Journal of Pain Research

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REVIEW

Investigating the Impact of Stress on Pain: A Scoping Review on Sense of Control, Social-Evaluative Threat, Unpredictability, and Novelty (STUN Model)

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Background: Stress can have paradoxical effects on pain, namely hyperalgesia and hypoalgesia. Four situational characteristics activate the hypothalamic–pituitary–adrenal axis, leading to a physiological stress response: lacking Sense of control, social-evaluative Threat, Unpredictability and Novelty (STUN). This scoping review reports on the types of evidence published on the effects of STUN characteristics on pain outcomes.

Databases/Data Treatment: Searches of primary electronic databases were performed to identify articles published on adults between 1990 and 2021 that contained search terms on pain and stress/STUN characteristics. A total of 329 articles were included in the analysis.

Results: Only 3.3% of studies examined simultaneously >1 STUN component. Almost all observational studies (177/180) examined the association between perceived stress and pain without measuring physiological stress responses. Of the 130 experimental studies, 78 (60.0%) manipulated stressful characteristics through nociception, and only 38.5% assessed if/how stress manipulation impacted perceived stress.

Conclusion: There is a clear lack of integration of the characteristics that trigger a physiological stress response in the pain field. Only 3.3% of studies examined simultaneously more than one STUN component and there is an unequal attention given to individual components of the STUN framework. Recommendations for future research include selection of stress manipulations/measurements that are more precisely inducing/reflecting neurobiological mechanisms of stress responses to insure valid integration of scientific knowledge.

Keywords: stress, pain, STUN, control, unpredictability, threat, novelty

Introduction

Stress can be defined as a psychophysiological process, which can be experienced as a negative emotional state resulting from psychosocial or physical demands.[1] According to the International Association for the Study of Pain, pain is an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[2] The impact of stress on pain is generally recognized, but, paradoxically, scientific studies report robust effects in both directions (stress-induced analgesia and hyperalgesic effects).[3–5] Type of stressors can have differential effects on pain. For example, in an acute stress situation, hypoalgesia can be observed, and it may enable the body to adapt to the threat and protect itself.[3] However, chronic stress lacks this adaptive function and can lead to maladaptive physiological responses, including hyperalgesia.[5,6] The available literature on pain and stress is vast, but understanding the conditions under which stress affects pain is critical to improve available theoretical models and further develop

Received: 21 November 2023
Accepted: 7 February 2024
Published: 20 February 2024

innovative interventional approaches. The stress system comprises various mechanisms that are activated under specific conditions and to various degrees in different individuals. The stress response involves the activation of the hypothalamic–pituitary–adrenal (HPA) axis to trigger a cascade of reactions leading to the release of cortisol to prepare for action when facing a potential or an actual threat. Four situational characteristics can activate the HPA axis, leading to the secretion of cortisol:[7,8] reduced Sense of control, Threat to ego (social-evaluative threat), Unpredictability or Novelty (STUN[9]). Lack of Sense of control (or uncontrollability) refers to situations in which behavioral responses are perceived to have little or no impact on an outcome (eg, self-management perceived as ineffective to prevent pain flare). Social-evaluative threat refers to situations in which aspects of self-identity are judged negatively by others, particularly in situations of poor performance, revealing a lack of valued ability or competency (eg, being reprimanded at work). Unpredictability refers to unforeseen situations (eg, people unexpectedly showing up for dinner). Finally, novelty refers to something you are experiencing that happens for the first time (eg, initiating a new treatment).

STUN characteristics might add useful information to existing biopsychosocial models of pain. For example, fear-based responses to pain[10] could be facilitated by the unpredictable nature of, or lack of control over, one's pain.[11] Misunderstanding of one's pain condition by others could be conceived as a social-evaluative threat.[12] STUN characteristics could further be integrated formally into well-accepted clinical models such as the Fear-Avoidance Model of Chronic Pain,[13] where patients might enter the vicious cycle of pain avoidance to minimize one or more stress characteristics of pain.[14] There are many challenges in developing integrative models on the influence of STUN characteristics on pain. The available research relies on a diversity of methods from various disciplines. Better understanding of types of evidence that support the impact of each of the individual STUN components and their interaction on pain would help further develop integrative theoretical neurobiopsychosocial models of stress and pain and identify novel research directions and therapeutic approaches.

The objective of this scoping review was to map the scientific literature at the intersection between pain and stress. More specifically, we report on the types of evidence published in observational and experimental literature on the effects of STUN characteristics on pain outcomes in adult human populations.

Methods

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMAScR) guidelines for scoping reviews were followed in this report.[15] Ethics approval was not necessary for this review.

Study Registration

This study was pre-registered in February 2023 on the Open Science Framework (OSF), after preliminary data search and extraction, but prior to final search and extraction in February 2023. The OSF registration (https://osf.io/fn9t8) contains comprehensive details about the study's objectives, methodology, data collection, and planned analysis.

Eligibility Criteria

Studies were included if they targeted adult human populations (≥18 years old), were published in French or English, and explored the associations between stress or its individual components (Novelty, Unpredictability, Threat to ego or Sense of low control) and pain outcomes. Articles that examined the reverse association, namely the impact of pain on stress levels, were not considered. Results were limited to literature published since 1990.

Studies were excluded if they reported on individuals with cancer-related pain, children (<18 years old), or animal models. Additional exclusion criteria included distal relations between stress and pain, namely when stressors referred to prior experiences (eg, childhood trauma and post-traumatic stress), and non-relevant stress conceptualizations (eg, cardiovascular stress and mechanical stress). Retrospective, prospective, experimental, observational, clinical, qualitative, and mixed-methods studies were included. Comments, letters, editorials, books, and dissertations were excluded. Reviews without original data were used to identify additional potentially relevant articles; the reviews themselves were not included in the results.

Operationalization of Key Constructs

Pain Outcomes

Outcomes of interest were those directly related to one or more dimensions of the pain experience, including pain threshold and tolerance, pain intensity, pain unpleasantness, pain-related interference or disability, multidimensional pain assessments (sensory, affective, evaluative components), or change in pain status. Outcomes were excluded if they did not relate directly to the pain experience, such as quality of life, global distress, or psychological distress.

Independent variables included experimental manipulation of stress or stress measures representing global stress or one or more of the STUN characteristics.

Experimental Stress Manipulation

Experimental procedures known to trigger a stress response were included, whether this manipulation included nociception (eg, unpredictable electric shocks) or non-nociceptive (eg, arithmetic test) stressor. They were divided into global stress measured or identified by one or more of the STUN characteristics that were manipulated.

Global Stress

General measures or non-specific manipulations of stress that did not allow a differentiation of the individual STUN components were grouped under the category global stress. This included, for example, threat manipulation of nociception or global measures of stress such as the Perceived Stress Scale.

Sense of Low Control

Manipulations or measures assessing perceived control over the stressor or general perception of control over ongoing pain experiences were considered. Characteristics related to self-efficacy, pain catastrophizing, or powerlessness were excluded. According to Lazarus and Folkman,[16] these latter characteristics are elements that relate to secondary appraisal of stress, and as such are more distal from the experience of stress itself.

Social-Evaluative Threat (Threat to the Ego)

Social evaluative threats included exposure to situations that threatens one's sense of self, social roles or competency (eg, cognitive or arithmetic stress induction), threatening social contexts, or threats to one's need for belonging (stigma, social exclusion, invalidation of one's experience).[7]

Unpredictability

Key constructs included unpredictable stressors, aversive stimuli, or events, including their timing of occurrence, intensity, duration, or frequency.

Novelty

Novelty, or lack of novelty in the case of habituation, was considered, whether it related to pain or other stressors. Characteristics considered included novelty (or lack thereof) of sensations, location, treatments, stimulus in the case of stress manipulation, or situations (eg, change in employment).

Information Sources

The following databases were searched for relevant studies on July 14, 2020: MEDLINE (via Ovid, 1946 to July 13, 2020) and APA PsycInfo (via Ovid, 1987 to July Week 1 2020). The search strategies designed by a librarian (BN) used text words and relevant indexing to identify relevant studies. The MEDLINE strategy was then applied to PsycInfo, with modifications to search terms as necessary. The search strategies were rerun on April 27, 2021, and again in February 20, 2023, in both databases. References from relevant review papers were also screened.

Search Strategy

The search strategy shown in Supplementary Table 1 used database-specific terms and terminology derived for specific conceptual groups (1) pain (including acute and chronic pain, pain perception, nociception); and (2) stress, including

stress characteristics (Novelty, Unpredictability, Threat to ego or Sense of low control). Controlled vocabulary and free-text searching were used for each database. Details of search terms and strategies can be found in Supplementary Table 2.

Selection of Source of Evidence

References were managed using EndNote X9[17] including removal of duplicates prior to being imported in Covidence.[18] Titles and abstracts were screened by one of four coders. Evaluation of the full text was then performed for the remaining articles by two of four independent coders. Conflicts were resolved by the third coder or through consensus among all coders.

Data Charting Process

Data charting was done using a data extraction template created in Covidence by one of the authors. The template was tested on 5 articles and then modified to adequately capture information relevant to the various study designs and populations of the included studies. The template was iteratively tested on additional articles until judged satisfactory by all three coders. Charting was done independently by coders, but ambiguities were discussed and resolved to insure standardization of data extraction.

Data Items

Data related to study characteristics (authors, publication reference, country), objectives, design (study type, design), population (eligibility criteria, recruitment procedure, setting, number, sex, gender, age, ethnicity), stress (manipulation/measure, STUN characteristic, timing of administration compared to pain outcome), pain outcome (dimension and definition, unit of measurement), statistical tests, and results were extracted.

Synthesis of Results

Observational, experimental, and qualitative studies were examined separately to assess the scope of investigations of the STUN components in relation to pain outcomes and population studied. A qualitative synthesis was done to provide a summary of study characteristics and findings of included studies, comment on the individual and interactive examinations of the STUN components and discuss gaps in the evidence in terms of study types (experimental/observational), populations, and STUN components.

Results

Selection of Sources of Evidence

A total of 20,522 articles were found (see Figure 1). Duplicates (n=3816) were sorted, which resulted in 16,706 articles for title and abstract screening. Evaluation of the full texts was performed on 1635 articles; 1306 articles were excluded. PRISMAScR flow chart of identified articles for inclusion and exclusion is shown in Figure 1. References of all 329 included studies are listed in Supplementary Table 3.

Characteristics of Sources of Evidence

Characteristics of included studies are summarized in Table 1. Most studies (80.3%) were from Europe or North America. Very few studies were qualitative or mixed methods (n=19; 5.8%) and slightly more than half (54.7%) were observational, defined as the measurement of stress in the absence of an experimental manipulation of stress or its STUN characteristics.

As shown in Figure 2 and detailed in Table 1, a large proportion of studies (49.5% (not taking into account the two studies that examined global stress and one or more STUN characteristics)) examined stress conceived as a global state not specified in a way that could be tied clearly to the STUN characteristics. Social evaluative threat (ego) was the characteristic of the STUN framework most often examined (17.9% of studies) while only 3.3% of studies simultaneously examined more than one STUN component. There is a marked increase in the number of studies examining

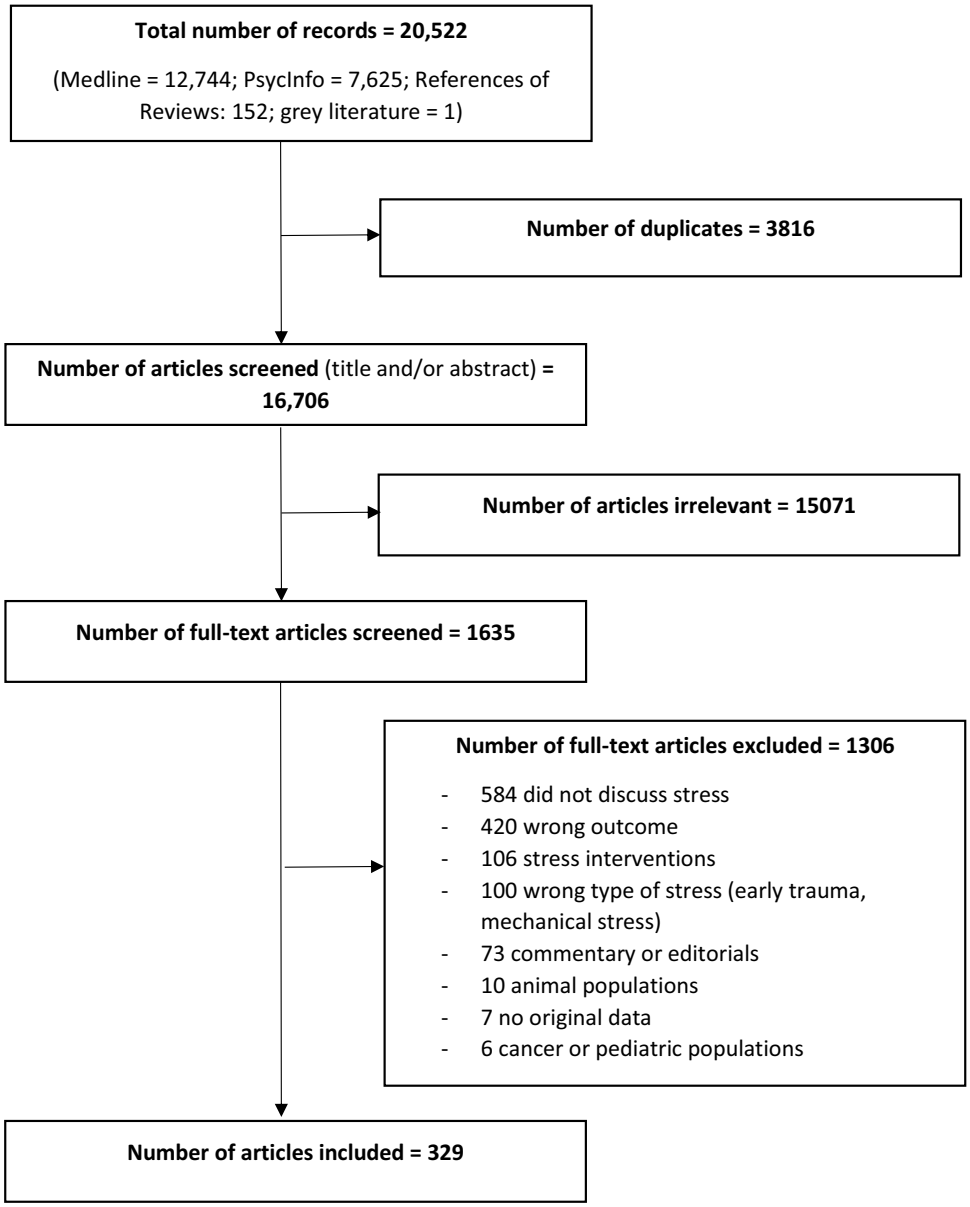


Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMAScR) flow chart of identified articles for inclusion and exclusion.

global stress or individual STUN components since 2005. Noticeably, there has been very little research on unpredictability, novelty and, to a lesser extent, social-evaluative threat, up until 2005.

Characteristics of observational, experimental, and qualitative studies are shown in Supplementary Tables 4–15, respectively.

Sources of Evidence

Observational Studies

STUN Components

Many observational studies (including the one article using mixed methods (Pagé et al 2021a)) focused on measures of global stress (N=156/181; 86.2%). No studies were found that examined novelty. Fifteen (8.3%) out of 181 studies examined sense of control, 7 (3.9%) studies examined social-evaluative threat, and one (0.6%) examined unpredictability. Only 4 (2.2%) studies have examined multiple STUN components.

Table 1 Characteristics of Included Studies

Characteristics	Number (N=329)	Proportion (%)
Year of publication		
1990–1994	19	5.8%
1995–1999	10	3.1%
2000–2004	23	7.0%
2005–2009	52	15.8%
2010–2014	61	18.5%
2015–2019	77	23.4%
2020–2023	87	26.4%
Geography		
Europe	144	43.8%
North America	120	36.5%
Oceania	20	6.1%
Asia	27	8.2%
Other	18	5.4%
Study type		
Observational examination of stress	180	54.7%
Experimental/laboratory manipulation of stress[a]	130	39.5%
Qualitative studies	18	5.5%
Mixed methods	1	0.3%
Stress characteristics[b]		
Global/general stress	165	50.2%
Sense of low control	39	11.9%
Social evaluative threat (threat to ego)	59	17.9%
Unpredictability	35	10.6%
Novelty	22	6.7%
Multiple characteristics	11	3.3%

Notes: [a]Experimental/laboratory study type does not refer to the study design, but rather to the manipulation of stress. For example, a randomized-controlled trial of a psychological intervention for pain that assessed stress at baseline but did not attempt to manipulate stress during the intervention will be classified under Observational examination of stress. [b]Two studies (Meredith et al 2006 and Scherrer et al 2022) examined STUN characteristics and global/general stress and are thus counted twice in this section.

Relations Between Stress and Pain Outcomes Examined

Figure 3 shows the possible associations between stress and pain that could be examined. Link a represents the association between objective manipulation or presence of STUN characteristics of stress exposure and pain outcomes, however it does not consider whether this stress exposure was perceived as stressful (link b), whether it generated a physiological stress response (link d) or whether this stress perception (link c) or physiological response (link e) are associated with pain outcomes.

All observational studies focused on the association between perception of stressful STUN characteristics or global stress and pain outcomes (link c). Only three also examined the link between physiological stress response and pain outcomes.

Stress Measures

A wide array of questionnaires were used to measure global stress, including daily stress/hassles, life events, occupational stress, psychosocial stressors, stress related to procedures or treatments, and non-standardized single-item stress scales. The Perceived Stress Scale (including original and revised versions) (n=39) and the Depression Anxiety and Stress Scale-21 (n=22) were the most frequently used. Measures of perceived control included the Illness Perception Questionnaire (8 studies; 53.3%), Iowa Dental Control Index (3 studies; 20.0%), and other perceived and anticipated control questions (4 studies; 26.7%). All studies measuring social-evaluative threat (n=7) used different scales focused on social exclusion or

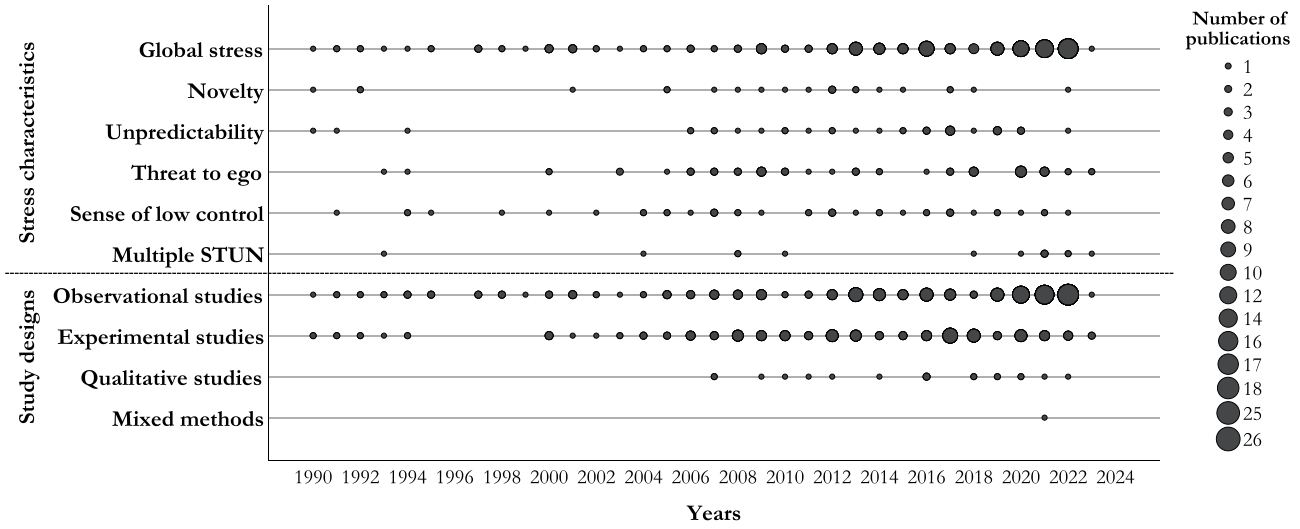
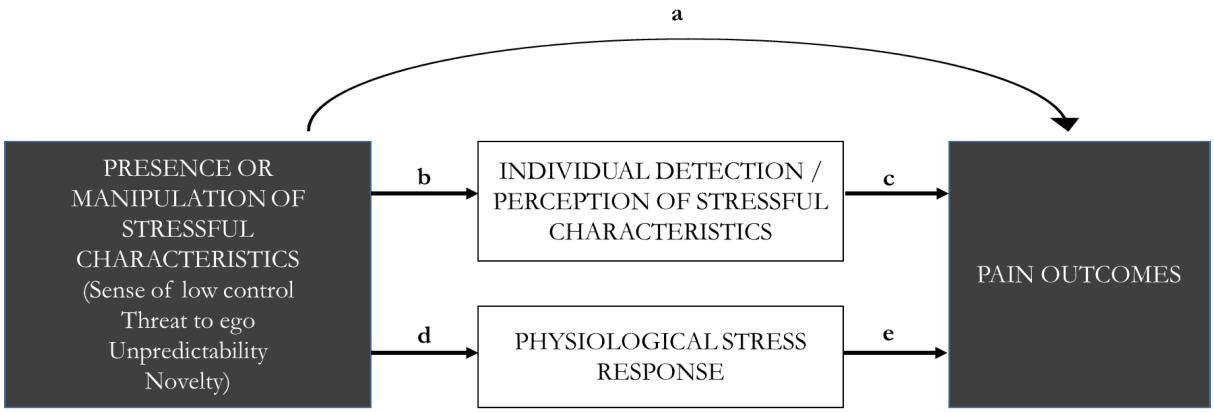


Figure 2 Distribution of articles according to year of publication and content. Top grey zone indicates the number of included articles based on their year of publication (x-axis) and study design (y-axis). The bottom white zone shows the number of included articles based on their year of publication (x-axis) and stress characteristics examined. The larger the circle, the greater the number of articles falling in a specific study design/stress characteristic on a given publication year, as shown on the legend right of the figure.

Abbreviation: STUN, Sense of low control, Threat to ego (social evaluative threat), Unpredictability, and Novelty framework.

A



B

Stressful characteristics	Observational studies					Experimental studies				
	a	b	c	d	e	a	b	c	d	e
Multiple STUN	0 (0)	0 (0)	4 (100.0)	0 (0)	0 (0)	4 (100.0)	1 (25.0)	1 (25.0)	0 (0)	0 (0)
Sense of low control	0 (0)	0 (0)	15 (100.0)	0 (0)	0 (0)	22 (100.0)	9 (40.9)	0 (0)	0 (0)	0 (0)
Threat to ego (social evaluative)	0 (0)	0 (0)	7 (100.0)	0 (0)	0 (0)	47 (94.0)	30 (60.0)	16 (32.0)	21 (42.0)	14 (28.0)
Unpredictability	--	--	1 (100.0)	--	--	28 (100.0)	9 (32.1)	1 (3.6)	0 (0.0)	0 (0.0)
Novelty	--	--	--	--	--	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Global stress	0 (0)	0 (0)	156 (100.0)	0 (0)	3 (1.9)	3 (75.0)	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)

Figure 3 Type of associations between stress and pain outcomes. The top figure (**A**) illustrates the possible relationships that can be examined. Link a represents an investigation of the impact of manipulating STUN characteristics (eg, administering uncontrollable nociceptive stimuli) on pain outcomes. Link b represents an examination of the impact of manipulating STUN characteristics on perceived stress (eg, manipulation check – whether participants perceived an uncontrollable nociceptive stimulus as actually uncontrollable). Link c examines the association between perceived stress and pain outcomes. Link d examines the association between presence or manipulation of STUN characteristics on physiological stress response, such as cortisol. Finally, link e examines the association between the physiological stress response and pain outcomes. The bottom figure (**B**) documents the proportion of studies in both experimental and observational studies that examines the various links shown in the figure, as a function of the STUN characteristics. Note that many studies examined more than one link such that the sum of % often exceeds 100%.

Abbreviation: STUN: Sense of low control, Threat to ego (social evaluative threat), Unpredictability, and Novelty framework.

rejection (n=2; 28.6%), criticism (n=1; 14.3%), perceived competence (n=1; 14.3%), stigma (n=1; 14.3%), abusive supervision (n=1; 14.3%), or stress associated with social isolation (n=1; 14.3%).

Population

More than half of studies examined the association between stress and pain outcomes in individuals with acute or chronic pain conditions (N=96/181; 53.0%). The remaining studies relied on volunteers recruited from the general populations including convenience samples defined by occupational status (eg, workers and students) and individuals with chronic conditions not defined primarily by pain (eg, depression and eating disorder). Important variations were observed in terms of studied population across STUN characteristics. Investigations on global stress examined acute or chronic pain populations in less than half of studies (N=77/156 studies on global stress; 49.4%), while these populations were the focus of 12 of 15 studies (80.0%) that examined sense of control, and 4 of 7 studies (57.1%) that investigated social-evaluative threat.

Pain Outcomes

Pain outcomes as a function of the STUN characteristics are shown in Figure 4A. Pain outcomes measured included pain intensity, pain unpleasantness, pain severity, pain burden, number of pain sites, pain onset, multidimensional pain, pain disability, functioning, interference, pain threshold/tolerance/sensitivity, and different aspects of pain frequency. Of note, pain unpredictability was only examined in relation to pain frequency. Sense of low control, social evaluative threat, and multiple STUN characteristics were examined in relation to various pain outcomes (see Figure 4A for details).

Experimental Studies

STUN Components

The number of studies that examined global stress and individual STUN components was relatively well balanced. Out of the 130 experimental investigations, 22 (16.9%) manipulated control, 50 (38.5%) manipulated social-evaluative threat, 28 (21.5%) manipulated unpredictability, 22 (16.9%) manipulated novelty, and 4 (3.1%) performed general stress induction. Only 4 (3.1%) studies manipulated more than one STUN component.

Relations Between Stress and Pain Outcomes Examined

As shown in Figure 3, almost all studies (n=126/130; 96.9%) examined the association between STUN characteristics (eg, manipulating predictability or controllability of nociception) and pain outcomes, while a minority of those studies verified whether this manipulation was perceived as stressful (50/130; 38.5%). Except for one global stress study, only studies examining social-evaluative threat (n=21) measured physiological stress response (eg, cortisol levels), or the association between physiological stress response and pain outcomes (n=14).

Stress Manipulation

Stress stimulations are shown in Figure 4B. Various experimental strategies were used to induce stress. In many studies (n=79/130) the stress induced was directly related to chemical, thermal, ischemic, electrical, or mechanical nociceptive stimulation. This is the case for most experimental studies testing sense of control (n=21; 95.5%), unpredictability (n=28; 100%), and novelty (n=22; 100%). Three out of four studies manipulating general stress (75%) also manipulated stressfulness of nociception. In contrast, almost all studies on social-evaluative stress (n=49; 98.0%) relied on a stress induction method unrelated to nociception (eg, mental arithmetic, public speaking, or other forms of social stress).

Population

Most experimental studies recruited exclusively healthy individuals from the general (N=80; 61.5%), student (N=28; 21.5%) or working (N=2; 1.5%) populations. Acute or chronic pain populations (N=6; 4.6%) or simultaneous examination of general and chronic pain populations (N=14; 10.8%) were investigated in the remaining studies.

There were fewer variations in terms of studied populations across STUN characteristics compared to observational studies. Investigations on global stress (n=4; 100.0%), sense of control (n=22; 100.0%), and multiples STUN components (n=4; 100.0%) focused on general populations. Most investigations of social evaluative threat (34/50; 68.0%) focused on

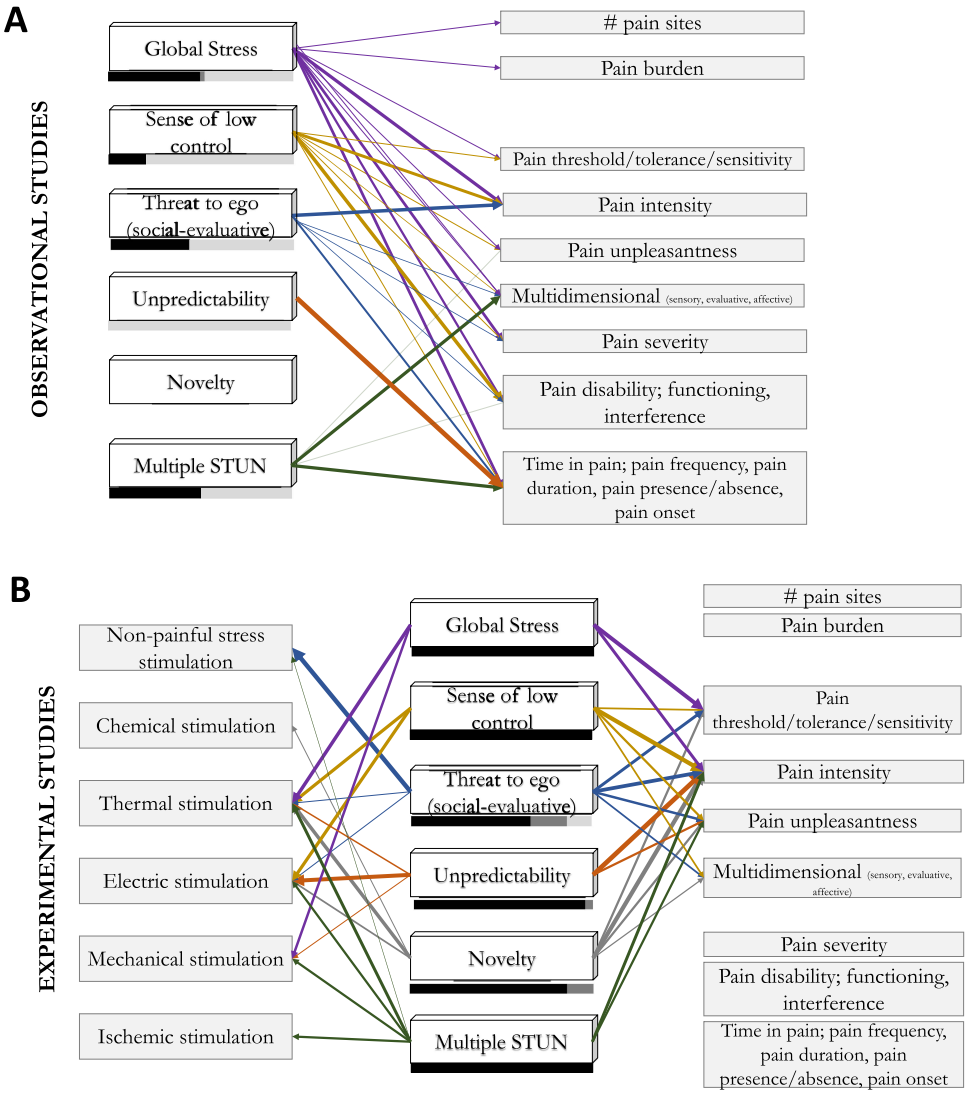


Figure 4 Overview of pain outcomes measured (right side) as a function of the STUN characteristics measured (left column) in observational studies (**A**). Overview of stress induction method (left side) and pain outcomes (right side) measured, as a function of the STUN characteristics manipulated (middle column) in experimental studies (**B**). The arrows indicate that this association was examined in at least one study; the thicker the arrow, the greater the proportion of studies that explored this pain outcome Purple arrows indicate type of stress stimulation and pain outcomes measured in studies focused on global stress, yellow arrows by studies focused on sense of low control, blue arrows by studies focused on social-evaluative threat (ego), Orange arrows by studies focused on unpredictability, grey arrows by studies focused on novelty, and green arrows by studies that focused on multiple STUN characteristics. The bar underneath each of the STUN characteristics reflects the proportion of studies that relied on a general population (in black), mixed population (general and pain populations; in dark grey), and pain populations (light grey).
Abbreviation: STUN: Sense of low control, Threat to ego (social evaluative threat), Unpredictability, and Novelty framework. #: Number.

general populations. Only one (3.6%) of the 28 investigations of unpredictability directly compared general and pain populations; most of these studies (27; 96.4%) focused on general populations. Finally, 19 of the 22 (86.4%) investigations on novelty focused on general populations.

Pain Outcomes

Pain outcomes as a function of the STUN characteristics are shown in Figure 4B. Pain outcomes measured in experimental studies were less varied than for observational studies and focused on pain threshold/tolerance/sensitivity, pain intensity, pain unpleasantness, and multidimensional pain (sensory, evaluative, and affective).

Qualitative Studies

STUN Components

Of the 19 qualitative studies (including one mixed methods study (Pagé et al 2021a)), 5 (26.3%) examined how global

stress impacts pain experiences and 6 (31.6%) explored the impact of unpredictability on participants' pain. Two (10.5%) other studies focused on sense of control, two (10.5%) focused on social-evaluative threat (ego), while four (21.1%) studies examined all STUN components in relation to multiple pain outcomes. None of the included qualitative studies examined novelty.

Stress and Pain Outcomes

Among qualitative studies exploring the link between global stress and pain outcomes, participants discussed how stress was a contributor to pain onset and an amplifier of pain experience. The notion of poor control over pain was explored in two studies and put in relation to functional limitations, pain-related psychological distress, and pain amplification. Social-evaluative threat (ego) was explored in two studies and participants focused on how stigmatization and contextual pain experiences are associated with a worsening of pain. Finally, six qualitative studies explored how unpredictability of pain is a source of stress that negatively impacts coping, bodily control, interference, and pain threshold.

Population

All qualitative studies focused on chronic pain populations, including heterogeneous chronic pain samples (N=5; 26.3%), neck or back pain (N=5; 26.3%), fibromyalgia (N=3; 15.8%), migraine (N=2; 10.4%), motor neuron diseases (N=1; 5.3%), whiplash (N=1; 5.3%), musculoskeletal pain (N=1; 5.3%), and endometriosis (N=1; 5.3%).

Synthesis of the Results

An overview of study results is provided in relation to the STUN characteristics of stress. As shown in Figure 5, many studying global stress showed that increased stress is associated with worsened pain outcomes, but many studies reported an absence of significant association or mixed associations between stress and pain. Heterogeneity in study findings is also present for sense of control, with positive, negative, or non-significant associations between these STUN characteristics and pain outcomes found across studies. Multiple characteristics may explain this heterogeneity, including the population, stress measures, study design, and pain outcome.

In experimental studies, no clear pattern of findings emerged, with most components being positively and/or negatively linked to pain outcomes as shown in Figure 5. Timing of occurrence between stress manipulation and pain outcomes, the type of stress manipulation (whether the stress manipulation itself involved nociception), in addition to type of population, study design, and pain outcome could explain the observed heterogeneity.

Discussion

Key Elements Characterizing the Existing Literature

Results of the literature search show an unequal attention given to individual components of the STUN framework and variations in number of studies published over time. Most of this literature was published by research groups in North America and Europe, potentially limiting the generalization of results to those populations. Social evaluative threat and sense of low control were the most explored STUN characteristics. Unsurprisingly, only 3.3% of studies examined simultaneously more than one STUN component.

The literature is heterogeneous in terms of pain outcomes examined, particularly in observational studies where spatiotemporal characteristics (sites, frequency, and onset), pain perception (intensity and unpleasantness), and burden (interference and disability) were commonly explored. In experimental studies, however, there is a clear focus on pain perception (intensity, unpleasantness) and sensitivity (threshold, tolerance), making it difficult to understand the global impact of stress manipulation on the various functional aspects of pain. Furthermore, pain populations were the focus of few experimental studies; those investigations focused mainly on general populations such as students or workers. This is particularly important considering that equivocal results have been found regarding the dysregulation of the HPA axis in different pain conditions[19] and variable effects of cortisol have been reported in different types of pain (eg somatic vs visceral)[20] and across gender.[20,21]

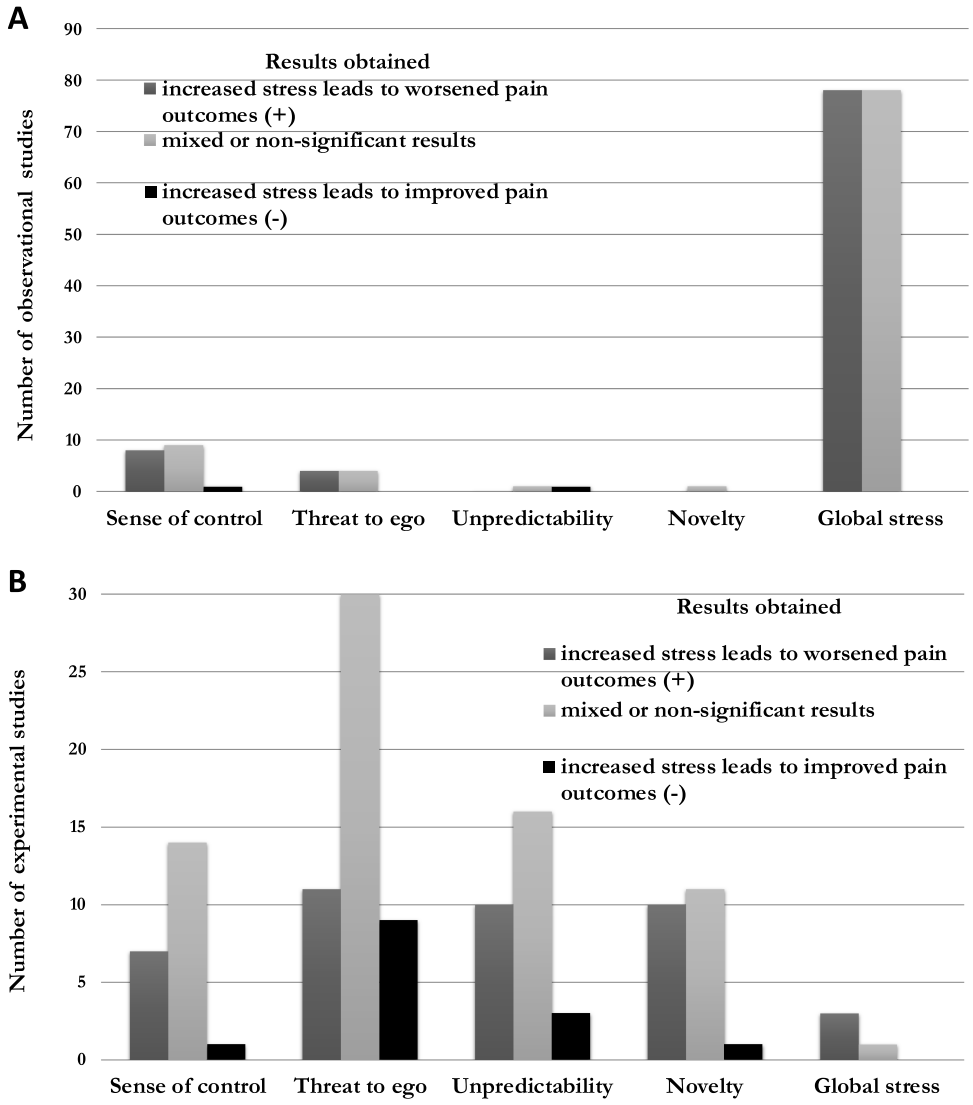


Figure 5 Number of observational studies (**A**) and experimental studies (**B**) examining each dimension of the STUN model according to directionality of study findings. Medium grey depicts study results that showed increased stress is associated with worsened pain outcome. Light grey depicts study results that showed mixed findings (some analyses showed a positive or negative association while others were not significant). Black depicts study results that showed increased stress is associated with improved pain outcome.

Another important finding is that many studies provided equivocal results (eg, non-significant findings or mixed findings depending on the relations examined). This is perhaps not surprising given the numerous aspects of stress and pain that can influence these associations.[22]

Results from this scoping review show the multifactorial relations that exist between stress and pain. The relationship likely relies on different physiological underpinnings depending on whether one is examining acute or chronic stress and pain.[23] Nature, duration, and intensity of stressors are important characteristics of stress that will determine whether it has a hyperalgesic or analgesic effect on pain.[24,25] Fewer studies have explored, however, the triggers of stress response (see, for example[26,27]) and whether it can further our understanding of the relationship between stress and pain in these contexts.

Limitations

This study has some limitations. First, our comprehensive and systematic search of the literature was limited to two main databases, as recommended for scoping reviews.[15] As such, it is not impossible that some relevant articles might have been

missed in the process. Second, screened articles were limited to English or French languages, likely increasing the proportion of studies found from North American and European countries. Finally, double coding was performed only for full-text screening, and not initial title/abstract screening. This decision was made based on an assessment of costs (time and resources) and benefits (eg, ability to screen a large volume of articles to be as comprehensive as possible). These limitations may be considered minor in the context of a scoping review attempting to map a broad field to identify major gaps.

Unexplored Domains and Outstanding Questions

There is a clear lack of integrative knowledge of stress characteristics in the pain field. This leaves many outstanding questions highlighted in Table 2.

Interactions Between Multiple STUN Characteristics

Do the STUN components simply have an additive effect such that the greater the number of STUN components, the larger their effects on pain responses? Or do some of these characteristics interact to have a differentiated impact on pain outcomes? The complexity of this question is illustrated in a study by Williams et al[28] in which participants faced with unpredictable and uncontrollable stimuli rated the sensation as less painful than their baseline pain measure, whereas individuals faced with predictable but uncontrollable experimental stimuli reported more pain.

Individual Differences in Magnitude and Timing of Stress Response to STUN Characteristics and Hypo/Hyperalgesic Effects

In most studies, cortisol or other physiological responses were not measured to validate stress manipulation. Some authors have shown that exposure to a stressor, such as a stress interview or a challenging arithmetic test, decreases pain tolerance, yet there was no significant association between physiological reactivity (ie heart rate) and pain tolerance.[29] One might question the validity of stress induction in this context. Interestingly, Timmers et al showed that the hypoalgesic effect of stress on pain was only true for participants who showed a cortisol response,[26] suggesting a

Table 2 Outstanding Questions and Recommendations for Future Research Directions

Outstanding questions
1. Interactions between multiple STUN characteristics: Do the STUN components simply have an additive effect or interact to have a differentiated impact on pain outcomes?
2 Individual differences:
Is the magnitude of the physiological stress response to STUN characteristics and its relation to pain outcomes influenced by:
2.1 Age, sex, or gender
2.2 Cognitive, affective, personality, social and cultural factors
2.3 Pain status (healthy individuals vs chronic pain populations)
2.4 Vulnerabilities to each of the individual STUN characteristics
3. What are the feature(s) of STUN characteristics (eg magnitude, temporal dynamics, etc.) and/or individual vulnerabilities to these characteristics that determine hyperalgesic or hypoalgesic outcomes?
4. What are the neurobiological and mechanistic underpinnings that can account for questions #1, 2 and 3?
Recommendations for future research directions
1. Expand research to other populations (eg, outside of North America and Europe) and groups (eg, elderly)
2. Study the interaction between stress and pain using the same experimental model in healthy volunteers and clinical pain populations
3. Harmonize stress measurement including all four STUN dimensions
4. Describe characteristics of the stressor and pain response for each STUN characteristic in terms of:
4.1 Magnitude (stress intensity and dose-response)
4.2 Temporal dimension: timing of the stress induction relative to the pain induction/measure and duration of stress (acute vs chronic)
4.3 Test linear and non-linear model and consider potential interactions between STUN characteristics
5. Test individual differences as potential moderators of the direction and magnitude of the effect of stress on pain (age, sex, gender, culture, STUN vulnerabilities, etc.).
6. Use of qualitative methods to explore the effect of multiple STUN characteristics on pain outcomes in healthy individuals and chronic pain populations

conditional or non-linear relation. A more comprehensive examination of these dimensions in relation to perceived STUN components is needed, particularly considering age, sex, pain status, and type of stress induction (painful vs non-painful) being used.

Neurobiological and Mechanistic Underpinnings

Threat learning has been posited to be a central mechanism in the dynamic interplay between stress and pain, whether they are acute or chronic.[30] This model proposes a formal integration of neurobiological processes underlying stress-responses, and particularly cortisol secretion, to explain associations between stress and pain. Based on this approach, threat detection leads to cognitive efforts geared toward learning and adapting behaviors according to the threat, which is facilitated by the stress system in acute conditions. As such, impaired threat-safety discrimination learning would facilitate the dysregulation of overlapping brain systems involved in stress and pain. This is important given that such maladaptive learning can lead to hypervigilance and avoidance behaviors that are often more incapacitating than pain itself, as highlighted in the fear-avoidance model of chronic pain.[31] The notion of controllability and to a smaller extent predictability are sometimes acknowledged as influencing the threat responses,[30] but rarely as central elements. As such, these approaches disregard or only indirectly acknowledge the central components that lead to threat detection to start with. Better consideration of individual components of the stress response could help shed light on apparent contradictory findings in the literature.

Recommendations for Future Research Directions

Key recommendations for future research directions are summarized in Table 2.

Expand Research to Other Populations and Determine Sources of Individual Variability

Consistent with the stress literature, it is essential to keep in mind that the same situation will not trigger the same physiological stress reactions across individuals.[9] Indeed, the physiological response to stress will be triggered only if the brain perceives the situation as a threat; this threat perception and ensuing activation of the HPA axis is thus dependent on the individual's perception and not only on the actual occurrence of a specific event. It is therefore central to measure individuals' sensitivity to STUN characteristics, not only their actual occurrence.

Experimental Models

In addition, research has shown a lack of cohesion across studies, particularly in terms of pain outcomes and stress manipulation/measurement. Testing experimental models in clinical populations and assessing relevant individual factors taken from clinical studies and similar outcomes in experimental research would improve the reciprocal translational power between basic and clinical research.

Harmonization of stress measurement is essential for better integration of knowledge across methodological designs and populations.[30,32] Most stress scales include several items related to the STUN components, however a global stress score does not allow capturing the potential subtleties associated with each component and assessing their interactions. It would be important to develop a new measure of pain-related STUN characteristics or adapt existing measures to capture all four dimensions and test its psychometric properties.

Magnitude, Temporality, and Non-Linear Associations

Decomposing stress into its STUN components (inducers) appears essential, but researchers must further consider immediate arousal (eg SNS) vs slower hormonal stress responses, acute vs chronic stress, acute vs chronic pain, and various types of models (linear vs conditional vs non-linear). Already in 1955, Hebb had recognized that many cognitive functions, such as learning and performance, are optimal at a moderate level of physiological arousal and worse at low or high levels of arousal (inverted U-shape relation).[33] Attempting to model such relationships between stress and pain will require more sophisticated statistical models beyond the linear models used in most studies in this scoping review.

Qualitative Approaches

While quantitative models could statistically explore how various factors influence the associations between stress and pain, qualitative inquiries could help us better understand these associations from the lived experience of patients.

Clinical Implications

This study is a first step towards building theoretical neurobiopsychosocial models of stress and pain and identifying novel therapeutic approaches including the STUN characteristics. From a clinical standpoint, it is important to recognize the characteristics inherent to the pain experience that might increase its threat value and trigger a cascade of stress and psychological reactions. For example, as predicted by the STUN model, not being able to predict fluctuations in pain intensity might be stressful for patients. Similarly, not being able to control pain intensity might also be stressful. However, what happens when two STUN characteristics are present at the same time, for example, how would an individual react when pain fluctuations are predictable (pain always increases at night) but there is no way to control these increases. In this case, if you cannot control pain increases, perhaps not knowing when they happen (ie unpredictability) might be protective compared to knowing when they happen (predictability) but there is nothing you can do about it. Being better able to understand these interacting characteristics of stress might help tailor pain management approaches to the needs of patients.

Conclusion

Stress is a critical element influencing pain responses. This scoping review shows a lack of integration of methodological and conceptual considerations in the scientific literature on stress and pain. It appears essential to decompose stress into its fundamental components to better understand these heterogeneous associations observed between stress and pain. A better understanding of stress-pain associations could lead to the development of innovative therapeutic approaches that consider the STUN characteristics.

Abbreviations

STUN, Sense of control, social-evaluative Threat, Unpredictability, and Novelty; PRISMAScR, Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

Funding

This study was funded by a project grant from the Canadian Institutes of Health Research, grant number 436406. MG Pagé is a Junior 2 research scholar from the Fonds de recherche du Québec - santé (FRQS).

Disclosure

The authors report no conflicts of interest in this work.

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