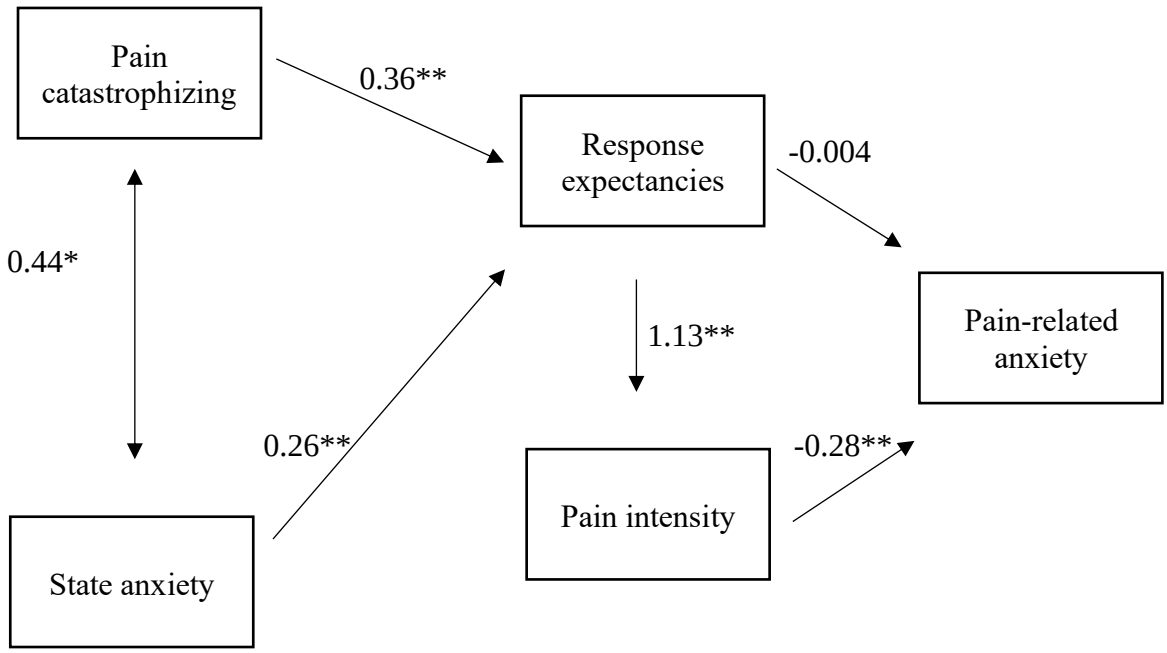
Various fit indices were used to assess the adequacy of the path model for the aversive and the neutral condition. For aversive condition, the goodness-of-fit index (GFI) was 0.983, indicating an excellent fit. The root mean square residual (RMSEA) was 0.024, the Tucker-Lewis coefficient was 0.93, and the comparative fit index (CFI) was 0.98, also indicating a good fit. In the case of the neutral condition, the goodness-of-fit index (GFI) was 0.951, RMSEA was 0.000, indicating a good fit, while the TLC was 0.27 and the CFI was 0.71, which indicates a medium-low fit with the model.

Table 4.
Direct and indirect paths for predicting pain-related anxiety

	Aversive condition		**Neutral condition**	
	Estimate 95%CI	*p*	Estimate 95%CI	*p*
Direct effects				
Pain catastrophizing → Response expectancies	0,36	0,006	0,12	0,34
State anxiety → Response expectancies	0,26	0,01	0,19	0,02
Response expectancies → Pain intensity	1,13	0	0,76	0
Pain Intensity → Pain-related anxiety	-0,28	0,005	-0,26	0,02
Response expectancies → Pain-related anxiety	-0,004	0,98	0,04	0,655
Indirect effects				
Pain Catastrophizing → Response Expectancies → Pain-related anxiety	-0,02	0,708	0,12	0,11
State anxiety → Response expectancies → Pain-related anxiety	-0,16	0,03	-0,08	0,12

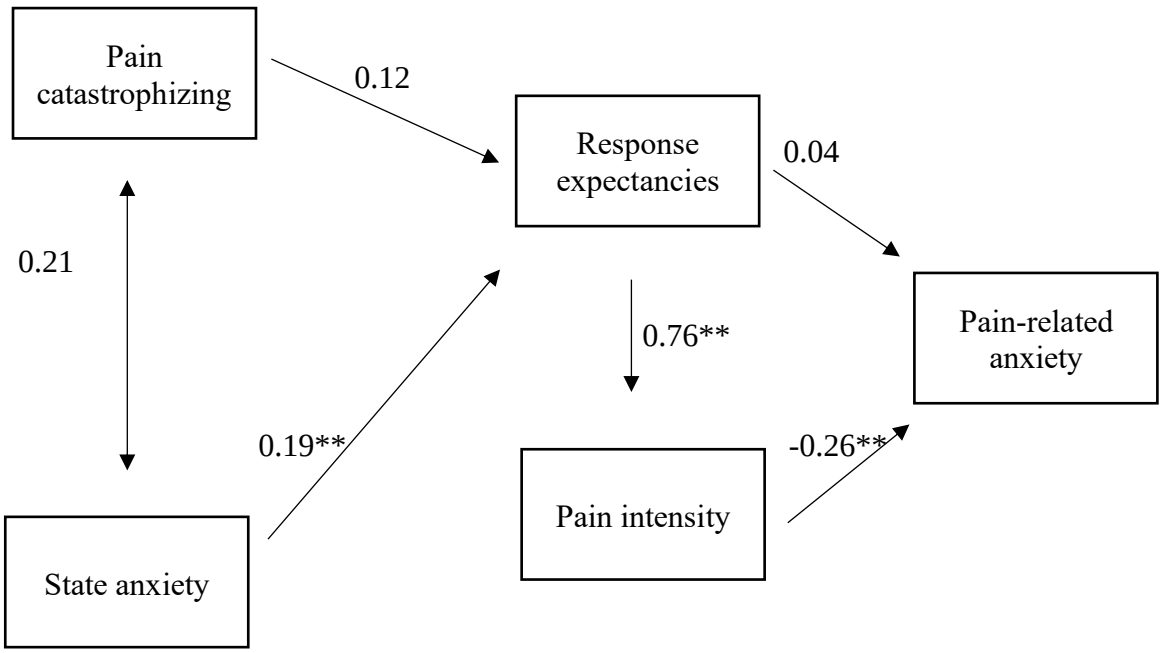
Response Expectancies → Pain Intensity → Pain-related anxiety	-0,35	0,009	-0,2	0,005
Pain catastrophizing → Response expectancies → Pain intensity → Pain-related anxiety	-0,11	0,03	-0,02	0,1
State anxiety → Response expectancies → Pain intensity → Pain-related anxiety	-0,08	0,03	-0,04	0,03

Figure 5.
Graphic representation of paths predicting pain-related anxiety in aversive condition



Note: *p<.05; **p<.01

Figure 6.
Graphic representation of paths predicting pain-related anxiety in neutral condition



Note: *p<.05; **p<.01

3.2.4. Discussion

The aim of the present study was to investigate whether pain catastrophizing and state anxiety are indirect predictors of pain tolerance and pain-related anxiety. Response expectancies for pain tolerance were tested as a mechanism for both pain tolerance and pain-related anxiety. Our results showed that the experimental manipulation was successful: participants in aversive condition reported significantly higher levels of anxiety prior to the task. The proposed path model, which was based in past research, fit the data well. Our study demonstrate that aversive contexts may have a strong influence on pain tolerance and pain-related anxiety

In the aversive condition, pain catastrophizing significantly predicts pain tolerance and pain-related anxiety, by the way of response expectancies and pain intensity, while in a neutral context it is not predictive. Therefore, as the previous literature suggests, pain catastrophizing might represent a latent construct, requiring sufficient activation in order to exert its effects (Edwards et al., 2008). Our study showed that cognitive and emotional factors are closely connected with pain tolerance and pain-related anxiety, especially in aversive condition. Also, these results highlight that pain tolerance and pain-related anxiety share common mechanisms when threat is perceived. In order to add data to the transdiagnostic model for pain and emotion, research suggest to emphasize how specific psychological processes have a causal contribution to the development and maintenance of various symptoms (Le Borgne et al., 2017). Therefore, our data may add significant support for the transdiagnostic model of pain and emotion, highlighting the significant paths for predicting pain tolerance and pain-related anxiety.

Theoretical and clinical implications

Personal experience of pain in aversive contexts may be explained by pain catastrophizing, state anxiety, response expectancies for pain tolerance, an pain intensity. The findings of the present study encourage a transdiagnostic perspective for treating pain-related outcomes, such as pain tolerance and pain-related anxiety. By identifying common factors in the relation between pain catastrophizing/ anxiety and pain tolerance/ pain-related anxiety, we would facilitate a better understanding of the processes involved, which will explain the high level of comorbidity of pain and emotional distress. (Harvey et al., 2004). Our study found similar mechanisms of pain tolerance and pain-related anxiety in aversive condition. As previously mentioned, it is relevant to highlight the overlapping features or common maintaining mechanisms in order to support a transdiagnostic view (McHugh, Murray, & Barlow, 2009). Our results also provide more empirical support for the use of the CBT approach with patients who suffer from acute pain by showing the association between cognitive/ emotional factors and clinically relevant aspects, and the path through which they affect pain outcomes.

The limitations of the present research have implications for the generalizability of the findings to clinical samples. The participants were undergraduate students who were not suffering from pain-related health conditions. The applicability of the results to patients suffering from a clinical condition or chronic pain is thus uncertain. The second issue is one of measurement. Although the measurement of pain-related anxiety and response expectancies using a visual analogue scale is common practice, it has several limitations (Wewers & Lowe, 1990) which may have influenced our results. First limit addressed by Wewers & Lowe (1990) is regarding the ability of participants to conceptually understand the method itself, although the VAS is described as a tool independent of language. VAS involves the ability of the subject to think abstract and imagine the line as a representation of a personal perceptual experience. Therefore, a mark along the line between is totally dependent upon the subject's unique interpretation (Wewers & Lowe, 1990). The second limit underlined by the authors mentioned above is based on the inaccuracy of reproduction of the instrument due to the distortion of the line that often appear on Xeroxing. Moreover, some other distortions may appear due to the medication intake; comprehension or eye-hand coordination problems; practical difficulties met in hospital settings (such as the placement of intravenous catheters), and other particular limitations caused by the physical problems of each participant (Wewers & Lowe, 1990). Furthermore, we used only observational and self-report data, which may result in under-reporting of the main outcomes. Future studies should also focus on physiological measures of the sensorial characteristics of pain and pain-related anxiety in order to gather more complex and valid information (Sweet & McGrath, 1998).

STUDY III. Predictors of Adaptation During the First-Year Post Mastectomy

3.3.1. Introduction

Research has shown that dysfunctional cognitive evaluations are important etiological factors for dysfunctional outcomes (David & Hofmann, 2013). Cognitive behavioral therapy assumes that certain cognitions are involved in specific psychological problems, generally concluding that the belief system is the main cause for emotional and behavioral problems (Dryden & David, 2008; Beck & Dozois, 2011). Significant data emphasized that cognitive and behavioral responses patients use in response to pain influence their perceptions of pain intensity and interfere with their coping strategies to manage or tolerate the intensity of pain (Turk, Meichenbaum, & Genest 1983; Spleen, Lengerich, Camacho, & Vanderpool, 2014).

The present study

Although pain and distress are often associated with some of the oncological treatments, some patients find functional adjustment strategies which help them maintain their quality of life (Asmundson & Katz, 2009). Given the significant individual variability in psychological responses to breast cancer treatment, it is important to specify the individual contribution to adjustment of pain catastrophizing, coping strategies, and baseline psychopathology (baseline anxiety and baseline depression). The contribution of pain catastrophizing on pain-related outcomes has been extensively investigated in the literature. However, little are known about its predictive value when coping strategies and baseline psychopathology are considered in predicting adjustment in time.

Specifically, we aim to investigate whether pain catastrophizing, coping strategies, baseline anxiety, and baseline depression may significantly predict adjustment (anxiety, depression, quality of life, pain intensity, and pain tolerance), prospectively from the point shortly following breast surgery through the first year. We also aim to explore the changes in outcomes across time and to test which of the supposed predictors may better explain the adjustment during the first-year post mastectomy. We hypothesize pain catastrophizing, coping strategies, and baseline psychopathology may add a significant variation in outcome one-year following mastectomy. Also, we hypothesize that pain catastrophizing will significantly predict each outcome.

3.3.2. Methods

Participants

Participants were women who followed breast cancer surgery. A number of 68 patients from Oncological Hospital "Ion Chiricuță" of Cluj-Napoca, Romania were included. All participants completed an informed consent. A number of 5 out of the initial 73 participants were excluded from the final analysis due to the incomplete responses on questionnaires or death.

Procedure

A longitudinal design was developed. Pain catastrophizing, coping strategies, baseline anxiety, and baseline depression were assessed 2 days post-surgery as predictors of subsequent adjustment. Outcome measures were anxiety, depression, quality of life, pain intensity, and pain tolerance. Consecutive patients were approached by a research assistant 2 days post-surgery, to participate in a study of adjustment to breast cancer. Measures at 6 and 12 months were collected via phone call.

Measures

Pain catastrophizing

The Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) is a 13-item self-report measure of pain catastrophizing. The scale evaluates dysfunctional thoughts associated with pain. The PCS instrument has three subscales that measure rumination, magnification, and helplessness.

Coping strategies

Coping strategies were measured using the Brief COPE scale (Carver, 1997). This is an instrument which evaluates how patients cope with the stress related to cancer using a number of 28 items, organized in 14 subscales, which can be grouped into 3 main coping styles: problem-focused coping, emotion-focused coping, and dysfunctional coping.

Anxiety and depression

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS is an instrument used to evaluate the psychological distress across different populations.

Pain intensity and pain tolerance

Pain intensity and pain tolerance were measured using a standard numerical scale. The end points for assessing pain intensity were labeled "no pain" and "pain as bad as it could be", while for pain tolerance they were labeled as "low tolerance" and "very high tolerance".

Quality of life

General quality of life was measured using The Functional Assessment of Cancer Therapy (FACT-G; Janda, DiSipio, Hurst, Cella, & Newman, 2009). This questionnaire has 4 subscales for evaluating the well-being in the following domains: physical (range 0-28), social (range 0-28), emotional (range 0-24), and functional (range 0-28). A higher score on each subscale is indicating a higher quality on that specific area. Also, a total score can be obtained. The instrument has good psychometric proprieties (Janda et al., 2009).

Statistical analyses

Standard univariate (means and standard deviations) and bivariate statistics were used to summarize and compare outcome measures. Before conducting the parametrical analysis we normalized the distribution for average pain intensity ratings by log-transformation. Imputation techniques were used to offer estimates of missing scores. All statistical tests were two-tailed and values of *p* less than 0.05 were considered significant. Due to the high number of variables entered in the correlational analysis, correction of the *p* significance was applied, therefore we considered significant only the associations at *p* less than 0.01.

Primary analyses were conducted by performing a linear mixed effects analysis of the relationship between coping strategies, pain catastrophizing, baseline anxiety, and baseline depression. We entered pain catastrophizing as random effect. We had pain catastrophizing, baseline anxiety, baseline depression, and coping strategies (dysfunctional coping, emotion focused coping, and problem focused coping) as fixed effects. *P*-values were calculated. We used IBM SPSS Statistics for Windows (Version 21.0) to perform these analyses. Predictive models of anxiety, depression, quality of life, pain intensity, and pain tolerance were constructed in several stages. A linear mixed model was tested for predicting 6 months and 12 months follow-up scores, by adding variables measured at baseline.

3.3.3. Results

Descriptive analyses

A number of 68 participants, with a mean age of 58.06 years old, were included in the study. Mean and standard deviation were calculated for each measure (See Table 1; See Figure 1-5).

Table 1.
Descriptive statistics

Time point	Measures	M	SD
	Pain catastrophizing	17,57	10,89

2 Days Post-Mastectomy	Emotion-focused coping	8,15	1,1
	Problem-focused coping	10,46	2,54
	Dysfunctional coping	13,13	3,39
	Anxiety	7,36	4,94
	Depression	5,95	4,48
	Pain intensity	1	3,34
	Pain tolerance	0,87	0,81
	Quality of life	60,4	42,97
6 Months Post-Mastectomy	Anxiety	3,38	2,64
	Depression	4,11	3,31
	Pain intensity	2,11	1,04
	Pain tolerance	2,4	1,39
	Quality of life	50,99	6,69
12 Months Post-Mastectomy	Anxiety	1,52	1,58
	Depression	2,8	2,68
	Pain intensity	1,61	0,75
	Pain tolerance	2,01	0,83
	Quality of life	64,43	6,91

Figure 1.Anxiety level over one year

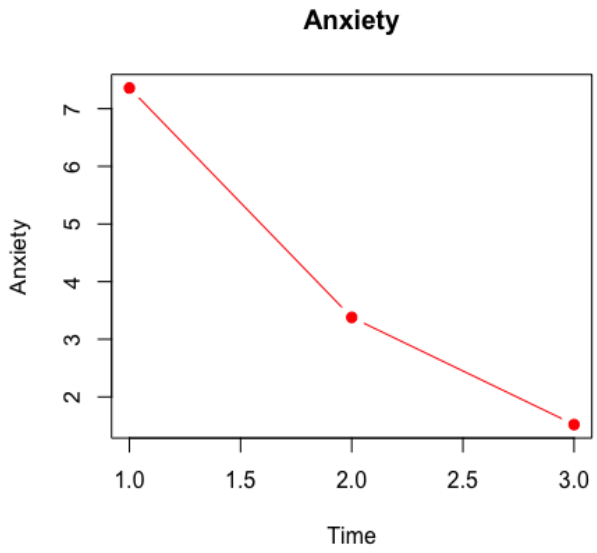


Figure 2.

Depression level over one year

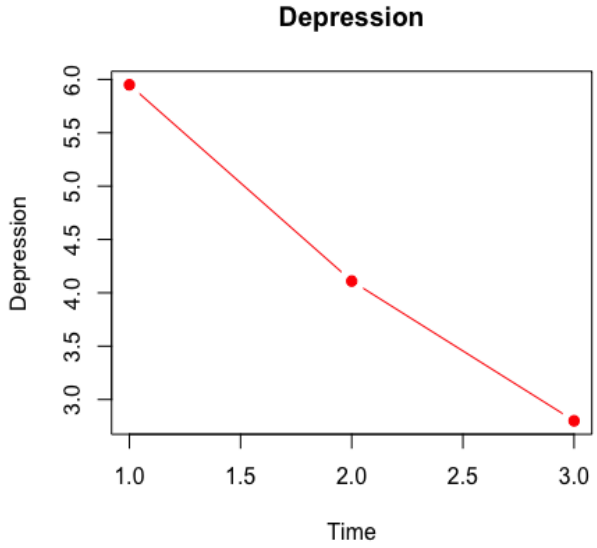


Figure 3.

Quality of life over one year

Figure 4.

Pain intensity level over one year

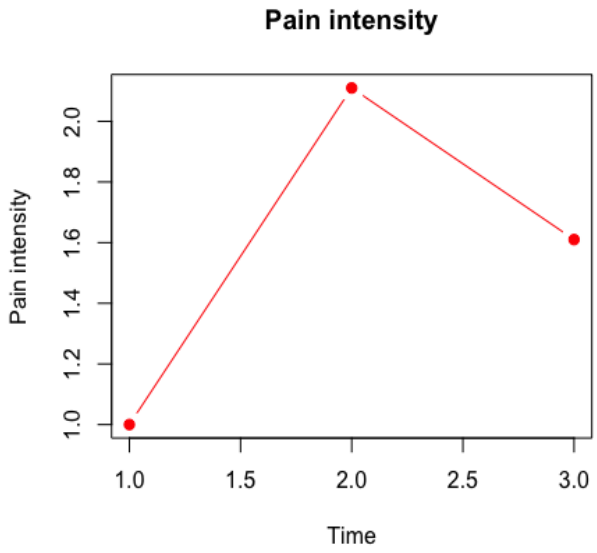
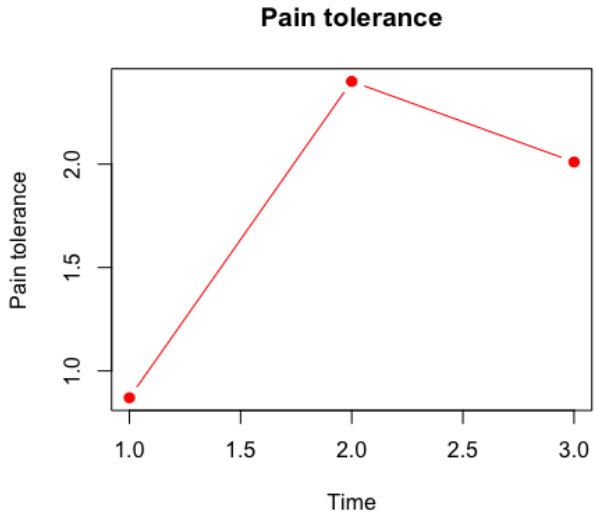


Figure 5.

Pain tolerance over one year



Correlational analyses

Bivariate correlation analyses showed that baseline anxiety correlated with baseline depression. Also, pain catastrophizing correlated significantly with baseline anxiety (See Table 2).

Table 2.
Correlations

Time	Measures	2 Days Post-Mastectomy									6 Months Post-Mastectomy					12 Months Post-Mastectomy				
		Pain catastrophizing	Emotion-focused coping	Problem-focused coping	Dysfunctional coping	Anxiety	Depression	Quality of life	Pain intensity	Pain tolerance	Anxiety	Depression	Quality of life	Pain intensity	Pain tolerance	Anxiety	Depression	Quality of life	Pain intensity	Pain tolerance
2 Days	Pain catastrophizing	1	0,023	0,102	0,042	0,522**	.358**	-0,19	0,173	0,2	0,219	0,193	-0,244*	0,077	.333**	.302*	0,097	-0,138	.251*	.301*
	Emotion-focused coping		1	-0,063	0,013	0,121	0,101	0,181	-0,145	-0,103	0,021	-0,128	0,081	0,009	0,023	0,109	-0,18	0,127	-0,229	-0,115
	Problem-focused coping			1	.311*	0,289*	-0,061	0,033	0,067	-0,146	-0,076	-0,316**	0,325**	-0,047	0,17	0,069	-0,202	0,156	0,072	0,105
	Dysfunctional coping				1	0,169	0,317**	-0,149	0,019	-0,018	0,178	386**	-0,107	0,096	0,11	0,075	0,314**	0,214	0,036	0,069
	Anxiety						0,583**	-0,361**	0,018	-0,009	.316**	0,165	-.250*	0,154	-0,287*	0,267*	0,07	-0,092	0,117	-0,275*
	Depression						1	-0,547**	0,078	-0,073	0,179	.454**	0,053	0,271*	-0,213	0,291*	0,378**	-0,373**	0,222	-0,212
	Quality of life							1	-0,036	0,114	-0,006	-0,125	-0,101	-0,245*	0,102	-0,102	-0,219	0,128	-0,084	0,029
	Pain intensity								1	0,616**	0,101	0,281*	-0,083	-0,051	0,01	0,277*	0,308*	-0,394**	0,317**	0,228
	Pain tolerance									1	0,217	0,135	0,082	-0,04	0,096	0,041	0,059	-0,12	0,103	0,097

** Correlation is significant at the 0.00 level (2-tailed).

Note - p correction was performed

Table 3.
Multicollinearity test

Measures	Pain catastrophizing (PCS)	Emotion-focused coping	Problem-focused coping	Dysfunctional coping	Baseline anxiety	Baseline depression
	VIF	**VIF**	**VIF**	**VIF**	**VIF**	**VIF**
Pain Catastrophizing (PCS)	Inf	1,05	1,11	1,02	2,09	1,55
Emotion-focused coping		Inf	0,94	0,97	1,18	1,14
Problem-focused coping			Inf	1,44	1,39	0,94
Dysfunctional coping				Inf	0,84	0,75
Baseline anxiety					Inf	2,4
Baseline depression						Inf

Primary results

The impact of time on adjustment

The differences in anxiety, depression, quality of life, pain intensity, and pain tolerance shortly after surgery, after 6 months, and after 12 months were highlighted (See Table 3). Paired differences are also presented (See Table 4 and Table 5).

Table 4.
One-way repeated measures ANOVA. The impact of time on the main outcomes

One-way repeated measures ANOVA										
Effect	Anxiety		Depression		Quality of life		Pain Intensity		Pain Tolerance	
	F	p	F	p	F	P	F	p	F	p
Time	59,7	0	13	0	108	0	10,6	0	73,59	0

Table 5.

One-way repeated measures ANOVA. Paired differences

Paired differences											
One-way repeated measures ANOVA											
		Anxiety		Depression		Quality of life		Pain Intensity		Pain Tolerance	
		F	p	F	p	F	p	F	p	F	p
Pair 1	T2-T1	-3,98	0	-0,22	0,89	-0,61	0	1,17	0	1,84	0
Pair 2	T3-T1	-5,84	0	-1,98	0	-0,45	0	0,66	0	1,23	0
Pair 3	T3-T2	-1,86	0	-1,76	0	0,13	0	-0,45	0,04	-0,63	0

Adjustment predictions one year post-mastectomy

The main outcomes investigated were: anxiety, depression, quality of life, pain intensity, and pain tolerance. Random and fixed effects are presented. Our results indicated that pain catastrophizing predicted significantly each outcome, excepting depression. Anxiety was predicted by pain catastrophizing, baseline anxiety, and time. Also, depression was predicted by problem-focused coping, dysfunctional coping, and baseline depression. Quality of life following mastectomy was best predicted by problem-focused coping, baseline depression, and time. For pain intensity and pain tolerance, besides pain catastrophizing, time may significantly explain the variation in outcome. The random model showed that pain catastrophizing add a significant variability in our outcomes (See Table 6 and Table 7).

Table 6.
Mixed models for predicting adjustment in time post-mastectomy

		Anxiety							Depression							Quality of life						
	Measures	Beta	t	p	Intercept	p	AIC	Covariance Type	Beta	t	p	Intercept	p	AIC	Covariance Type	Beta	t	p	Intercept	p	AIC	Covariance Type
Fix model	Pain catastrophizing	0.072	2.419	.017	86.904	.001	911.324	Toeplitz	.049	1.366	.174	6.190	.00	989.671	Scaled Identity	-.082	-1.156	.251	62.533	.000	1.576	Scaled Identity
	Problem-focused coping								.-159	-1.952	.054					.480	2.603	.012				
	Emotion-focused coping								.098	1.529	.129											
	Dysfunctional coping								.227	2.485	.016											
	Baseline depression								.490	9.910	.000					.237	2.460	.017				
	Baseline anxiety	.486	23.845	.000																		
	Time 1	2.474	2.139	.03					.988	1.072	.287					59.070	6.025	.000				
	Time 2	2.451	2.845	.005					1.345	1.609	.110					-17.737	-8.910	.000				
	Time 3																					
	Time 1 x PCS	.193	3.444	.001					.123	3.100	.002											
	Time 2 x PCS	.009	.232	.817					.034	.873	.384											
	Time 3 x PCS																					
Random model	Pain Catastrophizing	Intercept	p						Intercept	p						Intercept	p					
		.020	.071						.001	.286						.031	.010					

		Pain Intensity							Pain Tolerance						
	Measures	**Beta**	**t**	**p**	**Intercept**	**p**	**AIC**	**Covariance Type**	**Beta**	**t**	**p**	**Intercept**	**p**	**AIC**	**Covariance Type**
Fix model	Pain catastrophizing (PCS) Problem-focused coping Emotion-focused coping Dysfunctional coping Baseline depression Baseline anxiety	.036	2.785	.010	1.178	.000	881.037	ARMA(1,1)	.030	3.745	.000	1.605	.000	1.078	Huynh-Feldt
	Time 1 Time 2 Time 3	.092 .510	.239 2.912	.812 .005					.949 .420	.977 .433	.330 .666				
	Time 1 x PCS Time 2 x PCS Time 3 x PCS														
Random model	Pain Catastrophizing (PCS)	Intercept	p						Intercept	p					
		.004	0.000						.0005	0.01					

3.3.4. Discussion

Previous literature suggests that psychological factors are important in psychopathology and pain perception in different samples of patients who followed medical interventions (Dersh, Polatin & Gatchel, 2002). Also, it is well known that cognitions are central constructs in explanatory models of both anxiety and depression (David & Hofmann, 2013). This study aims to investigate whether pain catastrophizing, coping strategies, baseline anxiety, and baseline depression may significantly predict adjustment (anxiety, depression, quality of life, pain intensity, and pain tolerance), prospectively from the point shortly following breast surgery through the first year. We aim to explore the changes in outcomes across time and to test which of the supposed predictors might explain a greater variability of adjustment after one year following mastectomy.

Our primary analyses regarding adjustment during the first-year after surgery found that for each of the specified outcome measured, except depression and quality of life, pain catastrophizing was a significant indicator of adjustment. It positively predicted anxiety, pain intensity, and pain tolerance. Specifically, for anxiety, our results show that the best predictors were pain catastrophizing, baseline anxiety, and time. Also, we noticed that depression was predicted by problem-focused coping, dysfunctional coping, and baseline depression. According to Falgares, Lo Gioco, Verrocchio, & Marchetti (2018), denial and emotional ventilation could encourage avoidance behaviors, which may increase the risk of developing psychopathology. For pain intensity and pain tolerance, our data suggest that passing of time, beside pain catastrophizing, may significantly explain the variation in outcome. Our results showed that after one-year post-mastectomy, the variable that was adding the most variability in each outcome was pain catastrophizing. These results are of highly importance when it comes to conducting targeted interventions, limited in time and resources, by emphasizing the most predictive variables for specific areas of interest.

Also, our study indicates that anxiety, depression, pain intensity, and pain tolerance are decreasing in time, and quality of life is increasing.

Theoretical and clinical implications

Highlighting the most relevant predictors of pain-related outcomes may inform the psychological interventions, addressing relevant cognitions, emotions, and behaviors in these patients. Our primary results emphasize that pain catastrophizing is a significant predictor of post-mastectomy adjustment indicators. In line with previous studies, the present study indicate that problem-focused coping strategies would have a greater adaptational benefits for women who follow breast cancer surgery. Namely, seeking for instrumental support associates negatively with baseline anxiety, while pain catastrophizing associated positively with this outcome. Also, depression at 6 months was positively associated with dysfunctional coping (ex. denial). Consonant with previous research, our study has shown that while there might be certain coping strategies considered protective factors against psychopathology, others, such as dysfunctional coping (venting, denial) are predictors for different forms of dysfunctional adjustment (Stanton et al., 2002). As it was suggested by previous studies, catastrophizing is a significant predictor for persistent pain following different medical procedures (Sullivan et al., 2001). All in all, the present findings emphasize that besides pain catastrophizing, which is a significant predictor for anxiety, quality of life, pain intensity and pain tolerance, problem-focused coping strategies have a greater adaptational benefits for individuals in threatening situations, in terms of lower depression and higher quality of life. Baseline anxiety influence anxiety in time, while baseline depression impacts depression and quality of life during the first year post-mastectomy. Also, our data sustain

the previous studies, showing that psychological distress in breast cancer patients is common throughout the course of the disease and during recovery period (Somerset et al., 2004). As literature indicated, there is a need to recognize the emotional problems during oncological treatment and post-treatment in order to provide adequate interventions and to prevent emotional distress or pain to become chronic (Falgares, Lo Gioco, Verrocchio, & Marchetti, 2018).

Our results add more empirical support to CBT approach for breast cancer patients by showing the association of pain catastrophizing, coping strategies, and baseline anxiety and depression with clinically relevant aspects one year after cancer treatment. Moreover, risk factors for adjustment during the first year following mastectomy can be identified shortly post medical intervention. Early psychological assessment after surgical intervention may be helpful in identifying patients at risk for emotional distress, decreased quality of life, and pain symptoms (see also Kim et al., 2017). Unidentified emotional distress and untreated predisposing factors significantly reduces quality of life after cancer treatment, while early screening of cognitive, emotional, and behavioral factors activated by the illness would be a first step toward maintaining the quality of life in oncological patients (Reich et al., 2008).

The limits of the present study

As literature suggested, it is difficult to make strong statements on the causal value of pain catastrophizing when it is measured after the initiation of a painful condition. It may rather be a response then a cause of heightened pain and distress (Pavlin, Sullivan, Freund, & Roesen, 2005). Also, the limits of the present research have implications for the generalizability of results. Our participants were women diagnosed with breast cancer, who followed mastectomy. The applicability of the present data to patients suffering from non-cancer clinical conditions, or mixed samples, or other types of cancer, is thus uncertain.

STUDY IV. A Pilot Study to Compare Cognitive Behavioral Therapy with Virtual Reality vs. Standard Cognitive Behavioral Therapy for Oncological Patients

3.4.1. Introduction

Literature highlighted that for patients who suffer from chronic pain, CBT intervention was effective in comparison with no treatment (Morley, 2011). Also, VR intervention are efficient ways of treatment for chronic pain and related outcomes (Li et al., 2011; Botella et al., 2013). These results are not surprising, since it is widely accepted that CBT is the most empirically supported approach in a broad range of psychological conditions, while VR is an effective tool to deliver the relaxation component of treatment (see Herrero et al., 2014).

In this study, we aim to compare the effectiveness of standard CBT VR for relaxation with CBT Standard in improving pain-related outcomes (anxiety and depressive symptoms, quality of life, pain intensity, and pain tolerance). We hypothesized that relative to participants from CBT Standard group, participants who receive CBT VR would have lower anxiety and depression levels. Also, we expect a lower level of pain intensity, a higher level of pain tolerance, and increased quality of life.

[2] This study has been accepted for publication.
Cimpean, A. I. (2019). A Pilot Study to Compare Cognitive Behavioral Therapy with Virtual Reality vs. Standard Cognitive Behavioral Therapy for Oncological Patients, Journal of Evidence-Based Psychotherapies, Vol. 19, No. 1, March 2019, 115-127.

3.4.2. Methods

Participants

A number of twenty participants from Oncological Hospital "Ion Chiricuță" of Cluj-Napoca, Romania were included in the study. Patients diagnosed with cervical cancer were approached by a research assistant to participate to four psychotherapy sessions in order to reduce dysfunctional adjustment to cancer. All participants completed an informed consent. The study was approved by the Ethical Commission.

Procedure

Participants were non-randomly allocated in one of the two groups to receive either CBT VR or CBT standard. Cervical cancer patients who have or are at risk of having anxiety or depression symptoms were included in the study. Twenty participants were enrolled; ten participants were allocated to each group. During the first session, participants were informed regarding their group assignment and were administered the measures of interest. Participants also completed a second assessment after completion of therapy sessions. Patients who dropped out after starting the treatment were requested to complete the measures needed for the final assessment.

The protocol prescribe both groups to follow 15 minutes of relaxation via imagery or in VR exposure. Participants who were following imagery (group CBT Standard) were asked to imagine specific and relaxing contexts meant to create positive physical or emotional responses. Participants from CBT VR group were exposed to scenes with natural environment which aimed to promote relaxation. Both interventions are based on mental representations by recalling memories/ images, with the goal of changing the actual symptom experience (Marks, 1973). Therapy sessions were delivered by psychotherapists trained in cognitive-behavioral framework.

The potential mechanisms behind VR exposure are positive emotions, focused attention, and redirection of attention o stimuli which are not related to pain (Botella et al., 2013). This tool may be a part of CBT protocol, besides the well-known components: psychoeducation, cognitive restructuring, behavioral activation/ planification, skills training, and relapse prevention (Greer et al., 2010). The adapted intervention from Greer et al. (2010) proposed protocol was formed by four 60-minute individual sessions and focused on addressing the cognitive and behavioral factors as described above (see Greer et al., 2010). The sessions were following traditional treatment structure.

Measures

Pain catastrophizing

The Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) The Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) is a self-report measure of pain catastrophizing. The scale evaluates dysfunctional thoughts associated with pain by using 13 items.

Anxiety and depression

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS is an instrument used to evaluate the psychological distress across different populations.

Quality of life

The Functional Assessment of Cancer Therapy - General Scale (FACT; Cella, Tulsky, Gray, 1993). This instrument is used to assess the quality of life. It has good psychometric properties (Cella, Tulsky, Gray, 1993).

Pain outcomes: pain intensity and pain tolerance

Pain intensity and pain tolerance were assessed using a standard 10- cm visual analog scale (VAS). The end points for assessing pain intensity were labeled "no pain" and "pain as bad as it could be", while for pain tolerance they were labeled as "low tolerance" and "very high tolerance".

CBT protocol

The therapy sessions included the cognitive and behavioral features, following the protocol described by Greer et al. (2010). Specifically, it focused on: cognitive restructuring of catastrophic evaluations of eventual pain symptoms and other physical symptoms, coping strategies, and relaxation.

Statistical analyses

Standard univariate (means and standard deviations) were calculated to summarize outcome measures. Student's t-test and Mann-Whitney U test were used to compare groups. IBM SPSS Statistics for Windows, Version 21.0 was used to conduct these analyses.

3.4.3. Results

Descriptive statistics

The means and standard deviations of the participants' scores of the variables chosen for this investigation at the pre-test and post-test were calculated (See Table 1).

Table 1.
Descriptive statistics

Time		Pain catastrophizing		Anxiety		Depression		Quality of life		Pain Intensity		Pain Tolerance	
		M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Pre-Intervention	CBT VR	19,1	11,11	5,4	3,8	5,3	4,34	48,49	6,1	2	0,89	2,18	0,68
	CBT Standard	16,8	10,99	4,6	4,27	4,5	5,74	50,75	0,71	2,08	0,37	2,4	0,49
Post-Intervention	CBT VR	14,38	12,61	3,46	2,38	3,78	2,31	65,64	4,78	1,45	0,68	2,01	0,94
	CBT Standard	11,9	11,18	3,98	0,44	4,28	1,5	65,83	4,97	1,66	0,62	2,14	0,73

Group comparisons

Nonparametric and parametrical analyses were performed to investigate whether there are differences between the scores from pre-treatment to post-treatment on our main outcomes. No significant differences were observed between the two groups (See Table 2 and Table 3).

Table 2.
Nonparametric analysis. Group comparisons on pre and post intervention

Time	Nonparametric Test	Pain Catastrophizing	Anxiety	Depression	Quality of life	Pain Intensity	Pain Tolerance
Pre-Intervention	Mann-Whitney U	46	42,5	39	37,5	40	40,5
	Wilcoxon W	101	97,5	94	92,5	95	95,5
	Z	-0,3	-0,57	-0,84	-1,17	-0,94	-0,89
	Asymp. Sig. (2-tailed)	0,76	0,57	0,4	0,24	0,35	0,38
	Exact Significance	.796b	.579b	.436b	.353b	.481b	.481b
Post-Intervention	Mann-Whitney U	48	47,5	41	49	38	39
	Wilcoxon W	103	102,5	96	104	93	94
	Z	-0,15	-0,23	-0,84	-0,08	-0,96	-0,86
	Asymp. Sig. (2-tailed)	0,88	0,82	0,4	0,94	0,34	0,39
	Exact Significance	.912b	.853b	.529b	.971b	.393b	.436b

Table 3.
Parametric analysis. Group comparisons on pre and post intervention

Time	Pain catastrophizing		Anxiety		Depression		Quality of life		Pain Intensity		Pain Tolerance	
	t	p	t	p	t	p	t	p	t	p	t	p
Pre-Intervention	0,46	0,64	0,44	0,66	0,35	0,72	-1,16	0,26	-0,25	0,8	-0,83	0,41
Post-Intervention	0,46	0,64	-0,68	0,5	-0,57	0,57	-0,86	0,93	-0,71	0,48	-0,33	0,73

Overall comparisons

We compared the scores from pre-to post intervention, regardless of the group allocated. Paired-samples t test was performed. We found significant differences on quality of life and pain intensity, $p < .05$ (See Table 4 and Table 5).

Table 4.
Nonparametric test. Overall comparisons from pre to post intervention

Statistical test	Pain Catastrophizing	Anxiety	Depression	Quality of Life	Pain Intensity	Pain Tolerance
Wilcoxon Signed Ranks Test	-1.569b	-.785b	-.588b	-3.887c	-2.213b	-1.378b
Asymp. Sig. (2-tailed)	0.117	0.433	0.556	0	0.027	0.168

Table 5.
Parametrical test. Overall comparisons from pre to post intervention

Measures	t	p
Pain Catastrophizing	1.24	0.23
Anxiety	1.35	0.19
Depression	0.84	0.41
Quality of Life	-9.69	0.00
Pain Intensity	2.30	0.03
Pain Tolerance	0.94	0.36

3.4.4. Discussion

This is one of the few studies comparing CBT VR with CBT Standard as an alternative way to induce relaxation in the psychological treatment of cervical cancer. The protocol was adapted from Greer et al. (2010) and included elements of CBT. The intervention focused mainly on cognitive restructuring of catastrophic interpretations of eventual pain symptoms and other physical symptoms, and also included behavioral activation/ planification, coping strategies, and relaxation training.

Our results showed that there are no significant differences between the groups. However, a decreasing trend may be observed from pre-to post intervention in both groups. Still, the significance level was not attained. Literature suggested that pilot studies can mislead decision if the results are not carefully interpreted, since the sample sizes and the statistical power are usually small or not enough to identify significant differences in outcomes (Kraemer et al., 2006; Thabane et al., 2010). However, significant differences on quality of life and pain intensity, regardless of the group, were found on pre to post intervention. These results are not surprising, also different studies which investigated the psychological interventions in oncological settings (e.g., group support, individual psychotherapy, psychoeducation, relaxation training) showed effective results in treating psychological distress, manage pain, improve quality of life, and even extend survival in patients with cancer (Greer et al., 2010).

Theoretical and clinical implications

As previously mentioned, our results shown that CBT VR had the highest number of patients who completed all the sessions. Literature indicated that VR is accepted by patients, with significant efficacy for the induction of positive emotions, such as relaxation during a painful condition (e.g. Herrero et al., 2014). Patients reported feeling better after going through the VR procedure (see also Herrero et al., 2014). As we noted previously, there were significant differences from pre-to post intervention on quality of life and pain intensity on overall analysis. Considering that CBT was delivered in both groups, following the same components and structure, these results may indicate that CBT is a useful intervention for hospitalized patients with cervical cancer in reducing the level of perceived pain and in increasing quality of life.

The limits of the present study

The main limits of the present study are based on the low number of participants, which influenced the power of our study. Also, initial and final assessment was conducted by the same person that was also conducting the therapy sessions, which may have biased the responder's answer. Regarding the time for exposure in VR, it varied from 5 to 15 minutes due to cyber sickness declared by some participants, while in the standard CBT, imagery was delivered for 15 minutes. There is an inequivalence of time exposure which may have influence the results from CBT VR group. Nevertheless, the present study was non-randomized. Therefore, the conclusions based on the present data must cautiously be interpreted.

CHAPTER IV. GENERAL CONCLUSIONS AND DISCUSSIONS

This thesis investigated the role of pain catastrophizing as a transdiagnostic factor for pain and emotion. By addressing core features, such as pain catastrophizing, we aimed the generalization of treatment elements for both sensorial and emotional component of pain experience, as a way of effectively treating both problems. Pain and distress fit within the transdiagnostic paradigm, given the high rates of psychological comorbidity in pain populations or given the efficacy of coping strategies for managing chronic pain (see Allen, Tsao, Seidman, Ehrenreich-May, & Zeltzer, 2012).

It has been stated that rather than focusing on how pain and emotion are diagnostically different, identifying the similar underlying cognitive features would bring signifficant benefits to both problems (Harvey, Watkins, & Mansell, 2004). Although this is a promising path, there is still a strong need for data to support this perspective (Linton, 2013). In this project, in order to respond to the need for a more integrative perspective, four studies were conducted to investigate the associations and causal links between pain catastrophizing and relevant pain-related outcomes. The first study was the meta-analysis, conducted on mixed samples (acute, chronic, and experimental pain), Study 2 was conducted on a healthy sample, while Study 3 and Study 4 were conducted on oncological patients. The rationale of each study is summarized below.

Given the high heterogeneity of the data in the literature, our first study was a meta-analysis. We summarized the findings investigating the association of pain catastrophizing with a series of pain-related outcomes. We aimed to emphasize the similarities of the association's strength of pain catastrophizing with both pain and distress, namely the sensorial and emotional dimensions of pain. Our second study was conducted based on the results of the first study and based on the recent data in the literature, which indicated that pain catastrophizing and anxiety may independently explain variances across pain-related outcomes. We investigated the paths of pain catastrophizing and anxiety in pain related anxiety and pain tolerance, testing response expectancies and pain intensity as possible mediators. Our results indicated that anxiety is the only predictor for these outcomes. Therefore, the third study took into consideration the baseline level of psychopathology (anxiety and depression), together with pain catastrophizing and coping strategies, in predicting adjustment across time (anxiety, depression, quality of life, pain intensity, and pain tolerance) in a sample of cancer women who followed mastectomy. Our primary results showed the highly importance of pain catastrophizing, baseline psychopathology and dysfunctional coping in predicting anxiety, depression, quality of life, pain intensity, and pain tolerance. Our data showed significant predictive power of pain catastrophizing on adjustment indicators, excepting depression at both 6 and 12 months following mastectomy. As a result of study one, study two and study three, we conducted a pilot study to test the impact of CBT VR vs. CBT Standard in reducing pain catastrophizing and psychopathology in oncological patients. In both groups, a protocol focused mainly on cognitive restructuring, with elements of behavioral modification was focused on decreasing pain catastrophizing, anxiety, and depression, and on increasing the quality of life and pain tolerance. We expected superior results for CBT VR. Also, based on the findings from the previous studies, we expected that both groups to have significant results on targeted outcomes from pre to post intervention. We found no significant differences between groups. However, a significant result from pre to post intervention was noticed on overall comparisons.

4.1. Theoretical Advances and Implications

Based on the findings of the present thesis, several implications emerge. Our studies shown that pain catastrophizing is a common factor for pain and psychopathology, which often co-occur. It is important to underline these results, since literature stated that unified treatment principles would increase the efficiency of treatments (Wilamowska et al., 2010; Hanscom et al., 2015). The findings of the present research contribute to the transdiagnostic model and facilitate theoretical advances of the literature on pain and related emotions, by emphasizing systematic association of pain catastrophizing with pain and distress, by testing the paths that may explain its impact on pain and distress, and by showing if it has a significant contribution to the well- known predictors of adjustment in oncological patients.

First, in Study 1 the literature concerning the relationships between pain catastrophizing with pain and distress (anxiety, depression, fear of pain, emotional distress) was systematically reviewed. This is the first quantitative study to summarize these associations. Results indicate medium effect sizes. This study facilitates a step forward to a transdiagnostic approach for affective and sensorial components of pain by showing similar effect sizes for both emotional distress and pain intensity (see Harvey, Watkins, & Mansell, 2004 et al., 2004; Linton, 2013). The consequences of this perspective are strongly sustained by the literature, with multiple implications on prevention, etiology, as well as in the processes of maintaining a disorder (Harvey et al., 2004). Also, our findings showed differences between studies conducted on acute/ chronic vs. experimental pain. Specifically, chronic pain populations highlight a stronger association of pain catastrophizing with anxiety and depression. These results suggest that patients with medical diagnoses are more likely to suffer from dysfunctional emotions, such as anxiety and depression, which might indicate that the presence of an actual or inferred negative activating event, such as a specific illness, will activate maladaptive beliefs and conduct to dysfunctional outcomes (Dryden & David, 2005; David et al., 2008). Study 2 expands on the paths of pain catastrophizing and anxiety to predict pain related anxiety and pain tolerance in neutral and aversive context. The relation from anxiety to pain tolerance or pain related anxiety was mediated by response expectancies. Pain catastrophizing predicted significantly pain tolerance and pain related anxiety in aversive group, while in the neutral group in is not predictive. This study indicates the importance of contextual cues, since they provide important information about the likely outcome of a response (Linton, Flink, Schrooten, & Wiksell, 2016). Our study emphasized the relevance of response expectancies as factors that contribute to the development of dysfunctional pain related responses. As Edwards et al. (2008) suggested, these findings may emphasize that pain catastrophizing represent a latent construct that require a threatening context to be activated. Also, since pain catastrophizing needs a cue to become manifest, the experimental context is strongly relevant (Merskey & Bogduk, 1994) because it activates maladaptive beliefs, which impact significantly one's behavioral and emotional responses (David, Freeman, & DiGiuseppe, 2010; Szentagotai & Jones, 2010). Moreover, framing of a painful event in terms of threat increased the level of reported anxiety, which influenced pain tolerance and pain-related anxiety.

Given the results of Study 2, which emphasized that anxiety has an important contribution to pain-related anxiety and pain tolerance, we concluded that the initial level of psychopathology in a threatening health context may have significant impact on adjustment. Therefore, Study 3 aimed to specify the contribution to adjustment (anxiety, depression, quality of life, pain intensity, and pain tolerance) of baseline psychopathology (anxiety and depression) pain catastrophizing, and coping strategies. Although the impact of pain catastrophizing on pain-related outcomes has been extensively investigated in the literature, little are known about the predictive value of coping strategies and baseline psychopathology in the same model, in predicting adjustment prospectively from the point shortly following breast surgery through the first year. Except depression and quality of life, pain catastrophizing significantly predicted each outcome. Psychopathology and coping strategies added significant variability, relevant to predict adjustment one-year follow-up. In line with previous studies (Stanton, Danoff-burg, & Huggins 2002), our data indicate that, together with pain catastrophizing, problem-focused coping strategies (approach-oriented coping strategies) would have a greater adaptational benefits for women who follow breast cancer surgery. Specifically, pain catastrophizing predicted significantly anxiety, pain intensity, and pain tolerance one year post surgery. Moreover, anxiety was significantly predicted by pain catastrophizing, baseline anxiety, and time. Although depression was not predicted by pain catastrophizing, problem-focused coping, dysfunctional coping, and baseline depression added significant variability. Quality of life was significantly predicted by problem-focused coping, baseline depression, and time. Also, pain

intensity and pain tolerance were significantly predicted by pain catastrophizing and time. However, these results add more empirical support to CBT approach for breast cancer patients by showing the association of pain catastrophizing, dysfunctional coping strategies, and psychopathology with clinically relevant aspects one year after cancer treatment.

Considering the high level of co-occurrence of psychopathology symptoms observed in our previous study, and the identification of pain catastrophizing, coping strategies and baseline psychopathology as relevant for future adjustment, Study 4 was focused on reducing the psychological distress of hospitalized oncological patients. Therefore, we compared CBT VR with CBT Standard. We targeted the reduction of anxiety, depression, and pain intensity, and the increasing of quality of life and pain tolerance. Although CBT VR was not superior, as hypothesized, we found significant improvement on overall comparisons on pain intensity and quality of life, which may suggest the potential effectiveness of CBT for these patients on the specified outcomes.

Taken together, our data sustain that pain catastrophizing may have a transdiagnostic role in pain and emotion. By emphasizing systematic associations and significant predictive power, in different research contexts, pain catastrophizing might be considered a core feature of pain and emotion. The present findings may represent a step further to the theoretical understanding of the factors involved in pain and distress, which may influence the generalization of psychological treatments.

4.2. Methodological Advances and Practical Implications

Several methodological and practical features were refined by the studies of the present thesis. The implications for research and practice are explored below. Firstly, it is important to underlie the practical implications of the Study 2, which suggested that framing of painful events in terms of threat may increase the level of reported anxiety (Cameron, 2003), while the interaction of threat with distorted cognitions might lead to emotional and behavioral difficulties (Beck, Rush, Shaw, & Emery, 1979) and may influence the behavioral decisions and pain tolerance (Payne, Bettman, & Johnson, 1992). As it was stated in Study 2, it is important to underline the effect of information communication in health threatening situations, since numerous studies indicate that patients' behavioral and emotional outcomes are influenced by the interaction between patient's cognitions and by the general framing of the health problem (Krishnamurthy, Carter, & Blair, 2001). Also, given that literature emphasize the need for assessing pain catastrophizing in the context, Study 2 is one of the few experimental studies on pain that manipulate the context of the painful stimulus to highlight the interaction of the activating event with the distorted cognitions. The experimental procedure was adopted from experimental studies on anxiety induction and successfully used in pain context.

Nevertheless, the findings of the Study 3 indicated the trends of psychopathology in patients who followed mastectomy. The results have practical implications, suggesting that patients should be routinely screened for psychological distress. Also, these data suggest that there is a strong need to identify assessment tools to evaluate in real time the symptoms that might appear shortly post-medical intervention.

Also, Study 3 suggests that pain and psychological distress in breast cancer patients is common after treatment and during the first year of recovery. Risk factors for adjustment across this period following mastectomy can be identified shortly post medical intervention, with important benefits for clinical assessment and intervention. As literature indicated, unidentified and untreated psychopathology among breast cancer patients significantly compromises women's quality of life after medical intervention (Reich, Lesur, & Perdrizet-Chevallier, 2007). Psychological evaluation may be the key factor in providing the best care and support, due to the importance of early identification of patients with depression or anxiety symptoms. Our

study showed a significant drop in quality of life after six months It is widely highlighted in the literature that breast cancer surgery is significantly related with clinical psychological distress and a low quality of life (Reich et al., 2007). In order to manage these symptoms appropriately and to prevent recurrence of psychiatric disorders or decreases in quality of life (Reich et al., 2007) we should be aware of the most predictive psychological factors. Therefore, clinicians should consider the interaction of pain catastrophizing with emotional distress and overall pain experience and make necessary multidisciplinary referrals (see Fischer et al., 2010).

4.3. Limitations and Future Directions

This thesis has several limitations. The specific limits of each study have been outlined at the discussion section of each study. Therefore, we will focus on the general limits of the thesis.

The first limit of the present research is the high level of heterogeneity of the samples included. In Study 2 we had undergraduate young students, preponderantly women, while in Study 3 and Study 4 we had oncological patients diagnosed with breast and cervical cancer. The replication of the present findings on samples with different demographic characteristics and different types of pain or medical diagnoses is uncertain. A second limitations of this thesis is that only self-report assessment tools were used to assess pain intensity or pain-related outcomes. Also, some analyses (such as path analyses) are recommended to be ran on larger samples. Although acceptable in the literature, using the minimum sample size recommended per independent variable generates a reduced statistical power for these analyses. Nevertheless, manual recordings of pain tolerance time and pain threshold allow for human errors in measurement, which lead to artificial high variances of results on these outcomes.

In order to draw stronger conclusions, future studies should consider behavioral or physiological measures for pain-related outcomes on larger samples and simultaneously with when they occur. Given the need to track fluctuations in pain or to evaluate the health-related indices (such as daily symptoms of pain, sleep problems, the level of physical activity, and mood problems), and considering the positive attitude of patients about technology, electronic diaries might be a tool to collect and evaluate data from patients in real-time (see Jamison, Xu, Wan, Edwards, & Ross, 2019).

More specifically, mobile pain applications, due to their flexibility, simplicity, and increasing affordability, might help in the identification and monitorization of patients who have high levels of pain catastrophizing, anxiety, depression, or dysfunctional coping strategies, facilitating the communication of health status to health care providers (Richardson & Reid, 2013). These applications are reliable and safe in collecting data from patients and their family, and might improve pain management and pain interventions (Richardson & Reid, 2013). This is a proposed assessment strategy that needs further research to validate its stability and we also need to further understand whether computer-based interventions for pain population might be effective (Jamison et al., 2019). Nevertheless, larger controlled studies are needed to emphasize the potential improvements of VR to CBT protocol used for the treatment of pain-related outcomes.

However, despite the limitations of this thesis, significant theoretical advances and practical implications emerge. Firstly, this thesis sustains the transdiagnostic model for pain and emotion by adding significant data that highlight the role of pain catastrophizing for both pain and emotion in different samples. Secondly, our data suggests that relevant psychological predictors for pain-related outcomes might be assessed shortly post medical diagnosis in order to predict pain-related outcomes variances across time, emphasizing the role of pain catastrophizing. Screening for a mutual cognitive predictor of pain-related outcomes in acute and chronic pain and investigating the emotional consequences that this feature might have on

adjustment and on the overall quality of life is an accesible method to identify the patients who might benefit the most from psychological interventions. Nevertheless, a transdiagnostic perspective on the treatment of pain and distress may result in improved pain management, improved quality of life, and ease of implementation.

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Note* The marked studies from the reference list represent all the studies included in the meta-analysis.