ADVANCING THE ASSESSMENT OF PAIN-RELATED SENSITIVITY TO PHYSICAL ACTIVITY AMONG ADULTS WITH MUSCULOSKELETAL PAIN

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ABSTRACT

A common challenge encountered in clinical practice is that patients with musculoskeletal pain conditions often experience increasing discomfort when engaging in physical activity. **Sensitivity to physical activity (SPA)** refers to the multidimensional, pain-related reactions that can be experienced in relation to physical movements or exercise. SPA is an umbrella term that incorporates related terms that have been used in the literature, such as *movement-evoked pain*, *dysfunctional exercise-induced hypoalgesia*, and *activity-related repetition-induced summation of pain*. SPA can be assessed by measuring the pain-related changes evoked with a standardized physical task. There is, however, a dearth of research addressing the methods for assessing SPA, its ecological validity, and its prognostic value. This manuscript-based thesis includes four studies (using two datasets) that aim to address these gaps.

The first study was based on a cross-sectional dataset of 116 adults living with various chronic musculoskeletal pain conditions recruited from a local rehabilitation center's chronic pain program and from the community. The three other studies were based on a second, longitudinal dataset of 97 adults living with back pain recruited upon starting treatment at one of eight collaborating private rehabilitation clinics. Both datasets included an in-person testing session including a battery of pain-related and psychological questionnaires, quantitative sensory testing, and SPA assessment. The second dataset additionally included a three-month follow-up of self-reported pain and disability; also, a subset of 67 participants consented to a smartphone-based ecological momentary assessment to monitor pain and mood as they went about their daily life during the nine days immediately following the in-person testing session.

Study 1 included three SPA tasks in relation to which SPA-Pain was tracked (i.e., task-evoked changes in pain intensity). The novel, tailored SPA task required participants to complete

ten repeated lifts using a custom apparatus. The difficulty of this SPA task was individually tailored to each participant so that it evokes a clinically meaningful amount of pain (≥20/100) upon the first lift. This tailored SPA task was compared to two existing SPA tasks found in the literature – a lifting task using a standard set of weights for all participants and a self-paced six-minute walking task. The tailored SPA task was best associated with temporal summation of pain (supporting construct validity), and it was also the only SPA measure to be associated with pain-related outcomes (pain severity and interference). This tailored SPA task was carried forward in Study 2 to investigate prognostic value using a longitudinal dataset. Also, to broaden beyond a unidimensional assessment using only SPA-Pain, two additional indices were tracked: SPA-Psych (task-evoked situational pain catastrophizing) and SPA-Sensory (task-evoked changes in pressure pain threshold, measured distally and locally to participants' back pain). Only SPA-Psych was predictive of three-month pain and disability outcomes. Then, Study 3 was conducted to investigate ecological validity. This study found that clinically administered SPA measures were associated with corresponding daily-life measures; SPA-Pain was associated with daily-life momentary pain intensity and SPA-Psych with daily-life momentary mood. Finally, Study 4 was carried out to investigate daily-life prognostic value. This study found that SPA-Sensory (measured at a distal site) was associated with subsequent flare-ups in daily life.

This thesis contributes evidence supporting SPA's validity and prognostic value, and advances methodology for the assessment of this construct. The general discussion of this thesis considers the clinical and theoretical implications of these findings, as well as the advantages of assessing SPA using a multidimensional range of SPA indices and a tailored SPA task.

ABRÉGÉ

Les patients souffrant de douleurs musculosquelettiques éprouvent fréquemment une augmentation d'inconfort lorsqu'ils pratiquent une activité physique. La **sensibilité à l'activité physique (SAP)** fait référence aux réactions multidimensionnelles éprouvées en relation avec les mouvements physiques ou l'exercice. La SAP peut être évaluée en mesurant les changements liés à la douleur advenant lors d'une tâche physique standardisée. Il existe cependant une insuffisance d'études concernant les méthodes d'évaluation de la SAP, sa validité écologique et sa valeur pronostique. Cette thèse basée sur des manuscrits comprend quatre études (constituée de deux ensembles de données) qui visent à combler ces lacunes.

La première étude repose sur un ensemble de données transversales issues de 116 adultes souffrant de diverses douleurs musculosquelettiques chroniques. Les trois autres études émanent d'un second ensemble de données longitudinales, obtenues d'un groupe de 97 adultes souffrant de maux de dos. Ces deux ensembles de données comprenaient une session de tests effectués en présentiel, et sont constitués d'une batterie de questionnaires psychologiques et liés à la douleur, des tests sensoriels quantitatifs, ainsi que d'une évaluation de la SAP. De plus, le second ensemble de données comprends une évaluation écologique momentanée de neuf jours, qui a été effectuée auprès d'un sous-ensemble de 67 participants volontaires.

L'étude 1 est constituée de trois tâches de SAP, au cours desquelles un indice SAP-Douleur a été mesuré (changements d'intensité de douleur provoqués par la tâche). Une de ces trois tâches était la nouvelle tâche de SAP « sur mesure » (difficulté adaptée individuellement) qui exigeait que les participants effectuent dix levées de poids. Cette tâche de SAP « sur mesure » a été comparée à deux tâches de SAP existantes détaillées dans la littérature, soit une tâche de levée de poids standardisés et une tâche de marche « à son propre rythme » de six

minutes. La tâche de SAP « sur mesure » a été le plus fortement associée à la sommation temporelle de la douleur (ce qui supporte la validité de concept), et c'est également la seule mesure de SAP à être associée aux questionnaires liés à la douleur (intensité de la douleur et interférence). Cette tâche de SAP « sur mesure » a été reprise dans l'étude 2 afin d'étudier sa valeur pronostique à l'aide d'un ensemble de données longitudinales. En outre, pour aller au-delà d'une évaluation unidimensionnelle reposant uniquement sur la SAP-Douleur, deux indices supplémentaires ont été pris en compte : la SAP-Psy (catastrophisation de la douleur situationnelle due à la tâche) et la SAP-Sensorielle (changements du seuil de la douleur à la pression résultant de la tâche, mesurés de manière distale et locale par rapport au mal de dos des participants). Seul la SAP-Psy s'est avérée prédictive de la douleur et de l'incapacité au suivi de trois mois. Par la suite, l'étude 3 a été menée sur la validité écologique. Celle-ci a démontré que les mesures de SAP administrées cliniquement étaient associées aux mesures correspondantes de la vie quotidienne ; la SAP-Douleur était associée à l'intensité de la douleur momentanée de la vie quotidienne et la SAP-Psy, à l'humeur momentanée de la vie quotidienne. Enfin, l'étude 4 a été réalisée dans le but d'étudier la valeur pronostique de la vie quotidienne. Cette dernière étude a révélé que la SAP-Sensorielle (mesurée sur un site distal) était associée à des poussées de douleur dans le quotidien des participants.

Cette thèse apporte des données probantes supportant la validité et la valeur pronostique de la SAP, en plus de contribuer à l'avancement de la méthodologie utilisée pour évaluer ce concept. La discussion générale de cette thèse examine les implications cliniques et théoriques des résultats, ainsi que les avantages de l'évaluation de la SAP à l'aide d'une gamme multidimensionnelle d'indices de SAP et d'une tâche de SAP « sur mesure ».

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My PhD journey has been a formidable challenge. I was profoundly touched by many extraordinary people and their generous support, kindness, and belief in me. I cannot imagine doing this work without these people. First off, let me recognize my PhD primary supervisor, Dr. Timothy Wideman. Thank you. Tim, you are the gold standard for what a PhD supervisor should be like. You have always been extremely attentive, compassionate, available, and flexible to my needs. Your exceptional wisdom and expertise in research are only paralleled by your remarkable skills in mentorship. Many a time, you have skillfully helped me navigate the stormy waters of my PhD. As a result, I have grown not only in all aspects related to academia but also as a person. Tim's remarkable mentorship was further bolstered by my co-supervisor, Dr. Michael Sullivan, and by my supervisory committee advisor, Dr. Sara Ahmed. Thank you for all your insights which served to enrich my PhD work. I valued every conversation we had. I also want to highlight Dr. Marc O. Martel with a special thanks. Your generous help and mentorship were invaluable to the success of my last two studies. Thanks to you, I am taking away a whole new skillset in ecological momentary assessment and multilevel modelling analyses.

At Dr. Timothy Wideman's lab, I was very fortunate to benefit from the help of many lab members and fellow graduate students and scholars. Emilie Rose Casey, Ciara Doyle, Andrea Aternali, Antonina Pavilanis, Daniel Flegg, Alexandre Gervais, and Fatima Amari: thank you for all your help with participant recruitment, data collection, and organizing the raw data. Mushirah Hossenbaccus, thank you for your help with double data entry and for all your ad hoc help. Felipe Reis as a visiting scholar; Jordan Miller, Zakir Uddin, and Peter Stilwell as post-doc fellows; Anthony Teoli and Emilie Houston: thank you for enriching my work and thinking process with insightful conversations, and thank you for including me as a co-author in your

work. Patrick Ippersiel and Catherine Paré: thank you for the countless times that we have racked our brains to solve any challenges we were facing in our respective PhDs and thank you for all the venting sessions. I am very fortunate to be able to call you my friends and look forward to enjoying more meals (or drinks) with you beyond the PhD. Dr. Timothy Wideman's lab has been a very rich and supportive experience where I met wonderful people. I am also grateful for the people I met along the way from neighbouring labs, such as Dennis Radman who did not know me yet was generous with his feedback as I prepared my protocol presentation. Thank you also to the Constance-Lethbridge Rehabilitation Centre for the lab space. Thank you to CBI Health Group for offering space in your clinics and for all your help regarding recruitment.

My PhD also would not have been possible without the generous support from many organizations that provided funding for me and my research work. Thank you to: the Louise and Alan Edwards Foundation's Edwards PhD Studentships in Pain Research, the Canadian Institutes of Health Research (CIHR) (Funding Reference Number MFE-171322), the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST, supplement), the Fonds de Recherche Québec Santé (FRQS), the Richard and Edith Strauss Canada Foundation, and the Hearn Family Foundation. Thank you, Tim, in helping me with these successful applications.

Last but not least, I want to express my heartfelt thanks to all my friends and family. Melissa, thank you for keeping me sane. Claire, thank you for helping me overcome challenges. Mom, Dad, Vera, Grisha, and siblings, thank you for always being there for me. Most importantly, I am especially grateful to my wife Margarita and my daughter Adeline. I dedicate this PhD to you, Magy and Addy. I can never thank you enough for your incredible patience, understanding, and encouragement. You have stood beside me throughout the ups and downs of my PhD and kept me strong with your love. You made my PhD possible. Thank you so much.

CONTRIBUTION TO ORIGINAL KNOWLEDGE

This PhD thesis is composed of four original manuscripts, referred herein as "Studies". Studies 1 and 2 (Chapters 2 and 3 respectively) were accepted as peer-reviewed publications in *The Clinical Journal of Pain.* Study 3 (Chapter 4) was accepted as a peer-reviewed publication in *The European Journal of Pain.* Study 4 (Chapter 5) was submitted to a peer-review journal, *Pain Practice*, and pending a response.

As a first step, this thesis needed to contend with the challenge that there were various SPA assessment methods that were described in the literature. Study 1 (Chapter 2: "*Comparing Novel and Existing Measures of Sensitivity to Physical Activity Among People with Chronic Musculoskeletal Pain: The Importance of Tailoring Activity to Pain*") was the first to investigate a novel SPA measure proposed in the literature, which consisted of an individually tailored repeated lifting task. This study also included existing SPA measures from past research, a self-paced walking task and a standard pre-determined difficulty canister lifting task. Study 1 therefore contributed original knowledge to the SPA literature by being the first to concurrently compare these different SPA tasks for their relative advantages in terms of descriptive statistics of evoked pain and cross-sectional associations with pain-related outcomes and underlying processes (sensory, psychological). The findings of Study 1 provide initial guidance for future SPA research on which task-based SPA assessment method to select for further investigation, based on support for construct validity and potential prognostic value in musculoskeletal pain.

Study 2 (Chapter 3: "*The Prospective Prognostic Value of Biopsychosocial Indices of Sensitivity to Physical Activity Among People with Back Pain*") sheds more light on how to assess SPA by concurrently exploring a multidimensional range of SPA indices (SPA-Pain: task-evoked pain intensity, SPA-Sensory: task-evoked pre-post sensory changes in pressure pain

threshold, and SPA-Psych: task-related situational pain catastrophizing). This study was the first to provide insights on the interrelationship between these different SPA indices. This study was also the first longitudinal study using multidimensional SPA indices to investigate prognostic value for pain-related outcomes at three-month follow-up. Study 2 thus extends past SPA research which was predominantly cross-sectional and unidimensional (only one SPA index).

Study 3 (Chapter 4: "*Task-based measures of sensitivity to physical activity predict daily-life pain and mood among people living with back pain*") contributed to original knowledge on the extent to which lab-based multidimensional SPA measures are representative of corresponding constructs in real-life as participants go about their daily lives and are monitored using ecological momentary assessment (EMA). This study was the first to provide preliminary support for the ecological validity of SPA by showing associations between the lab-based SPA-Pain and daily-life pain intensity, and the lab-based SPA-Psych with daily-life mood. This study also extends past research that considered the extent to which self-reported pain-related questionnaires are representative of daily-life pain and mood captured with EMA, by controlling for the Brief Pain Inventory's pain severity subscale and the Pain Catastrophizing Scale.

Study 4 (Chapter 5: "*Dysfunctional exercise-induced hypoalgesia predicts pain flare-ups in daily life among people with back pain*") was the first study to investigate the prognostic value of lab-based SPA measures for pain fluctuations and flare-ups in daily life, calculated as indices of intraindividual pain variability using EMA raw data. Study 4 contributed to original knowledge with its finding that SPA-Sensory has prognostic value for pain flare-ups in the immediate days following the in-person evaluation of SPA. This study therefore extends research on the prognostic value of lab-based SPA measures, in addition to contributing to research on the prognostic factors for pain fluctuations and flare-ups in the daily life of people with back pain.

CONTRIBUTION OF AUTHORS

Both datasets were funded, designed, and collected by my primary supervisor (Dr. Timothy Wideman) and his research staff. Ethics approval for Dataset #1 (for Study 1) was obtained by my primary supervisor through the Research Ethics Board of the CRIR (Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain) on 2014/10/22 (see Appendix 5 for the ethics certificate). Ethics approval for Dataset #2 (for Studies 2-4) was obtained by my primary supervisor through the Research Ethics Board of McGill University's Faculty of Medicine on 2014/11/24 (see Appendix 6 for the ethics certificate).

Although the data collection was carried out by my primary supervisor and his research staff, I was trained on the data collection procedures of both datasets by the research staff. I also assisted on a few data collection sessions for both datasets in order to have a first-hand understanding of the data collection procedures and how they were executed from start to finish. It is worth noting that the data for the first dataset was collected by paper and required manual transcription into the computer (directly into SPSS, the statistical analysis software primarily used in my primary supervisor's lab). Although this was done primarily by research staff, I also did some of it in order to have first-hand experience of this process. I then led and fully executed the double data entry and verification procedures, with assistance from a research assistant, as a method for reducing the risk of errors that may occur with manual transcription of raw data from paper to computer. For the second dataset, nearly all the data was entered directly into REDCap, with the exception of the first set of entries which were initially on paper and needed to be transcribed to computer and merged with the REDCap data. For the latter, research staff did the double data entry, whereas I led and executed the merging of paper-based data with REDCap data in collaboration with the research staff. Also, for both datasets, with some assistance from

the research staff, I was responsible to clean the raw data (e.g., using verification procedures such as verifying the minimum and maximum values of variables of interest in order to detect values that fall outside the possible ranges of scores, looking over the distribution of the values for variables of interest, taking a close look at the central tendency descriptive statistics and outliers, etc.). I also computed the necessary indices for my analyses, by learning various functions of SPSS such as using the SPSS syntax function. Finally, with initial assistance from research staff, I organized the data for the purpose of my analyses.

For all the Studies (1-4) of my thesis, I am the first author. As first author, I led and executed on the original idea (research question) and conception, all aspects of data analysis as well as data interpretation and visualization (tables, figures, graphs), and all aspects of writing for all four manuscripts (from rough draft to final draft). This was all done in collaboration with my primary supervisor (Dr. Timothy H. Wideman). My co-supervisor (Dr. Michael J. L. Sullivan) was consulted as well for all the Studies, providing input on the findings, their interpretation, and the drafting of the manuscripts. My supervisory committee member (Dr. Sara Ahmed) was similarly consulted for Studies 3 and 4, providing input on the findings, their interpretation, and the drafting of the manuscripts.

Dr. Marc O. Martel is the second author for Studies 3 and 4. Dr. Martel is a co-investigator on the grant that funded the data collection for these studies, contributing his expertise in ecological momentary assessment and multilevel model analyses. Dr. Martel provided me (Arthur Woznowski-Vu) with extensive mentorship in how to clean, organize, compute necessary indices using ecological momentary assessment data, as well as on how to conduct multilevel linear model analyses (multilevel linear regression, random intercept modelling) and generalized linear mixed model analyses (multilevel logistic regression, random

intercept modelling). Dr. Martel also shared with me the necessary SPSS syntax codes, which I then was mentored on how to adapt them to the needs of my analyses. Using this new knowledge, I led all steps of the analyses for Studies 3 and 4, though I was able to obtain assistance as needed from Dr. Martel.

In addition to the aforementioned co-authors, the following co-authors were also consulted for the first two studies: Dr. Zakir Uddin, Daniel Flegg, Andrea Aternali, Rebekah Wickens, Dr. Shane N. Sweet, and Dr. Søren T. Skou for Study 1; Andrea Aternali, Alexandre Gervais, Antonina D.S. Pavilanis, and Dr. Jo Nijs for Study 2. The co-authors Dr. Zakir Uddin, Dr. Shane N. Sweet, Dr. Søren T. Skou, and Dr. Jo Nijs were invited due to their subject matter expertise. Daniel Flegg, Andrea Aternali, Rebekah Wickens, Alexandre Gervais, and Antonina D.S. Pavilanis were invited due to their extensive involvement in the data collection procedures and expertise in the raw data. All of these co-authors had the opportunity to discuss the methodology and results, provide input on the results, and help draft the manuscripts and approved them. In collaboration with my primary supervisor (Dr. Timothy Wideman), I led the full process to publish Studies 1 through 3 in peer-reviewed journals (*The Clinical Journal of Pain*, *The European Journal of Pain*) as well as to submit Study 4 for publication (currently pending a response from the peer-reviewed journal *Pain Practice*). As part of the peer-review process, Studies 1 through 3 also benefited from the feedback from the peer-reviewers which resulted in substantial revisions to improve the manuscripts. In collaboration with my primary supervisor (Dr. Timothy Wideman), I led and executed on the required revisions and responses to reviewers. The other co-authors had the opportunity to provide input and approved the final revisions and responses to reviewers.

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LIST OF ABBREVIATIONS

Δ: Change

β: Standardized regression coefficient

$\chi 2$: chi-square statistic

AEM: Avoidance-Endurance Model

ANOVA: Analysis of variance

b: Unstandardized regression coefficients

BMI: Body mass index

BPI: Brief pain inventory

BPI-Pain: Brief pain inventory (pain severity subscale)

CIHR: Canadian Institutes for Health Research

cm: Centimeters

DF betas: Difference in beta values

EIH: Exercise-induced hypoalgesia

EMA: Ecological momentary assessment

EMA-Mood: aggregated momentary mood in daily life (using ecological momentary assessment)

EMA-Pain: aggregated momentary pain in daily life (using ecological momentary assessment)

f/u: Follow-up

FAM: Fear-Avoidance Model

FCS: Fully conditional specification (model convergence)

FRQS: Fonds de Recherche Québec Santé

GLMM: Generalized linear mixed model

iAC: Intraindividual autocorrelation

ICC: Intraclass correlation

iMSSD: Intraindividual mean square successive difference

iPAC: Intraindividual probability of acute change

IPV: Intraindividual pain variability

IQR: Interquartile range

IRSST: Institut de recherche Robert-Sauvé en santé et en sécurité du travail

iSD: Intraindividual standard deviation

IV: Independent variables

kg: Kilograms

kPa: Kilopascal

LAEF: Louise and Alan Edwards Foundation

m: Meters

MDC: Minimal detectable change

MEP: Movement-evoked pain

ML: maximum-likelihood (parameter estimation method)

MLM: Multilevel linear model

mm: Millimeters

mN: Millinewton

NMDA: N-methyl-D-aspartate

NRS: Numerical rating scale

p: p-value

PCS: Pain catastrophizing scale

PDI: Pain disability index

PPT: Pressure pain threshold

PROGRESS: PROGnosis RESearch Strategy

PRV: Proportional reduction in variance (pseudo-R^2 statistic)

QPRN: Québec Pain Research Network

QST: Quantitative sensory testing

r: Correlation coefficient

R^2: Coefficient of determination

RISP: Repetition-induced summation of activity-related pain

SCQ: Situational catastrophizing questionnaire

SD: Standard deviation

SPA: Sensitivity to physical activity

SPA-Pain: task-evoked changes in pain intensity (pain response index of sensitivity to physical activity)

SPA-Psych: task-evoked situational pain catastrophizing (psychological response index of sensitivity to physical activity)

SPA-Sensory: task-evoked changes in pressure pain threshold, measured distally and locally to participants' clinical pain (sensory response index of sensitivity to physical activity)

STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

t: t-statistic

TSK-11: Tampa scale of kinesiophobia (11-item version)

TSP: Temporal summation of pain

VIF: Variance inflation factor

w/: With

CHAPTER 1: GENERAL INTRODUCTION

1.1. THE BURDEN OF CHRONIC PAIN

The leading global cause of disability is chronic pain (1-3). The International Association for the Study of Pain and the World Health Organization's International Classification of Disease (ICD-11) define chronic pain as disease in its own right (4, 5). Chronic pain is mainly characterized as pain that has persisted for more than three months, with the implication that typical tissue healing time has passed (4, 5). The economical burden of chronic pain and its associated disability has been estimated at $56-60 billion annual in Canada, which is greater than the cost of cancer, heart disease, and HIV combined (6, 7). An interesting observation is that costs associated with loss of productivity due to disabling chronic pain were found to be greater than healthcare expenditures (8). In fact, improving the level of function for a proportion of 3 to 5% of Canadians living with activity-limiting chronic pain has been estimated to potentially "result in an average annual saving of $132.4 million to $217.4 million (2020 CAD) in indirect costs between 2020 and 2030" according to a preliminary analysis by Health Canada (9). Beyond productivity concerns, it is also estimated that chronic pain limits or prevents participation in activities of daily living to a partial or full extent in approximately 2/3 of people living with pain (8). Altogether this highlights the importance of rehabilitation for chronic pain. It is also important to note, that among chronic pain conditions, musculoskeletal pain such as back pain is specified as the most common source of chronic pain and disability (1, 10-12). Back pain can be defined as pain felt between the gluteal folds and shoulders (13), and it is experienced at least once in a lifetime by an estimated 70-80% of people (14, 15). Thus, the patient populations of interest for this thesis are people living with chronic musculoskeletal pain and back pain.

1.2. AN IMPORTANT BARRIER TO PHYSICAL ACTIVITY-BASED TREATMENTS

To alleviate pain and pain-related disability, clinical practice guidelines for musculoskeletal pain conditions such as back pain consistently recommend physical activity-based treatment interventions (16-21). Reviews report that exercise therapy is effective for chronic low back pain and associated disability, compared to no treatment, usual care, other treatments, or placebo comparisons (22-24). The effect size is estimated to be small but significant (22-24). Similar findings are reported in other physical activity-based interventions, such as having a higher physical activity level (e.g., medium-level of physical activity versus being sedentary) (25, 26) or graded activity interventions (27). Physical activity-based interventions show small but significant effect sizes not only for back pain, but for other chronic pain conditions as well (28). A small effect size is expected among non-pharmacological treatment options for pain and does not take away from exercise therapy and other physical activity-based interventions from being considered as one of the most effective nonpharmacological treatment options for pain and disability, with wide-ranging health benefits and limited adverse events (17, 22, 28-30).

The main adverse events reported for physical activity-based treatment interventions are temporary increases in pain and muscle soreness (22, 28). Indeed, while research supports the therapeutic benefit of physical activity, over 70% of patients with chronic musculoskeletal pain report that physical activity increases their pain when engaging in it (31). This can be referred to as **sensitivity to physical activity** and it is the focus of this PhD thesis. Sensitivity to physical activity has been reported by patients with musculoskeletal pain conditions as an important barrier to participation in physical activity-based treatment interventions (30, 32-35). Although these pain-related sensitized reactions to physical activity are typically transient, they may

nonetheless jeopardize the success of physical activity-based interventions. Therefore, sensitivity to physical activity is an important area of investigation. The following sections will define sensitivity to physical activity for the purpose of this thesis and identify gaps in the literature related to its assessment.

1.3. DEFINING SENSITIVITY TO PHYSICAL ACTIVITY (SPA)

Sensitivity to physical activity (SPA) exists at the interface between physical activity and pain. SPA broadly refers to any negative pain-related reactions to repetitive or sustained movement, activity, or exercise (36-39). The broad definition of SPA aims to extend the past research in this area. Breaking down the term "sensitivity to physical activity" into "sensitivity" and "physical activity" helps to clarify the scope of SPA. **Sensitivity** is a versatile term which has been used to refer to the degree to which pain changes or "reacts" in relation to a stimulus (40-42). In relation to SPA, the term "sensitivity" is conceptualized multidimensionally to allow for the inclusion of any immediate negative reactions that are evoked and/or worsened by physical activity. This multidimensional conceptualization for SPA recognizes that a variety of sensitized reactions to physical activity may be relevant, consistent both with the biopsychosocial model of pain (35, 43, 44) and the official definition of pain from the International Association for the Study of Pain, "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (45). Furthermore, when considering "sensitivity to physical activity", it is important to note that the term "sensitivity" is specifically contextualized to "physical activity." **Physical activity** is defined by the World Health Organisation as "any bodily movement produced by skeletal muscles that requires energy expenditure" (46). "Physical activity" is intended as a comprehensive term that captures all specific terms related to physical activity such as exercise,

movement, and activity (being active). Of note, SPA assessment focuses on single bouts of physical activity, rather than the regular practice of physical activity over several sessions.

The breadth of the SPA construct, however, introduces some complexity in navigating the research literature. Indeed, there are many specific constructs that are encompassed by SPA: "movement-evoked pain" (MEP) referring to momentary pain increases evoked by movement (47-50); "repetition-induced summation of activity-related pain" (RISP) referring to the cumulative pain increase evoked by a repetitive or sustained physical task (51-54); and dysfunctional "exercise-induced hypoalgesia" (EIH) or dysfunctional "endogenous analgesia during exercise" referring to exercise-induced pre-post changes in sensory testing such as pressure pain threshold (32, 39, 55-57). Compared to these specific terms, an important advantage in using the broad term "sensitivity" is that it can encompass all of those related specific terms and is flexible enough to allow for a multidimensional conceptualization of sensitized reactions. Recognizing the scope of these different terms that exist under the SPA umbrella term is important for reviewing the literature to date on SPA and identifying gaps.

1.4. UNDERSTANDING THE MECHANISMS OF SPA

Assessing SPA requires, to a certain extent, an understanding of what processes affect the SPA phenomenon itself. There is a detailed literature base on the underlying mechanisms related to SPA, however this literature is only tangentially related to the focus of this thesis. Therefore, the underlying mechanisms of SPA will be reviewed only insofar as to aid in understanding how to approach the assessment of SPA.

1.4.1. Biopsychosocial sensitization mechanisms underlying SPA

The underlying sensitization mechanisms of SPA are still being determined but emerging evidence paints a complex biopsychosocial picture. While mechanisms typically refer to basic

science methodology that identifies physiological processes underlying a phenomenon, in the context of this thesis the use of the word mechanism will be broadened to include biopsychosocial process that were identified using clinical research. Indeed, biological and psychosocial factors appear to be inextricably linked and should be equally considered when looking at mechanisms. Therefore, both SPA and its underlying mechanisms are considered from a biopsychosocial lens. There are examples in research that are emerging which illustrate the importance of a biopsychosocial perspective, such as the study by George et al. which found that the catechol-O-methyltransferase genotype, characterizing either low or high/average pain sensitivity, interacted with pain catastrophizing to be the strongest predictor of SPA among healthy individuals (58). Another example is a recent systematic review that linked psychological factors, such as pain catastrophizing, to structural and functional changes in areas of the brain associated with pain processing (59).

1.4.1.1. Excessive activity or injury

Excessive activity refers to when a person tries to physically do more than their current ability or tolerance, and it may or may not result in injury. Excessive activity or injury (60) may result in mechanical nociceptor activation, muscle fatigue metabolites (e.g., lactic acid, adenosine triphosphate) (30, 61-63), delayed onset muscle soreness (neurotrophic factors by nerve growth factor and glial cell line-derived neurotrophic factor pathways) (49, 64), and/or inflammation (49, 65, 66) (Figure 2-3 of page 26 from Sluka (35) summarizes the mechanisms by which inflammation can activate/sensitize nociceptors), which in turn may lead to nociceptor sensitization (lowered activation threshold) that underlies SPA.

1.4.1.2. Sedentary lifestyle and other personal characteristics factors

It is also possible that for reasons other than excessive activity or injury (e.g., previous activity levels, lifestyle, demographics), a person is predisposed to SPA. For instance, there is research evidence from animal studies suggestive of greater proportion of M1 macrophage phenotype presence (releasing pro-inflammatory cytokines such as interleukin-1β) relative to M2 macrophage phenotype presence (releasing anti-inflammatory cytokines such as interleukin-10) among sedentary individuals, meaning that excessive activity is more likely to be pro-inflammatory and therefore sensitizing for sedentary individuals (30, 67-69). Similarly, delayed onset muscle soreness can underlie SPA and it more easily occurs among sedentary individuals (49, 64). There are also other personal characteristics factors which seem to be relevant for SPA. For instance, older age (70, 71) and female sex (54, 61) appear to show certain trends for greater sensitization related to SPA, though not consistently for age (53, 72) nor for sex (73, 74) and sometimes the reverse was found such that women had lower SPA than men (72, 75).

1.4.1.3. Dysfunctional endogenous pain modulation mechanisms

Dysfunctional endogenous pain modulation can occur through a variety of mechanisms and contribute to SPA (30, 39, 49, 56). For instance, in the brainstem (rostral ventromedial medulla), increased activation of the N-methyl-D-aspartate (NMDA) receptor and increased phosphorylation of the NMDA's NR1 subunit (excitatory neurotransmitter activity related to nociceptive and motor modulation) can facilitate SPA (30, 61, 76). It also appears that dysfunctional endogenous pain modulation can happen through low endogenous opioid system expression (endogenous opioids, μ-opioid receptors) (30, 61, 77), low serotonergic system expression (serotonin 5-HT levels) (30, 61, 77), and low endocannabinoid system expression (2-AG) during activity, thus contributing to SPA (61, 73, 78-80). Dysfunctional endogenous pain

modulation can also occur through the immune system. The immune system can sensitize central nociceptive processing (and therefore SPA) by tipping the balance of inflammatory mediators (30, 35, 67-69, 81, 82). Specifically, immune cells (e.g. macrophages, glial cells) can influence the release of pro-inflammatory cytokines (e.g. interleukin-6) to be in greater proportion (68, 81) relative to anti-inflammatory cytokines (e.g. interleukin-10) (67, 69, 83), and thus favour the sensitization that underlies SPA. Furthermore, it is important to note that while research is advancing the understanding of each endogenous pain modulation system in isolation, there is emerging research that is considering that there can be interactions. For instance, the antagonistic interaction between the endogenous opioid and serotonergic systems whereby high tone of both systems (or low tone of both) may contribute to further SPA whereas a contrasting tone level results in reduced SPA (84).

Other contributors to dysfunctional endogenous pain modulation are also suspected, but research in those areas is only starting to emerge or have shown mixed findings. For instance, there are mixed findings in the emerging body of research investigating the potential association between SPA and stress response systems (39, 56) (e.g., autonomic nervous system (85), endocrine system (70, 86, 87), and cardiovascular system (88-90)). Further research is needed to elucidate if any of these stress response systems consistently contribute to dysfunctional endogenous pain modulation or, as the mixed findings suggest, if the extent to which a stress response system may contribute is individual to each person, or may depend on measurement methods or other context-specific factors.

1.4.1.4. Psychological factors

Research shows mixed findings for the association between psychological factors and SPA among adults with chronic musculoskeletal pain conditions. Although one review

synthesizes several studies supporting that pain catastrophizing, pain-related fear, and depressive symptoms are associated with SPA (91), two other reviews mostly highlight studies that failed to find an association between those same psychological factors and SPA (39, 92). The most strongly supported psychological factor association with SPA in Leemans et al.'s review is pain catastrophizing (91), yet several studies can be found which failed to find such an association (51, 52, 54, 93, 94). Other psychological factors have also been investigated such as anxiety, distress, positive well-being, resilience, optimism, positive/negative affect, perceived injustice, self-efficacy, and chronic pain acceptance, but to a limited extent (few studies) and often with mixed findings (39, 91, 92). A key observation that can be made across these review studies is that there is important heterogeneity in how SPA is assessed (39, 91, 92). This may have contributed to an unclear and mixed relationship between psychological factors and SPA. Therefore, it will be important for future research to elucidate which methods for assessing SPA are superior. This in turn may help to reduce the heterogeneity in how SPA is assessed in future studies, which may clarify conclusions in future research syntheses on the role of psychological factors in relation to SPA.

1.4.1.5. Relevance to SPA assessment

In sum, there is a wide range of ways in which sensitization may develop in relation to physical activity. While some mechanisms appear to be a cascade resulting from excessive activity or injury or the consequences of a sedentary lifestyle or trends associated with personal characteristics, others appear to be pre-existing sensitization mechanisms occurring at the level of one or many dysfunctional endogenous pain modulation mechanisms or from psychological factors. It is also worth noting that this sensitization can be localized (i.e., peripheral sensitization, such that local nociceptors express a greater responsiveness to stimuli and lower

threshold for activation (35)) as is typically expected from the mechanisms described in relation to excessive activity or injury, or it can be widespread (i.e., central sensitization, such that central nociceptive processing has increased facilitation and/or decreased inhibition of nociceptive activity and potentially responding to subthreshold afferent input (35, 41, 95)) as is typically expected from dysfunctional endogenous pain modulation mechanisms, psychological factors, the consequences of a sedentary lifestyle, or other personal characteristics. Recognizing that SPA and its underlying biopsychosocial mechanisms can be expressed at a localized or widespread level is likely relevant when considering assessment methods for SPA.

Furthermore, the literature does show significant variance in whether certain biopsychosocial factors are associated with SPA or not. In addition to the supposition that the set of relevant underlying processes for SPA vary from one individual to another much in the same way as the relevant set of factors of any pain experience varies between individuals, it is likely that variations in assessment methods for SPA have an important influence on these findings. Therefore, the following section will review the research area of assessment methods for SPA and identify important gaps to address.

1.5. ASSESSMENT OF SPA

1.5.1. Background on SPA assessment development

The assessment of SPA extends traditional functional task assessments by integrating indices of sensitization. Functional tasks, such as the six-minute walk test, are recommended for the performance-based assessment of physical functioning (96). It is recognized that it is important to evaluate physical functioning in order to obtain insights into endurance, strength, mobility, limitations for activities of daily living, and participation restrictions (38, 96). However, an important aspect that has been insufficiently incorporated in functional task

assessment is SPA. This type of composite measure that considers pain along with functional task assessment has been recommended in the literature (38, 49, 96, 97). Monitoring pain-related sensitized reactions extends functional task assessment only modestly in terms of the burden on the clinician or researcher, yet enriches the overall assessment with important insights on SPA (38). Given that SPA has been identified by patients as an important barrier to physical activity-based interventions (33, 34), it likely has the potential to contribute additional prognostic value as well as other insights relevant to managing daily life. However, research is still in the process of developing standardized methods of assessing SPA (49, 50). Standardized measures of sensitization, on the other hand, have a more established body of research which may help inform the development of standardized SPA assessment.

Standardized measures of sensitization (i.e., sensory hypersensitivity) were first developed with quantitative sensory testing (QST). QST typically consists of psychophysical measures used in experimental clinical settings whereby a standardized stimulus (e.g., pinprick, mechanical pressure, thermal, electrical) is applied according to a specific protocol (e.g., temporal summation of pain, pressure pain threshold, conditioned pain modulation) and the patient is asked to report their subjective response experience according to specific rating scales and instructions (41, 98-102). For instance, changes in a measure used in a QST test (e.g., pressure pain threshold) can be tracked. Alternatively, evoked pain intensity may be tracked, such as by using a 0-100 numerical rating scale consistent with recommendations on measuring pain intensity but with potentially more granularity than a 0-10 scale (103). The choice of which pain-related response to track depends on what aspects of sensitization are the object of the QST measure. An issue that may be raised, however, is that the stimuli used in QST (e.g., pin pricks)

can seem artificial and abstract from the typical complaints raised by patients during clinical consultations (e.g., that certain physical activities are painful in their daily life (34)).

Ecological validity is commonly defined as the extent to which lab-based research is representative of the targeted real-life experience (104-106). Given that other definitions exist and that there is debate about the historical roots of the term "ecological validity" in relation to the idea of representative design (105, 107), Holleman et al. recommend to not only explicitly state the definition one choses for ecological validity but also to specify what aspects of the "real-world" are targeted (104). Schmuckler highlights that there are three main dimensions of ecological validity: "the nature of the setting, stimuli, and response" (106). For SPA, the real-world experience that is targeted for ecological validity is the sensitization response in relation to a physical activity that is naturally encountered in daily life, such as walking or lifting. A standardized physical task is used in SPA assessment instead of an experimental sensory stimulus (e.g., pinprick, mechanical pressure, thermal, electrical). Thus, the *ecological-relevance* of the stimulus used in SPA assessment is the key design distinction from QST (36).

SPA measures otherwise have many design similarities with QST. For instance, a repetitive or sustained task (e.g., lifting, walking) is akin to the temporal summation of pain paradigm (also referred to as "wind-up" pain) where a noxious stimulus of stable intensity is repetitively or continuously applied and changes in evoked pain responses are tracked as proxies for the "progressively increasing activity of dorsal horn neurons" (99). Indeed, significant correlations were found in past studies between SPA measures (e.g., a standardized walking task, canister lifting task, bicycling, isometric exercise) and QST based temporal summation of pain measures (e.g., repetitive pin prick stimulation, cuff algometry) (36, 93, 108). From a construct

validity standpoint, future SPA measures are expected to also have a similar association with temporal summation of pain measures.

1.5.2. Gaps in knowledge

It was noted earlier that considerable variability exists in the methods for assessing SPA. This is an important gap to address. Standardizing SPA assessment would allow for more meaningful syntheses of evidence, which currently bring together a heterogenous mix of SPA measures. This heterogeneity in how SPA is assessed can be broken down into two components: the **SPA task** and the **SPA index.** In the ecological validity paradigm, these considerations can be respectively referred to as the stimulus and the response (106).

In navigating the literature related to SPA, a variety of aerobic and resistance exercises and physical activity have been used as a SPA task (39, 48, 55, 56). From a standpoint of ecological validity, it is of interest to consider SPA tasks that simulate a physical activity that is typically encountered in daily life and is a common pain complaint for the studied population. There are also other considerations, such as how to set the difficulty of the SPA task. For instance, one SPA task which has been used in past research is a standardized lifting task of pre-determined difficulty, in which all participants lift the same set of weighted canisters (51-54, 109). Another SPA task that has been used in past research is a self-paced walking task in which participants walk as much as they can within a specified timeframe (36-38). Also, individually tailored approaches for a SPA task, similar to temporal summation of pain measures as part of QST, have also been suggested but not yet tested (36). Future research has yet to concurrently compare these different SPA tasks in order to guide future research on which SPA task to use moving forward. These comparisons can be made, for instance, on the basis of prognostic value which will be discussed in the next section. In addition to the SPA task, there is also variability

in the literature regarding the SPA indices that are tracked (38, 39). It is recommended for future research to consider reflecting a broad conceptualization of SPA for the SPA indices selected, as detailed earlier in section 1.3 of this introduction. This would allow for better alignment with the biopsychosocial model of pain and more comprehensive clinical management. Also, from an ecological validity standpoint, a broad conceptualization is more closely aligned with the natural complexity encountered in the real-world than the artificially narrow focus that is sometimes employed in research (104).

1.6. PROGNOSTIC VALUE OF SPA

SPA is suspected to be a potentially valuable prognostic factor for musculoskeletal pain conditions such as back pain. SPA (expressed as increased pain with activity) has been reported as an important barrier to physical activity-based treatment interventions (32-34). SPA has also been identified as an important component of the pain experience among individuals with musculoskeletal pain conditions (31, 49). Therefore, it is plausible that SPA may have prognostic value. Prognostic value refers to the ability of baseline measures to predict future outcomes that are clinically relevant. In addition to showing prognostic value on its own, it is also helpful to provide justification for expanding current clinical assessment practices by showing that there is additional prognostic value beyond existing measures commonly used in clinical assessment (110, 111). Moreover, when discussing prognostic value, it is helpful to identify the outcome variables for which one seeks to have prognostic value. For this thesis, pain intensity (or severity) and pain-related disability (or pain-related interference on functioning) will be the top two outcome variables considered, consistent with recommendations in the pain literature (97).

1.6.1. Gaps in knowledge

Prognostic factor research on SPA is lacking. A recommended first step is to consider previous research on SPA for indications that there is potential for prognostic value in order to justify starting to conduct exploratory prognostic factor research (110, 111). Previous cross-sectional research has found that high SPA is associated with high overall pain and disability (36-38, 52-54, 109, 112). This association remained even when statistically controlling for other factors associated with pain and disability (age, sex, ethnicity, pain duration since onset, pain intensity at rest, pain catastrophization, pain-related fear, physical task performance, sleep disturbance, baseline pressure pain threshold) (36-38, 53, 109, 112). However, this past research was mostly all done using a cross-sectional design (except for Trolle et al.'s study (112)). To advance knowledge on the prognostic value of SPA for pain and disability, it is important to first contend with the heterogeneity of SPA measures in the literature. A cross-sectional comparison may be conducted initially. For instance, the potential prognostic value of different measures of SPA can be evaluated concurrently in order to identify which SPA measure seems to be the most promising. Then, this promising SPA measure can be explored for prospective prognostic value using a longitudinal study design. This research can be even more informative if the analyses control for existing measures commonly used in clinical practice for musculoskeletal pain conditions such as back pain. Two important knowledge gaps can thus be addressed: exploring the prospective prognostic value of SPA and providing justification for adding it to current commonly used assessments. Moreover, by shedding light on which method of assessing SPA holds the strongest prognostic value for pain and disability outcomes, this research can guide the selection of a SPA measure from the current heterogeneous array of SPA measures.

1.7. RELATIONSHIP OF SPA WITH DAILY LIFE

While the prognostic value for timeframes extending months or even years into the future is highly informative for both guiding clinical management and advancing research that characterizes pain conditions, it has also been recommended in the pain literature to consider daily-life outcomes that occur in timeframes of only days following the clinical encounter or in-person testing session for research (97, 113, 114). Namely, this includes various pain fluctuations indices that can be computed in terms of intraindividual (within the same person) variability in pain intensity characterized by magnitude, frequency, temporal and/or spatial aspects (97, 113, 114). Among these pain fluctuation indices, acute exacerbations in pain intensity can be referred to as pain flare-ups (113, 115-117). Pain flare-ups are especially disruptive to an individual's life when having at least one other co-occurring dimension such as a negative impact on mood, activity, or quality of life, and thus experts agree that pain flare-ups are best defined as a multidimensional construct (115-117). In day-to-day life, pain fluctuations and flare-ups are common for people living with musculoskeletal pain conditions such as back pain (116, 118, 119). This can make the experience of pain unpredictable. Research has found that the greater the unpredictability of pain, the greater the pain intensity, disability, distress, and interruptive effect on daily life (120-126). In addition to the importance of investigating the prognostic value of SPA for pain fluctuations and flare-ups, ecological validity is another important aspect to consider when investigating the relationship of SPA with daily life (104, 106).

In order to evaluate these important daily-life outcome measures, ecological momentary assessment (EMA) is recommended (113, 114, 127). EMA is a measurement method that collects momentary data, typically nowadays using a smartphone application, as a person is going about their usual daily life activities in their natural environment as opposed to a lab or

clinic (106, 114, 127). Therefore, an important advantage of EMA is its ecological validity from the standpoint of the setting (106, 114, 127). EMA circumvents the issue that lab-based or clinically-administered assessments may be influenced by the artificial setting of evaluating an individual in a lab or clinic using where the individual is especially aware that they are being assessed (104-106, 128). EMA is recommended for measuring constructs occurring in daily life over self-report questionnaires and paper journals due other advantages as well. For instance, although self-report questionnaires could be used, they are at risk of recall bias which can be described in terms of the gap between memory and actual lived experience (129, 130). Pain is especially prone to recall bias since it is a negative memory which makes it more likely to be influenced by a range of factors including retention interval, patient state-related and trait-related characteristics, and exaggerated peak and end effects (peaks and recent experiences of pain are influential in how the overall pain experience is recalled) (129-131).

1.7.1. Gaps in knowledge

It is not yet known the extent to which there may be a discrepancy between lab-based SPA measures and their corresponding constructs in daily life. This represents an important gap for research on the construct and ecological validity of SPA as a lab-based assessment administered in a clinical or lab setting. Future research should aim to address this gap. This future research should also take into account that similar research has been conducted on the gap between retrospective pain intensity self-report collected in a lab setting and its EMA-based daily life measurement (132).

Pain fluctuations and flare-ups are important daily-life outcome variables for which prognostic research is only emerging (133, 134). Since having high SPA can be defined as the degree to which sensitized responses to physical activity are experienced, it is likely that high

SPA is associated with greater odds of experiencing pain fluctuations and flare-ups as an individual goes about their usual daily life activities. However, no research to date has directly investigated this hypothesized association. Exploratory prognostic factor research needs to be conducted to shed light on whether baseline lab-based SPA assessment is associated with pain fluctuations and flare-ups on subsequent days.

1.8. OBJECTIVES

The **overall objective** of this manuscript-based thesis is to advance the assessment of sensitivity to physical activity (SPA) among people with chronic musculoskeletal pain (dataset #1 for Study 1) and back pain (dataset #2 for Studies 2-4), by addressing the gaps in knowledge in SPA assessment (see section 1.5.2.), prognostic value (see section 1.6.1.), and relationship with daily life (see section 1.7.1.). The overall objective of this thesis was met using four studies/manuscripts.

The objective of Study 1 *(Chapter 2: Comparing novel and existing measures of sensitivity to physical activity among people with chronic musculoskeletal pain: the importance of tailoring activity to pain)* was to compare existing and novel task-based measures of SPA regarding their potential prognostic value in terms of cross-sectional associations with pain severity and pain interference, their support of construct validity through associations with sensory and psychological measures, and their descriptive characteristics of evoked pain responses among adults with chronic musculoskeletal pain (dataset #1). It was **hypothesized** that the novel individually tailored lifting SPA task, due to being designed similarly to the QST protocol for temporal summation of pain (102, 135), would best mitigate floor and ceiling effects and thus achieve the greatest amount of evoked pain responses across and within participants; and that this would translate into better cross-sectional associations with pain-related outcome

measures. At the outset of the study, it was also believed that all existing and novel SPA measures would support construct validity by showing associations with sensory and psychological measures.

The objective of Study 2 *(Chapter 3: The prospective prognostic value of biopsychosocial indices of sensitivity to physical activity among people with back pain)* was to explore the prognostic value of SPA for three-month outcomes in self-reported pain and disability, using a prospective longitudinal study of adults with back pain (dataset #2). Moreover, another objective of this study was to consider SPA from a multidimensional lens by evaluate four SPA indices (task-evoked pain intensity, task-evoked situational pain catastrophizing, and pre-post task-related changes in pressure pain threshold at a local and distal body site to the clinical back pain) for their prognostic value but also their associations with one another. It was **hypothesized** that all four SPA indices would show prognostic value for the three-month pain and disability outcome measures and that all four SPA indices would be correlated with one another.

The objective of Study 3 *(Chapter 4: Task-based measures of sensitivity to physical activity predict daily-life pain and mood among people living with back pain)* was to contribute preliminary evidence in support of the ecological validity and construct validity of clinically administered SPA measures by estimating the extent to which they are associated with corresponding constructs (momentary pain, momentary mood) collected in daily life. This was done using the 67 adults with back pain sub-sample of dataset #2 that participated in the EMA portion of the study. Also, commonly used retrospective questionnaires (The Brief Pain Inventory's pain severity subscale and the Pain Catastrophizing Scale) were to be controlled for in the analyses in order to shed light on the additional contribution of SPA measures for closing

the gap between clinically administered measures and the reported experience occurring in daily life. It was **hypothesized** that the SPA measures would indeed show significant associations with corresponding constructs measured by EMA, and that this would provide additional explanatory variance over those commonly used retrospective questionnaires.

The objective of Study 4 *(Chapter 5: Dysfunctional exercise-induced hypoalgesia predicts pain flare-ups in daily life among people with back pain)* was to explore the prognostic value of SPA for daily-life outcome measures of pain fluctuation and flare-ups among adults with back pain (dataset #2 sub-sample participating in EMA). It was **hypothesized** that SPA would predict greater pain fluctuations and flare-ups in the days following the in-person lab-based assessment of SPA but it was not known which SPA index would perform best as this was an exploratory study with no similar precedent.

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PREFACE TO CHAPTER 2 (STUDY 1)

The introduction of this thesis highlighted the heterogeneity in SPA assessment methods used in the research literature. There is uncertainty regarding which SPA assessment method is superior. As a starting point for this thesis, the objective of Study 1 was therefore to address this gap in knowledge by concurrently comparing existing and novel SPA task-based measures from the literature in terms of potential prognostic value for pain-related outcomes, associations with sensory and psychological measures supporting construct validity, and descriptive statistics of task-evoked pain intensity.

Study 1 used *dataset #1*, which consisted of a sample of 116 adults with a range of chronic musculoskeletal pain conditions recruited from the chronic pain program waitlist of a local rehabilitation center and from the local community using flyers. This was a single-visit cross-sectional observational study that included a standardized lifting SPA task, a self-paced walking SPA task, and a novel tailored lifting SPA task. Potential for prognostic value was considered in terms of the strength of cross-sectional associations with self-reported pain severity and interference. Sensory measures considered for supporting construct validity included baseline quantitative sensory testing using pressure pain thresholds and temporal summation of pain, whereas as psychological measures included questionnaires on pain catastrophizing and pain-related fear. The evoked pain intensity from each SPA task was considered using various descriptive statistics including the proportion of participants who experienced a minimally clinically important change in pain, average magnitude in evoked pain intensity, and floor and ceiling effects. This was the first study to concurrently compare different SPA measures in these respects. This was also the first study to include the novel tailored lifting SPA task.

CHAPTER 2: COMPARING NOVEL AND EXISTING MEASURES OF SENSITIVITY TO PHYSICAL ACTIVITY AMONG PEOPLE WITH CHRONIC MUSCULOSKELETAL PAIN: THE IMPORTANCE OF TAILORING ACTIVITY TO PAIN (STUDY 1)

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2.1. ABSTRACT

Objectives: Increasing pain during physical activity is as an important, but often poorly assessed, barrier to engaging in activity-based rehabilitation among people with chronic musculoskeletal pain. Preliminary work has addressed this problem by developing new clinical measures of sensitivity to physical activity (SPA). Indices of SPA are generated by evaluating how pain changes in relation to brief physical tasks. Three strategies have been identified for structuring SPA-related physical tasks (self-paced, standardized, and tailored). This cross-sectional study aimed to comparatively estimate the extent of the three SPA tasks' evoked pain responses, predictive value of pain severity and pain interference, and their underlying psychological and sensory constructs, among 116 adults with chronic musculoskeletal pain. **Methods:** Testing included questionnaires, quantitative sensory testing and the three SPA measures (self-paced, standardized, and tailored). The primary analysis estimated the predictive value of each SPA measure for pain severity and pain interference. Correlational analyses were first conducted between all variables of interest to determine what variables will be included in the hierarchical regression analysis, which in turn was conducted for each outcome. **Results:** Analyses revealed that the tailored SPA index was most effective at evoking activity-related pain, was uniquely associated with temporal summation of pain and was a unique predictor of pain and pain-related interference, even when controlling for established psychological and sensory risk factors. **Discussion:** This study further emphasizes SPA as an important and unique attribute of the pain experience and reveals the added value of using a tailored approach to assess SPA.

Key words: Sensitivity to physical activity; Activity-related pain; Movement-evoked pain; Chronic musculoskeletal pain; Clinical assessment

2.2. INTRODUCTION

Persistent musculoskeletal pain is the most prevalent type of chronic pain (1, 2) and a leading cause of socioeconomic burden (3, 4). One of the most common complaints among people with chronic musculoskeletal pain is pain during physical activity (5, 6). When compared to other forms of pain (e.g. pain at rest, spontaneous pain), pain associated with physical activity is characterized by distinct underlying mechanisms (7, 8), more severe intensity ratings (6, 9) and divergent responses to treatment (7, 9-12). Increasing pain during exercise has also been identified as a major barrier to engaging in activity-based interventions, but one that is often overlooked by clinicians, thus raising the potential for treatment failure (13, 14). Past work has highlighted that standardized approaches to assessing pain during physical activity are needed to better address these barriers within clinical practice and to advance research in this area (9, 15).

Recent work has started to address this gap by developing novel approaches to evaluating how pain intensity changes in response to standardized physical tasks, a construct referred to here as sensitivity to physical activity (SPA) (5, 16). Indices of SPA are generated by calculating the difference in pain ratings in relation to brief physical tasks, thus making them specific to activity-evoked pain and broadly aligned with daily fluctuations in activity-related pain (5, 10, 17-21). Previous studies have associated higher SPA with elevated scores on clinical indices of sensory hypersensitivity (5, 16) and psychological risk factors (5, 16, 17), and have shown that SPA predicts a range of pain-related outcomes even after controlling for established psychological and sensory risk factors (5, 18, 19, 21). Clinical measures of SPA are expected to be particularly helpful in identifying and managing patients that may be at an elevated risk for treatment failure due to their sensitized responses to physical activity (9, 15).

While a growing body of work highlights the novel, added value of SPA, there is important variation in how this construct is measured. For instance, several studies have measured SPA by evaluating changes in pain in relation to a standardized lifting task, in which participants lift an

identical set of weighted canisters (10, 17-20). Other studies have evaluated how pain changes in relation to a self-paced walking task in which participants walk varying distances within a specified timeframe (5, 16, 21). Previous work has also highlighted, but not yet tested, the potential value of using a tailored approach to measure SPA (5). This strategy involves tailoring the intensity of the physical task to individual pain levels – similar to how sensory stimuli are tailored to pain levels within certain quantitative sensory tests (22, 23) – and is expected to help mitigate floor and ceiling effects and potentially improve responsiveness and predictive value (5). Despite this work, there have been no direct comparisons between these different approaches to measuring SPA. Better understanding the potential merits and limitations of these assessment strategies is an essential step in developing SPA as a clinical assessment tool and helping integrate sensitized responses to physical activity within clinical management (9, 15). This study addresses this gap by cross-sectionally comparing the standardized, self-paced and tailored measures of SPA among people with chronic musculoskeletal pain, with respect to the characteristics of their evoked pain responses, predictive value of pain severity and pain interference, and their underlying psychological and sensory constructs.

2.3. MATERIALS AND METHODS

2.3.1. Design

This study used a cross-sectional design and adhered to the STROBE statement guidelines (24) (see Appendix 1 for the completed STROBE checklist for this manuscript).

2.3.2. Participants

Participants were recruited based on the following inclusion criteria: (1) age 18 years or older, (2) presence of musculoskeletal pain for more than three months, (3) presence of pain-related disability, and (4) medically stable (no serious health conditions, no pending surgery or invasive medical procedure, no contraindication to physical activity). Research assistants recruited participants from the wait list of the chronic pain programs at two Montreal-based tertiary-care rehabilitation centers, as well as from recruitment flyers posted in the community and circulated among local chronic pain support

groups. Presence of musculoskeletal pain and pain-related disability was confirmed by phone prior to inviting potential participants to proceed to the informed consent process. Musculoskeletal pain was defined as pain that potential participants report feeling in the muscles, joints or bones. This pain could be localized, regional, or widespread (25, 26). Presence of co-existing pain conditions of other origins did not lead to exclusion as long as chronic musculoskeletal pain was the primary condition (i.e. predominant subject of symptom complaints). Presence of pain-related disability was screened simply by asking participants whether their pain interfered with their daily life functioning (27). Recruitment and data collection occurred between January 2015 and August 2017.

2.3.3. Procedures

As illustrated in Figure 2.1 (see below), all participants came in for a single in-person testing session which started with the informed consent process, followed by a battery of questionnaires (demographic, pain-related, and psychological). Participants then completed clinical indices of sensory hypersensitivity, which consisted of pressure pain thresholds and temporal summation of mechanical pain. Finally, participants completed three SPA tasks, each preceded by a 5-minute break: (1) SPA – self-paced walk, (2) SPA – tailored lift, and (3) SPA – standardized lift. This order of SPA tasks was standardized for all participants to ensure a uniform experience of the battery of tasks, which in turn allowed for the entire sample size to be used as a single group in analyses studying the relationship of these SPA measures with the other study variables. The study protocol was approved by the research ethics board of the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal. All participants provided informed consent prior to testing.

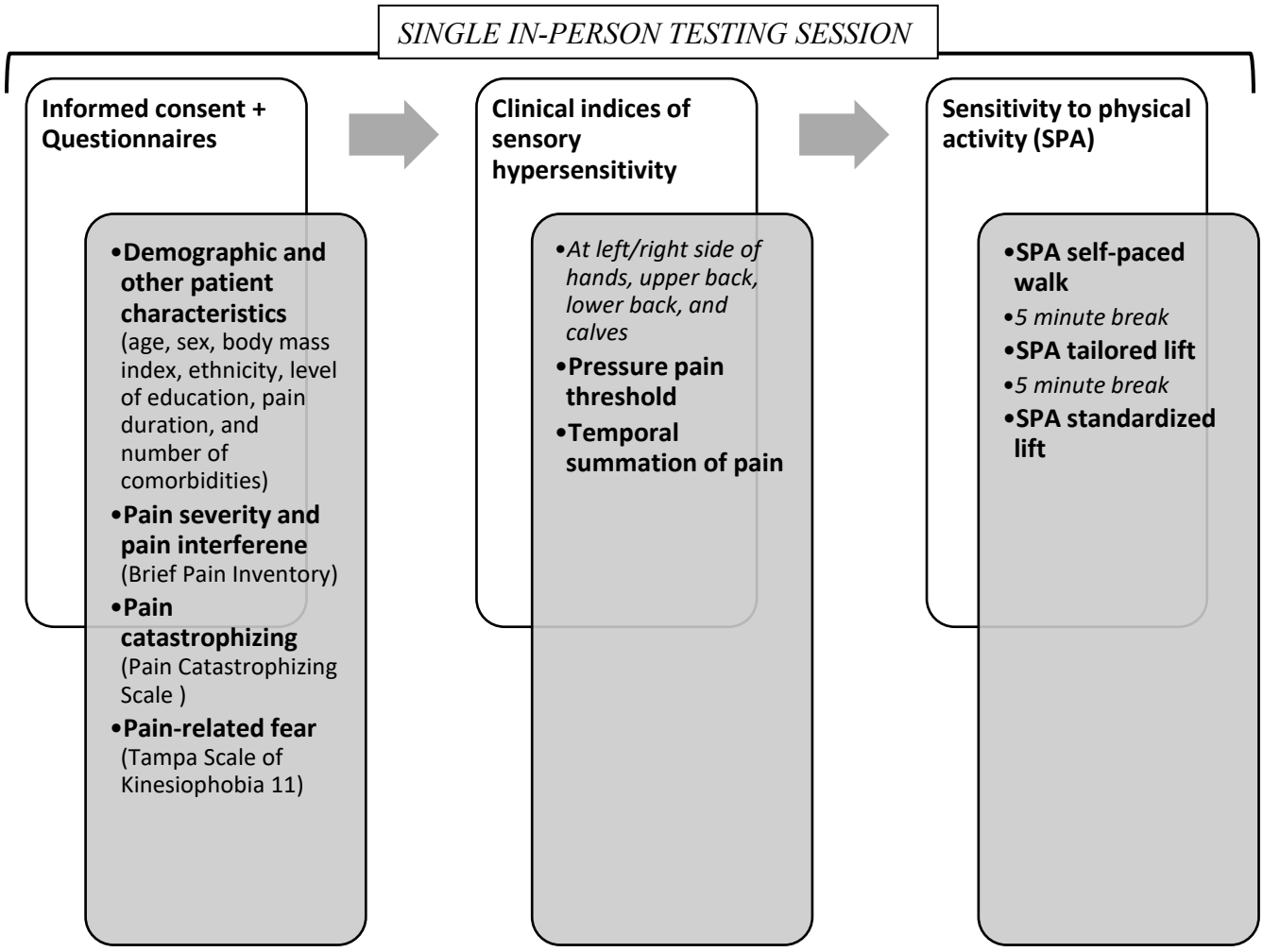

FIGURE 2.1. Overview of data collection procedures. Within a single in-person testing session, participants completed the informed consent process, followed by a battery of questionnaires (demographic, pain-related, and psychological), followed by clinical indices of sensory hypersensitivity (pressure pain thresholds and temporal summation of mechanical pain at the left/right side of hands, upper back, lower back, and calves), and finally followed by three SPA tasks: (1) SPA – self-paced walk, (2) SPA – tailored lift, and (3) SPA – standardized lift. Five-minute breaks were included in-between each SPA task.

2.3.4. Self-report questionnaires

2.3.4.1. Covariates

A list of demographic and health-related questions was used to collect information on potential covariates (age, sex, body mass index, ethnicity, level of education, pain duration, and number of comorbidities). This list of potential covariates was selected based on past pain-related and SPA-related research (5, 18, 19).

2.3.4.2. Pain severity and pain interference

The Brief Pain Inventory (BPI) was used to measure pain severity and pain interference. Pain severity was used to represent musculoskeletal pain intensity and pain interference was used to represent pain-related disability. The pain severity subscale is composed of four items that ask for present pain intensity ratings as well as worst, least and average pain ratings over the previous 24-hour period. Pain ratings are provided on an 11-point numerical rating scale in which 0 indicates “no pain” and 10 indicates “pain as bad as you can imagine”. The pain interference subscale is composed of seven items that ask about the degree to which pain has interfered with various aspects of their life, including general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. Items are rated on an 11-point numerical rating scale in which 0 indicates “does not interfere” and 10 indicates “completely interferes”. Pain severity and pain interference subscales were calculated as the mean score of their respective items. The BPI is a widely used and recommended outcome measure, with strong reliability and validity among people with musculoskeletal pain (27, 28).

2.3.4.3. Pain Catastrophizing

The Pain Catastrophizing Scale (PCS) was used to measure pain catastrophizing. Pain catastrophizing can be defined as an exaggerated negative perception of pain and is well established as an important psychological risk factor for pain-related outcomes (29). The PCS is composed of 13 items that relate to a magnified perception of pain-related threats, ruminating thoughts about pain symptoms, and feelings of helplessness when confronted with pain. The frequency of thoughts

associated with each item is ranked on a 5-point Likert-type scale in which 0 indicates “not at all” and 4 indicates “all the time”. The total score was calculated as a sum of all items. The PCS is the most commonly used measure of pain catastrophizing and has been shown to have strong reliability and predictive value among people with musculoskeletal pain (29).

2.3.4.4. Pain-Related Fear

The 11-item version of the Tampa Scale of Kinesiophobia (TSK-11) was used to measure pain-related fear. Pain-related fear is well established as an important psychological risk factor for pain-related outcomes (30-32). The TSK-11 is an abbreviated, 11-item version of the original TSK (30-32). Each item addresses fear-avoidance related beliefs about pain and physical activity. Respondents are asked to rate the extent to which they agree with each item using a 4-point Likert-type scale in which 1 indicates “strongly disagree” and 4 indicates “strongly agree”. Total scores are calculated by summing all items. The TSK-11 is a widely used measure with strong reliability and predictive value among people with musculoskeletal pain (30-32).

2.3.5. Clinical indices of sensory hypersensitivity

Pressure pain threshold and temporal summation of mechanical pain were included in this study as clinical indices of sensory hypersensitivity. These measures were consistent with previously validated protocols (22, 33) and past research (5). Both pressure pain threshold and temporal summation of pain were tested bilaterally at the hands (web-space between thumb and index finger), upper back (5cm laterally from T1 spinous process), lower back (5cm laterally from L3 spinous process), and upper calf (upper third of the gastrocnemius muscle belly).

2.3.5.1. Pressure Pain Threshold

For pressure pain threshold, the participant was instructed to indicate when an increasing pressure stimulus first became painful. Thresholds were evaluated using an algometer (FDX 10, Wagner instruments, Greenwich, CT, USA) with a $1cm^2$ rubber tip that was oriented perpendicular to the skin. Pressure was gradually applied at a rate of one pound-force per second until the participant

indicated that he or she first experienced pain. This was repeated for three trials at each site, with a 30-second break in-between trials. An average was calculated from those three trials and values were recorded in kilopascals (5, 33).

2.3.5.2. Temporal Summation of Pain

Temporal summation of pain was measured by evaluating changes in pain ratings in relation to repeated pin prick stimuli. Consistent with previous work, pin prick stimuli were administered using weighted punctate probes (PinPrick stimulators, MRC Systems, Heidelberg, Germany) (22, 34). The contact surface of the probes was small (0.2mm in diameter), but flat, which helped ensure that that the stimuli was safe and non-invasive. Four different probes that weighed 32mN, 64mN, 128mN, and 256mN were used for testing. Consistent with previous approaches, in ascending order, each probe was first used to provide a single stimulus before one probe was selected for administering repeated stimuli (5, 35). Following each stimulus, participants were asked to rate their pain intensity on a numeric rating scale that ranged from 0 (no pain) to 100 (worst pain imaginable). The lightest probe to evoke a minimum pain rating of 20/100 was selected to apply repeated stimuli. A series of ten stimuli were applied at one second intervals. A metronome was used to time the repetitions. Immediately following the application of these repeated stimuli, participants were asked to report their peak pain intensity. Consistent with past work, an index of temporal summation of pain was generated by calculating the difference between the two pain ratings that were evoked by the selected probe, such that the pain rating from initial single pinprick was subtracted from the pain rating following the repeated stimuli (5, 22). One trial of temporal summation of pain measurement was administered at each site.

2.3.6. Sensitivity to physical activity (SPA)

Three measures of SPA were included in this study – SPA self-paced walk (5, 16, 21), SPA standardized lift (17, 19, 20) and SPA tailored lift (5). Participants completed the SPA tasks in the following order: first the self-paced walk task, then the tailored lift task and finally the standardized lift task. Each SPA task was preceded by a 5-minute break, which was designed to mitigate carry-over pain

and exertion between SPA tasks. To help evaluate any potential carry-over effects, ratings of resting pain and of perceived exertion were taken immediately prior to initiating the SPA tasks. Consistent with past work, each SPA index was generated by calculating the difference between two pain ratings, an initial rating (SPA pain rating #1) subtracted from a follow-up rating (SPA pain rating #2) (5, 16, 18-20, 36). All pain ratings referred to overall pain intensity (i.e. not localized to one body site) and used a 0 (no pain) to 100 (worst pain imaginable) numerical rating scale (NRS).

2.3.6.1. SPA – Self-paced walk

Consistent with past work, participants were instructed to walk as far as possible within six minutes by walking back-and-forth along a 50m track (5, 16, 21). Participants were asked to rate their pain intensity immediately before starting the task and then after each minute. Consistent with past work, the SPA self-paced walk index was calculated by subtracting pre-walk pain ratings (SPA self-paced walk, pain rating #1) from the highest pain rating provided during the walking task (SPA self-paced walk, pain rating #2) (5, 16, 21).

2.3.6.2. SPA – Standardized lift

Consistent with previous work (10, 17, 19, 20), participants were asked to lift a series of 18-canisters that were arranged in a standardized pattern on a waist-high table. Detailed descriptions of the canister weights and positions have been previously provided (17, 19). Briefly, canisters were visually identical, but had different weights (2.9kg, 3.4kg, or 3.9 kg). Canisters were arranged in six columns and three rows. Rows were adjusted to align with the following three lift positions: Position 1 required a straight back and the elbow bent to 90 degrees; Position 2 required a straight back with the arm fully outstretched; and Position 3 required the back to be bent forward at the waist with the arm fully outstretched. Canisters were arranged in a double Latin square, such that each of the canister weights was represented once in each of the six columns. Participants were instructed to briefly lift one canister at a time and report their pain in relation to each lift. Mean pain ratings were calculated for each of the six columns. Consistent with previous work, the SPA standardized lift index was calculated by

subtracting the mean pain ratings for column 1 (SPA standardized lift, pain rating #1) from the mean pain ratings for column 6 (SPA standardized lift, pain rating #2) (17, 19, 20). It should be noted that in some previous studies this index has been referred to as repetition-induced summation of activity-related pain (17, 19) and activity-related summation of pain (20).

2.3.6.3. SPA – Tailored lift

The SPA tailored lift task protocol was developed for the purpose of this study, combining aspects of the standardized lift and temporal summation of pain protocols that are described above. The tailored lift task involved lifting a series of weights using a custom-made lifting apparatus that is shown in Figure 2.2.

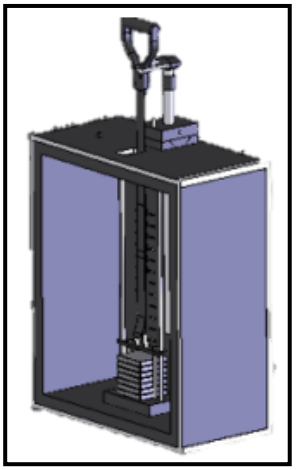

FIGURE 2.2. Lifting apparatus for the tailored lift SPA task. This custom-built lifting apparatus includes a rectangular box (90cm high x 60cm wide x 60cm deep) which allows for blinding of participants to the weight, weights plates offer 0.5 kg increments, and handle is height adjustable.

The apparatus consisted of a rectangular box (90cm high x 60cm wide x 60cm deep) with a height-adjustable handle. Within the box, and concealed from the participant, was a weight rack that was attached to the adjustable handle via a strap. Weight plates of 0.5kg could be added or removed from the rack. During the task, participants were instructed to stand in front of the lifting apparatus in one of three positions and to lift the handle vertically until a marker on the strap was revealed (the marker indicated when the target 5 cm lift height had been reached). The three lifting positions were identical to those described above in the SPA standardized lift task protocol (i.e. Position 1, Position 2, and Position 3).

The approach to tailoring was based on the described temporal summation of pain protocol in that participants were first asked to rate their pain in relation to a series of standardized single lifts and then rate their peak pain following ten repeated lifts that were tailored to their individual pain levels. Tailoring was based on pain responses to specific lift weight-position combinations. The initial series of standardized single lifts consisted of lifting four different weights (1.0kg, 2.0kg, 3.0kg, and 3.5kg) in each of the three lifting positions. The weight-position combinations for the standardized lifts were organized from easiest to most difficult. Specifically, weights were progressively increased from lowest to highest, first in Position 1, then in Position 2 and finally in Position 3. Each individual lift was separated by a 30-second break. Participants were asked to rate their pain intensity in response to each of these lifts. Tailoring was based on the lowest weight and position that evoked a minimum pain rating of 20 on the numeric rating scale. Participants were then asked to complete ten repeated lifts using this tailored weight-position combination and to report their peak pain. The SPA tailored lift index was generated by calculating the difference between the two pain ratings that were evoked by the same weight-position combination, such that the pain rating from initial single lift (SPA tailored lift, pain rating #1) was subtracted from the pain rating following the repeated lifts (SPA tailored lift, pain rating #2).

2.3.7. Data analysis

2.3.7.1. Sample size

A sample size of 100 was targeted based on previously reported effect sizes (5, 10, 19, 21, 36).

2.3.7.2. Data cleaning and missing data analysis

Descriptive statistics and plots (histograms, box-plots, and scatter plots) were reviewed to evaluate errors in data entry and to ensure alignment with statistical assumptions. Corrections were made if required. Next, data was evaluated to determine the pattern at which missing data occurred (missing completely at random, missing at random, missing not at random). Consistent with recommendations (37-41), multiple imputations were used to replace missing data. All data analysis was conducted using IBM SPSS statistics 24.

2.3.7.3. Evaluating potential carry-over pain between SPA tasks

A one-way repeated measure ANOVA was used to evaluate whether mean levels of pre-task resting pain intensity and of pre-test ratings of perceived exertion were consistent across all SPA tasks.

2.3.7.4. Comparing descriptive characteristics across SPA measures

Three analyses were conducted to evaluate and compare the magnitude of pain evoked by each of the SPA tasks. First, three paired-samples t-tests were conducted to evaluate changes in pain ratings in relation to each of the SPA tasks. In line with our study's objective, paired-samples t-tests were done in order to look at each SPA task separately. Specifically, the paired-samples t-tests evaluated whether SPA pain rating #2 was significantly greater than SPA pain rating #1 in relation to each of the three SPA tasks. This was also verified by one-way repeated measures ANOVA with contrasts (three simple contrasts corresponding to the three SPA tasks) using a Bonferroni correction (original alpha level $p<0.05$ was divided by three to obtain the Bonferroni-correct alpha level 0.016667). Effect sizes of these mean differences were calculated by following recommendations from Kazis, Anderson, and Meenan (42). Specifically, effect size was calculated the following way: Effect size = (mean SPA pain rating #2 - mean SPA pain rating #1) / standard deviation of SPA pain rating #1. Kazis et al.

recommend following Cohen's definition for interpreting effect sizes whereby 0.20, 0.50, and "0.80 or greater" are considered respectively as small, moderate, and large effect sizes (42). A consistently small effect size across the entire sample might be suggestive of floor or ceiling effect of exposing SPA with this measure (see next paragraph for additional methods used in this study to assess for floor or ceiling effect). Second, a one-way repeated measures ANOVA with post-hoc comparison tests was used to compare the magnitude of the three SPA indices. Third, chi-squared tests were used to compare the proportion of participants that experienced a clinically important increase in pain in relation to each of the SPA tasks. Consistent with previous literature, the minimum threshold for a clinically important increase in pain was defined as experiencing at least a 20-point increase in pain ratings (i.e. between SPA rating #1 and SPA rating #2) (43, 44).

Next, the distribution of scores for SPA pain rating #2 was compared across the three tasks to evaluate potential floor and ceiling effects associated with each measure. The potential for floor effects was evaluated by comparing the proportion of participants that scored 0 on the SPA pain rating #2 for each test. A higher proportion of these responses indicates that the task may have been inadequate in evoking sufficient activity-related pain among participants. The potential for ceiling effects was evaluated by comparing the proportion of participants that scored 100 on the SPA pain rating #2 for each test. A higher proportion of these responses may indicate that the task may have been too intense, evoking more pain than could be measured on the numeric rating scale. Chi-squared tests were used to evaluate whether proportions of these scores were significantly different across the SPA tasks.

2.3.7.5. Evaluating the predictive value of SPA measures

To estimate the extent to which SPA predicts pain severity and pain interference, correlational analyses were first conducted between all of the study's variables to determine what variables will be included in the hierarchical regression analysis. Next, hierarchical regression analysis was conducted for each outcome of interest (pain severity, pain interference). The significant covariates (age, sex, body mass index, ethnicity, level of education, pain duration, and number of comorbidities) were

entered in the first step, the significant psychological variables (pain catastrophizing, pain-related fear) and significant clinical indices of sensory hypersensitivity (pressure pain threshold, temporal summation of pain) were entered in the second step, and the significant SPA indices were entered in the final step.

2.3.7.6. Evaluating the correlates and predictors of SPA measures

To estimate the extent to which psychological (pain catastrophizing, pain-related fear) and sensory (pressure pain threshold, temporal summation of pain) constructs explain variance in the different SPA indices, correlational analyses were first conducted between all of the study's variables to determine what variables will be included in the hierarchical regression analysis. Next, hierarchical regression analysis was conducted, but only if the predictors of interest (psychological and sensory constructs) were significantly correlated ($p < 0.05$) with the respective SPA index. Hierarchical regression analysis was conducted similarly as for the pain-related outcomes; that is, the significant covariates (age, sex, body mass index, ethnicity, level of education, pain duration, and number of comorbidities) were entered in the first step, and the significant psychological variables (pain catastrophizing, pain-related fear) and the significant clinical indices of sensory hypersensitivity (pressure pain threshold, temporal summation of pain) were entered in the final step.

2.4. RESULTS

2.4.1. Characteristics of the study sample

One hundred eighty-five people expressed their interest in participating in the study and were provided with additional information. Of these individuals, 116 met the inclusion criteria and agreed to participate. Evaluation of missing data revealed that a total of 6.54% of individual data points were missing at random. Missing data appeared to mainly be a result of participants declining to complete aspects of either quantitative sensory testing or the physical tasks. All results presented below are based on the multiple imputations pooled data, thus preserving the full sample size. Data generated by multiple imputations was pooled from five imputed datasets, based on ten iterations each. Data was

consistent with the assumptions of the statistical analyses conducted and did not require transformation or correction. No influential outliers were found (Cook's distance < 1, standardized DF betas < 2) (45). Data analysis was repeated using only participant-generated data (i.e. without multiple imputations; not presented) and revealed a consistent pattern of findings.

Table 2.1 presents characteristics of the study sample. Of note, our sample was characterized by widespread (five out of seven body sites were identified as painful, on average) and highly chronic pain (10 years pain duration, on average). Because many of this study's participants had widespread pain, we decided to adopt a comprehensive approach to quantitative sensory testing (i.e. did not collapse or drop measures from right/left sides of hands, upper back, lower back, and calves). Otherwise, participants were 53 years old and had a body mass index of 29.5 kg/m^2, on average. A third of participants were women, two-thirds completed post-secondary education, the majority self-identified as Caucasian (80.2%) and reported at least two comorbidities (81.9%). Table 2.2 presents descriptive statistics for the pain-related, psychological, and clinical indices of sensory hypersensitivity measures of this study.

TABLE 2.1. Participants characteristics

Characteristics	**Values**
Age (years), mean (SD)	53.33 (13.82)
Sex, n (%)	
Women	81 (69.83%)
Men	35 (30.17%)
Body mass index (kg/m^2), mean (SD)	29.34 (7.36)
Ethnicity, n (%)	
Caucasian	93 (80.17%)
Other	23 (19.83%)
Highest level of education, n (%)	
Elementary school	9 (7.76%)
High school	38 (32.76%)
Post-secondary education	69 (59.48%)
Pain duration (years), mean (SD)	10.67 (10.96)
Number of sites of pain (0-7)[1], mean (SD)	5.05 (1.94)
Identified this body site as painful, n (%)	
Right upper extremity[1]	78 (67.83%)
Left upper extremity[1]	75 (65.22%)
Right lower extremity[1]	91 (79.13%)
Left lower extremity[1]	90 (78.26%)
Front trunk[1]	71 (61.74%)
Back[1]	103 (89.57%)
Head, face, and/or neck[1]	73 (63.48%)
Number of comorbidities, n (%)	
0	6 (5.17%)
1	15 (12.93%)
2	36 (31.03%)
3	25 (21.55%)
4	18 (15.52%)
5 or more	16 (13.79%)

Values based on pooled multiple imputations data (n = 116), except all variables with superscript "1", which were not imputed (not part of any analysis) and had n = 115.

TABLE 2.2. Means and standard deviations for pain-related, psychological, and clinical indices of sensory hypersensitivity variables

Variables	Values
Pain severity (0-10), mean (SD)	5.70 (1.79)
Pain interference (0-10), mean (SD)	5.79 (2.13)
SPA: self-paced walk (pain NRS 0-100), mean (SD)	15.70 (18.12)
SPA: tailored lift (pain NRS 0-100), mean (SD)	24.46 (21.09)
SPA: standardized lift (pain NRS 0-100), mean (SD)	10.62 (13.39)
Pain catastrophizing (0-52), mean (SD)	26.74 (13.01)
Pain-related fear (11-44), mean (SD)	30.04 (7.37)
Pressure pain threshold (kPa)	
Right hand, mean (SD)	187.02 (117.13)
Left hand, mean (SD)	173.56 (117.10)
Right upper back, mean (SD)	207.36 (138.04)
Left upper back, mean (SD)	205.38 (151.13)
Right lower back, mean (SD)	224.58 (171.16)
Left lower back, mean (SD)	227.85 (182.02)
Right calf, mean (SD)	241.10 (156.27)
Left calf, mean (SD)	229.00 (173.00)
Temporal summation of pain (evoked change in pain NRS 0-100)	
Right hand, mean (SD)	17.68 (22.62)
Left hand, mean (SD)	23.00 (24.92)
Right upper back, mean (SD)	18.53 (22.37)
Left upper back, mean (SD)	22.87 (22.80)
Right lower back, mean (SD)	27.53 (27.49)
Left lower back, mean (SD)	30.08 (25.84)
Right calf, mean (SD)	28.43 (26.12)
Left calf, mean (SD)	28.97 (24.53)

Values based on pooled multiple imputations data (n = 116)
SD = Standard Deviation; kPa = kilopascals; NRS = Numerical Rating Scale; SPA = Sensitivity to Physical Activity (higher score signifies greater SPA).

2.4.2. Evaluating potential carry-over pain between SPA tasks

The one-way repeated measures ANOVA revealed that mean pre-task resting pain intensity did not statistically differ ($p = 0.174$) between the three SPA tasks, nor did the mean pre-task ratings of perceived exertion ($p = 0.901$).

2.4.3. Comparing descriptive characteristics across SPA measures

Table 2.3 and Figure 2.3 summarize the descriptive characteristics across the three SPA indices with respect to the magnitude of the evoked sensitized pain response, as well as the extent of their floor and ceiling effects.

TABLE 2.3. Sensitivity to physical activity indices characteristics

Variables	**SPA: self-paced walk (pain NRS 0-100)**	**SPA: tailored lift (pain NRS 0-100)**	**SPA: standardized lift (pain NRS 0-100)**
Magnitude of change statistics:			
SPA pain rating #1, mean (SD)	46.22 (24.41)	32.01 (20.05)	32.91 (25.69)
SPA pain rating #2, mean (SD)	61.92 (25.51)	56.48 (25.90)	43.53 (27.05)
SPA pain rating #2 – rating #1, mean (SD)	15.70 (18.12)	24.46 (21.09)	10.62 (13.39)
Paired-samples t-test for SPA pain ratings #1 and #2, t-statistics (effect size)	9.34 (0.64)**	12.49 (1.22)**	8.54 (0.41)**
Proportion for which difference between SPA pain ratings #1 and #2 is ≥ MCIC (20/100 NRS), n (%)	47 (40.52%)	67 (57.76%)	26 (22.41%)
Floor and ceiling effect statistics:			
Proportion with SPA pain rating #2 = 0/100 NRS, n (%)	1 (0.86%)	0 (0.00%)	4 (3.45%)
Proportion with SPA pain rating #2 = 100/100 NRS, n (%)	3 (2.59%)	6 (5.17%)	1 (0.86%)

Values based on pooled multiple imputations data (n = 116)

SD = Standard Deviation; SPA = Sensitivity to Physical Activity (higher score signifies greater SPA); NRS = Numerical Rating Scale; MCIC = Minimally Clinically Important Change; SPA pain rating #1 = refers to initial SPA task-related pain; SPA pain rating #2 = refers to either the highest or the final SPA task-related pain; Effect size = (mean SPA pain rating #2 - mean SPA pain rating #1) / standard deviation of SPA pain rating #1.

* $p < 0.05$
** $p < 0.01$

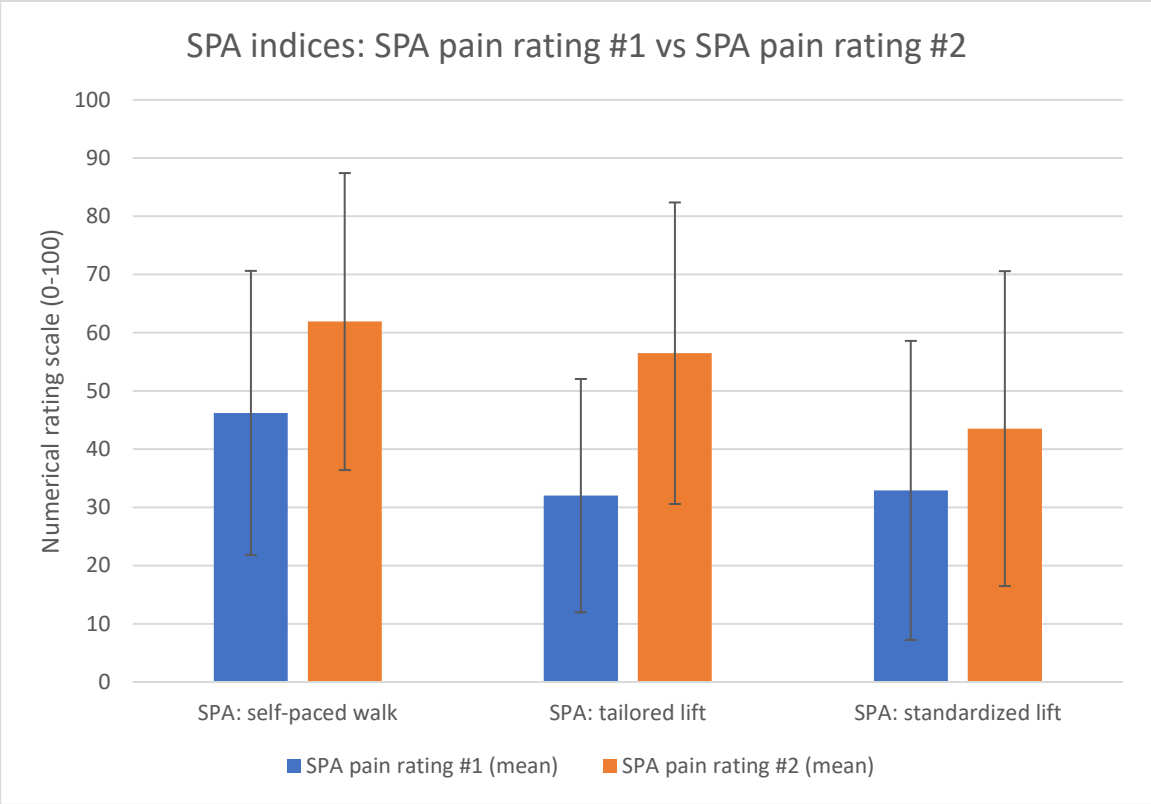

FIGURE 2.3. SPA indices: SPA pain rating #1 vs. SPA pain rating #2. SPA = Sensitivity to Physical Activity (higher score signifies greater SPA); SPA pain rating #1 = refers to initial SPA task-related pain; SPA pain rating #2 = refers to either the highest or the final SPA task-related pain. Error bars indicate standard deviations.

First, SPA pain rating #2 was significantly different ($p < 0.001$) from SPA pain rating #1 for all three SPA tasks, based on paired-samples t-test and based on one-way repeated measures ANOVA with contrasts (three simple contrasts corresponding to the three SPA tasks) using a Bonferroni correction (original alpha level $p<0.05$ was divided by three to obtain the Bonferroni-correct alpha level 0.016667). Similar to the effect sizes calculated for each SPA index (Table 2.3), the SPA index mean was largest for the SPA tailored lift task (24.46 on 0-100 NRS), followed by the SPA self-paced walk task (15.70), and then the SPA standardized lift task (10.62). These SPA index means were

significantly different from one another ($p < 0.001$), based on one-way repeated measures ANOVA (Greenhouse-Geisser correction) with post-hoc comparisons for each pair (with Bonferroni adjustments). Moreover, the SPA tailored lift task evoked a clinically important increase in pain intensity for 57.76% of participants, a significantly greater proportion of participants than the other SPA tasks, as verified by a comparison of proportions between each SPA task using chi-squared tests (SPA tailored lift task vs. SPA self-paced walk: $p = 0.009$, SPA tailored lift task vs. SPA standardized lift: $p < 0.001$).

Second, as illustrated in Figure 2.3, the floor and ceiling effect did not seem to have any important effect on any of the three SPA indices, for which neither of SPA pain rating #1 or SPA pain rating #2 approached the limits of the 0-100 NRS. In fact, less than 4% of participants finished with a SPA pain rating #2 of 0/100 NRS and less than 5% of participants finished with a SPA pain rating #2 of 100/100 NRS. These proportions were considered equivalent across the three SPA tasks, according to a comparison of proportions between each SPA task using chi-squared tests ($p>0.05$).

2.4.4. Predictive value of SPA measures

A correlational matrix of all study variables of interest is presented in Table 2.4, while hierarchical regression analyses are presented in Tables 2.5 and 2.6. Pain severity was significantly correlated with pain catastrophizing ($r = 0.360$, $p <0.001$), temporal summation of pain at several body sites (right upper back $r = 0.226$, $p = 0.018$; left upper back $r = 0.239$, $p = 0.025$; right lower back $r = 0.248$, $p = 0.020$; left lower back $r = 0.205$, $p = 0.041$; right calf $r = 0.291$, $p = 0.023$), and the SPA tailored lift index ($r = 0.257$, $p=0.006$). Variables with significant correlations were entered in the final regression model for predicting pain severity, with the SPA tailored lift index entered in a separate step. The SPA tailored lift index contributed unique predictive value for pain severity ($\beta = 0.225$, $t = 2.457$, $p=0.014$) beyond pain catastrophizing and temporal summation of pain. No significant violations of statistical test assumptions were found and no corrective action was required. Of note, despite presence of multiple temporal summation of pain measures (different body sites), multicollinearity did not occur

– none of the Tolerance values were less than .1 (lowest Tolerance value was 0.385) and none of the VIF values were above 10 (highest VIF value was 2.617) (46).

Pain interference was significantly correlated with pain catastrophizing ($r = 0.475$, $p<0.001$), pain-related fear ($r = 0.185$, $p=0.049$), temporal summation of pain at several body sites (right lower back $r = 0.243$, $p = 0.022$; left lower back $r = 0.195$, $p = 0.043$; right calf $r = 0.233$, $p = 0.037$), and the SPA tailored lift index ($r = 0.256$, $p=0.006$). As shown in Table 2.6, these significant variables were entered in the final regression model for predicting pain interference, with the SPA tailored lift index entered a separate step. SPA tailored lift index contributed unique predictive value for pain interference ($\beta = 0.214$, $t = 2.329$, $p=0.021$) beyond pain catastrophizing, pain-related fear, and temporal summation of pain. No significant violations of statistical test assumptions were found and no corrective action was required. Of note, despite presence of multiple temporal summation of pain measures (different body sites), multicollinearity did not occur – none of the Tolerance values were less than .1 (lowest Tolerance value was 0.484) and none of the VIF values were above 10 (highest VIF value was 2.081) (46).

2.4.5. Correlates and predictors of SPA measures

Temporal summation of pain measures significantly correlated with both the SPA tailored lift index (temporal summation of pain at left upper back $r = 0.195$, $p = 0.046$; right lower back $r = 0.351$, $p < 001$; left lower back $r = 0.219$, $p = 0.024$) and the SPA standardized lift index (temporal summation of pain at left upper back $r = 0.251$, $p = 0.010$; right lower back $r = 0.240$, $p = 0.014$), however none of the psychological risk factors and none of the pressure pain threshold measures were correlated with any of the SPA indices. Otherwise, from the potential covariates, the number of comorbidities significantly correlated with the SPA tailored lift index (spearman's rho = 0.198, $p=0.039$) and sex correlated with SPA standardized lift (point-biserial $r = 0.224$, $p=0.019$). In Table 2.7, the final regression model for predicting the SPA tailored lift index is presented. Temporal summation of pain (measured at the right lower back) was the only statistically significant predictor ($\beta= 0.336$, $t = 2.706$, p

=0.007). None of the psychological or sensory constructs significantly predicted the self-paced walk SPA index nor the standardized lift SPA index. No significant violations of statistical test assumptions were found and no corrective action was required. Of note, despite presence of multiple temporal summation of pain measures (different body sites), multicollinearity did not occur – none of the Tolerance values were less than .1 (lowest Tolerance value was 0.716) and none of the VIF values were above 10 (highest VIF value was 1.405) (46).

TABLE 2.4. Correlation matrix of pain-related, psychological, and clinical indices of sensory hypersensitivity variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1. Pain severity	1																					
2. Pain interference	0.660**	1																				
3. SPA: self-paced walk	0.025	0.028	1																			
4. SPA: tailored lift	0.257**	0.256**	0.064	1																		
5. SPA: standardized lift	0.042	0.055	0.207*	0.138	1																	
6. Pain catastrophizing	0.360**	0.475**	0.068	0.060	-0.039	1																
7. Pain-related fear	0.122	0.185*	0.140	0.052	0.110	0.464**	1															
8. PPT: right hand	-0.012	0.015	0.063	-0.109	-0.200	-0.014	-0.081	1														
9. PPT: left hand	-0.024	-0.064	0.005	-0.188	-0.181	-0.014	-0.121	0.881**	1													
10. PPT: right upper back	-0.030	-0.045	0.053	-0.176	-0.135	-0.008	0.015	0.596**	0.651**	1												
11. PPT: left upper back	0.003	-0.040	0.067	-0.101	-0.149	0.001	0.034	0.579**	0.633**	0.908**	1											
12. PPT: right lower back	-0.120	-0.124	0.043	-0.170	-0.166	0.037	0.037	0.630**	0.718**	0.796**	0.816**	1										
13. PPT: left lower back	-0.059	-0.074	0.037	-0.167	-0.174	0.064	0.057	0.585**	0.710**	0.759**	0.757**	0.918**	1									
14. PPT: right calf	-0.016	-0.020	0.031	-0.071	-0.113	-0.046	-0.013	0.651**	0.702**	0.649**	0.679**	0.764**	0.753**	1								
15. PPT: left calf	-0.034	-0.127	-0.053	-0.100	-0.135	0.047	0.065	0.610**	0.726**	0.649**	0.654**	0.763**	0.776**	0.837**	1							
16. TSP: right hand	0.074	0.057	-0.066	0.180	0.016	-0.002	0.015	-0.312**	-0.362**	-0.188	-0.144	-0.126	-0.166	-0.129	-0.155	1						
17. TSP: left hand	0.022	0.003	0.014	0.137	0.098	0.053	0.076	-0.296**	-0.334**	-0.326**	-0.275**	-0.229*	-0.268**	-0.226*	-0.228*	0.727**	1					
18. TSP: right upper back	0.226*	0.070	-0.054	0.166	0.037	0.081	0.063	-0.274**	-0.254**	-0.229*	-0.147	-0.211*	-0.250**	-0.236*	-0.208*	0.493**	0.536**	1				
19. TSP: left upper back	0.239*	0.086	-0.050	0.195*	0.251*	0.085	0.086	-0.350**	-0.391**	-0.288**	-0.239*	-0.300**	-0.319**	-0.266**	-0.277*	0.575**	0.568**	0.650**	1			
20. TSP: right lower back	0.248*	0.243*	0.043	0.351**	0.240*	0.135	0.155	-0.323**	-0.408**	-0.201*	-0.207*	-0.192*	-0.232*	-0.278**	-0.287**	0.506**	0.434**	0.544**	0.589**	1		
21. TSP: left lower back	0.205*	0.195*	0.062	0.219*	0.026	0.219*	0.136	-0.343**	-0.392**	-0.227	-0.206	-0.218*	-0.237*	-0.309**	-0.330**	0.463**	0.511**	0.477**	0.619**	0.630**	1	
22. TSP: right calf	0.291*	0.233*	-0.019	0.083	0.033	0.118	0.087	-0.326**	-0.307**	-0.211	-0.184	-0.151	-0.138	-0.277**	-0.284**	0.365**	0.398**	0.467**	0.528**	0.523**	0.686**	1
23. TSP: left calf	0.195	0.118	0.075	0.122	0.149	0.102	0.204*	-0.329**	-0.377**	-0.207	-0.157	-0.182	-0.236*	-0.373**	-0.343**	0.408**	0.523**	0.588**	0.613**	0.578**	0.661**	0.622**

All correlations are Pearson r values (multiple imputation data, n=116)
**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
SPA = Sensitivity to Physical Activity (higher score signifies greater SPA); PPT = Pressure Pain Threshold; TSP = Temporal Summation of Pain.

TABLE 2.5. Hierarchical regression analyses for the outcome: **pain severity**

Step Number	Variables	β	*t* (P value)	R^2 Change	F Change (P value)
1	Pain catastrophizing	0.343	3.857 (<0.001)**	0.229	5.446 (<0.001)**
	TSP: right upper back	0.058	0.494 (0.622)		
	TSP: left upper back	0.100	0.615 (0.544)		
	TSP: right lower back	0.014	0.088 (0.931)		
	TSP: left lower back	-0.215	-1.302 (0.201)		
	TSP: right calf	0.292	2.090 (0.041)*		
2	SPA: tailored lift	0.225	2.457 (0.014)*	0.044	6.546 (0.016)*

All parameter estimates listed are from the final regression model using pooled multiple imputation data (n = 116).
SPA = Sensitivity to Physical Activity (higher score signifies greater SPA); TSP = Temporal Summation of Pain.
* $p < 0.05$
** $p < 0.01$

TABLE 2.6. Hierarchical regression analyses for the outcome: **pain interference**

Step number	Variables	β	*t* (P value)	R^2 Change	F Change (P value)
1	Pain catastrophizing	0.488	5.257 (<0.001)**	0.284	8.743 (<0.001)**
	Pain-related fear	-0.065	-0.718 (0.473)		
	TSP: right lower back	0.095	0.688 (0.497)		
	TSP: left lower back	-0.165	-1.276 (0.203)		
	TSP: right calf	0.228	1.779 (0.079)		
2	SPA: tailored lift	0.214	2.329 (0.021)*	0.040	6.456 (0.018)*

All parameter estimates listed are from the final regression model using pooled multiple imputation data (n = 116).
SPA = Sensitivity to Physical Activity (higher score signifies greater SPA); TSP = Temporal Summation of Pain.
* $p < 0.05$
** $p < 0.01$

TABLE 2.7. Hierarchical regression analyses for the outcome: **SPA tailored lift**

Step number	Variables	β	t (P value)	R^2 Change	F Change (P value)
1	Number of comorbidities	0.171	1.904 (0.057)	0.046	5.503 (0.023)*
2	TSP: left upper back	-0.034	-0.272 (0.785)	0.108	4.734 (0.005)**
	TSP: right lower back	0.336	2.706 (0.007)**		
	TSP: left lower back	0.020	0.162 (0.871)		

All parameter estimates listed are from the final regression model using pooled multiple imputation data (n = 116).
SPA = Sensitivity to Physical Activity (higher score signifies greater SPA); TSP = Temporal Summation of Pain.
* $p < 0.05$
** $p < 0.01$

2.5. DISCUSSION

This study adds to the growing body of research suggesting that SPA is an important construct that offers novel added value in predicting pain-related outcomes beyond established psychological and sensory risk factors (5, 16, 18, 19, 21). This study also extends past work by being the first to compare three distinct measures of SPA and by highlighting the value of a newly developed tailored approach to the measurement of this construct. These findings are expected to have important implications for clinical practice, theoretical models and future research.

Our comparison across SPA measures highlights several strengths of the tailored task. Consistent with previous work, each of the SPA-related tasks evoked statistically significant increases in pain (5, 16-20). While the magnitude of the SPA indices for the self-paced walk and standardized lift tasks were broadly consistent with previous findings (5, 16-20), the newly developed tailored lift task stood out. When compared to the previously established SPA tasks, the tailored task evoked the largest mean SPA index (56% and 130% greater than the self-paced walk and standardized lift tasks, respectively), the largest effect size (91% and 198% greater than the self-paced walk and standardized lift tasks, respectively) and the highest proportion of participants with a clinically meaningful increase in pain (42% and 158% more participants than the self-paced walk and standardized lift tasks respectively). Together these findings suggest that purposefully tailoring the intensity of the physical task to individual pain levels helps generate a more evocative stimulus, which may help this SPA measure to capture additional meaningful variance in this construct compared to non-tailored SPA measures.

The newly developed tailored index of SPA also emerged as being uniquely associated with pain-related outcomes and correlates. The SPA tailored lift index significantly predicted both pain severity and interference outcomes even after controlling for established risk factors. Specifically, these factors included pain catastrophizing and pain-related fear, which are widely recognized for their prognostic value (47, 48). These factors also included measures of sensory hypersensitivity, such as

pressure pain threshold and temporal summation of pain. Altogether, the overall explained variance (R^2) for the regression model for pain severity was 27.3% and for pain interference was 32.4%. Yet, despite considering these established psychological and sensory measures in the first step of the hierarchical regression models, the SPA tailored lift index was able to contribute additional unique predictive value. The R^2 change value contributed by the SPA tailored lift index was of approximately 4% in both regression models. As suggested by recent findings (16), it is possible that greater explained variance would be found for physical function outcome measures that are more specific to the SPA task tested (e.g. SPA lift tasks may predict forward bending and lifting tasks to a greater extent than overall pain interference with activities). Future work will need to estimate the extent to which SPA with specific activities (e.g. walking, lifting) reflects overall physical activity SPA, captured using methods such as ecological momentary assessment. Furthermore, our regression analysis revealed that only the tailored SPA index was predicted by measures of temporal summation of pain (at three out of eight tested body sites). Together these findings show that, compared to the self-paced and standardized approaches to measuring SPA, the tailored approach to measuring SPA was better suited to capturing processes related to sensory sensitization and was uniquely associated with pain-related outcomes even when controlling for psychological and sensory factors.

One surprising deviation from past work is that neither of the previously established SPA indices were significantly correlated with either of our pain-related outcomes. This may be a partial reflection of the outcomes used in this study. In two previous studies that used either the self-paced walk or standardized lift tasks, indices of SPA were shown to predict pain-related functional performance measures, but failed to predict self-reported outcomes (16, 18). Similar discrepancies between the predictors of self-report versus performance-based measures have been reported within the broader pain literature (49, 50). It is possible that by only using self-reported outcomes within our study, the threshold for significance was raised to a level that only the strongest predictor (i.e. the tailored lift index) could surpass. On the other hand, this pattern of findings may also reflect our study

population. In previous studies addressing SPA, participants were typically characterized by localized pain complaints, such as knee pain (5, 21) or neck pain (18, 19), whereas our study was the first to assess SPA's predictive value among a sample with more widespread and chronic pain. Future research will need to explore whether this pattern of findings is replicated among other samples with similar characteristics and in which both self-reported and performance-based outcomes are used.

These findings have important implications for clinical practice. First, our findings suggest that integrating measures of SPA within clinical assessment may help improve prognostic accuracy by capturing a unique aspect of the pain experience that is not fully explained by other psychological and sensory risk factors. Moreover, SPA measures may be a viable alternative for clinicians to get insight into sensitization in a way that patients may perceive as better relating to their activity-related complaints than quantitative sensory testing. Our findings further suggest that using a tailored approach to measuring SPA is expected to generate a more responsive and predictive clinical prognostic tool, when compared to other assessment strategies. Future research will need to evaluate these potential benefits using prospective study designs.

Second, these findings help guide future clinical research in shedding light on potential targets for evaluating interventions that reduce elevated levels of SPA. Our findings indicate that sensory, but not psychological factors, were predictive of SPA. Our findings are consistent with one other study that failed to show correlations between SPA and these two psychological factors (10). Other research suggests some inconsistency in the relationship between SPA and these psychological constructs. For instance, four of the six studies that have evaluated the relationship between SPA and pain-related fear found no significant correlations between these constructs (10, 16-20). Similarly, three of the five studies that have evaluated the relationship between SPA and pain catastrophizing no significant correlations between these constructs (5, 10, 17, 18, 20). On the other hand, our finding that SPA is uniquely associated with temporal summation of pain (at three out of eight tested body sites), but not pressure pain threshold (none out of the eight tested body sites), is consistent with both of the previous

studies that have evaluated the relationship between SPA and clinical indices of sensory hypersensitivity (5, 16). Unique links between SPA and temporal summation of pain are also broadly consistent with animal research that highlights the important role of the central nervous system in contributing to sensitized responses to physical activity (8). Together, these findings suggest that interventions directed toward a sensitized nervous system may be particularly valuable targets for reducing elevated levels of SPA. Indeed, in recent studies, transcutaneous electrical nerve stimulation, a sensory-based intervention affecting the central nervous system, was recently found to be effective at reducing SPA in a cohort of healthy adults (7, 10-12). Also, certain centrally acting pharmacological agents have been shown to have a unique effect on reducing pain during movement among patients with musculoskeletal pain (9). Future research should build on these findings by evaluating the effects of sensory-based interventions among people that have both musculoskeletal pain and elevated levels of SPA.

These findings also relate to our theoretical understanding of the relationship between pain and physical activity. Current leading theoretical models of pain-related disability focus on psychological risk factors as a common conduit for how pain interferes with physical activity (49). However, our findings join other recent work in highlighting the important role that sensitivity factors play within these relationships (49, 51, 52). What still needs to be explored is how SPA should be linked to theoretically-relevant coping behaviours. Previous theoretical work has emphasized the importance of both avoidance and persistence patterns of activity engagement (53). It is possible that individual variance in SPA may be particularly valuable in tailoring the dosage of theoretically-driven interventions designed to increase physical activity, such as graded activity. Current approaches to dosing graded activity are often dependent on unstandardized and retrospective reports of pain associated with physical activity (54-56). These evaluation strategies may be particularly susceptible to patients' perceived threat value of pain and thus inadvertently facilitate an overly conservative approach to prescribing activity quotas for individuals with elevated fear or catastrophizing. This is

consistent with a recent meta-analysis that showed that activity pacing interventions tend to increase, rather than decrease, levels of pain and disability (57). Similarly, systematic reviews on graded activity interventions reveal little to no difference compared to control groups (58, 59). Using evoked measures of SPA to tailor activity quotas may help mitigate these poor responses. For instance, people with low levels of SPA may stand to benefit from encouragement to persist with physical tasks despite pain, while those with elevated SPA may benefit from a more gradual approach. Future research will need to investigate how individual variance in SPA can be best used to tailor activity engagement and mitigate maladaptive coping behaviour.

Several limitations should be considered when interpreting these findings. First, the order of the three SPA measures was not randomized and thus may have influenced our findings. However, our finding that there was no significant difference between the ratings of resting pain and of perceived exertion preceding each of the SPA tasks suggest that these potential influencing factors would have likely only had a modest effect on our results. Nonetheless, standardizing the order of SPA tasks may have influenced our findings. Second, as discussed above, this study was cross-sectional and only used self-reported outcome measures. Third, the clinical indices used in this study to assess sensory hypersensitivity are psychophysical measures with known limitations. While they are widely used in pain research (23, 52), they should not be interpreted as direct measures of sensory processing. Finally, while pain medication use by participants was monitored, no instructions were provided to the participants regarding use of pain medication. Thus, the effects of pain medication during testing could have influenced our results. That being said, this study was designed to offer a pragmatic reflection of the clinical context in which the studied physical activities might be performed, without attempting to alter the normal analgesics used by patients. Requiring participants to withhold medications might have potentially influenced who opted to complete this study, which in turn may further limit generalizability.

Despite these limitations, this is the first study to present a tailored approach to evaluating SPA and to compare and contrast different strategies for measuring sensitized responses to physical activity. This study adds to the growing literature base on SPA by showing that a tailored approach to measuring SPA generates significantly greater evoked responses and offers greater predictive value compared to previously established measures of SPA and predicts pain-related outcomes beyond established risk factors. Our findings also help direct future research in this area by highlighting the potential value of sensory-based interventions in reducing elevated levels of SPA, as well as the potential for using SPA to tailor activity-based interventions among patients with musculoskeletal pain.

2.6. ACKNOWLEDGEMENTS

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PREFACE TO CHAPTER 3 (STUDY 2)

The introduction of this thesis highlighted that there is a dearth of prognosis research in the SPA literature. Study 1 provided some preliminary indication of potential prognostic value for SPA. However, similar to most SPA research to date, it used a cross-sectional study design. Study 2 is one of the first studies to explore the prospective prognostic value of SPA for pain-related outcomes using a longitudinal study design. Specifically, *dataset #2* was used, which included a baseline in-person testing session and a three-month follow-up among a sample of 97 adults recruited as they sought out physiotherapy treatment for their back pain at one of eight participating local private rehabilitation clinics.

Moreover, similar to Study 1, Study 2 also contributes to advancing research on the methods for assessing SPA. In the introduction of this thesis, SPA was defined using broad terminology that allows for a multidimensional conceptualization which is compatible with the biopsychosocial model of pain and the official definition of pain as a sensory and emotional experience. Unidimensional assessment of SPA, however, dominates the SPA literature. Study 2 is the first study to concurrently include a broad range of multidimensional SPA indices in relation to a SPA task, and to evaluate them for their prognostic value for pain-related outcomes as well as for their correlations with one another. Specifically, using the individually tailored lifting SPA task described in Study 1, the SPA indices tracked in Study 2 included: SPA-Pain (task-evoked changes in pain intensity), SPA-Sensory (task-evoked pre-post changes in pressure pain thresholds at a local and a distal body site from the clinical back pain), and SPA-Psych (task-specific situation pain catastrophizing). Thus, in addition to shedding light on the prospective prognostic value of SPA by using range of indices, Study 2 also advances knowledge by exploring how multidimensional indices of SPA relate to one another.

CHAPTER 3: THE PROSPECTIVE PROGNOSTIC VALUE OF BIOPSYCHOSOCIAL INDICES OF SENSITIVITY TO PHYSICAL ACTIVITY AMONG PEOPLE WITH BACK PAIN (STUDY 2)

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3.1. ABSTRACT

Objectives: Many people living with musculoskeletal pain conditions experience a range of negative biopsychosocial responses to physical activity, referred to as increased Sensitivity to Physical Activity (SPA), that may undermine successful rehabilitation. This exploratory study aims to provide the first prospective analysis of the potential prognostic value of three biopsychosocial indices of SPA in relation to rehabilitation outcomes. This study also aimed to shed light on the cross-sectional inter-relationships between these three biopsychosocial indices of SPA. **Methods:** Adults with back pain were evaluated upon starting physical therapy and then again three months later. The initial testing session consisted of self-reported pain-related questionnaires and assessment of activity-related changes in pressure pain thresholds (SPA-Sensory), pain intensity ratings (SPA-Pain) and situational catastrophizing (SPA-Psych). The three-month follow-up consisted of self-reported disability and pain questionnaires. Correlational and hierarchical linear regression analyses were conducted. **Results**: 97 participants completed both the initial visit and three-month follow-up. The SPA-Pain index and the SPA-Psych index were significantly inter-correlated, but neither were correlated with the SPA-Sensory index. The SPA-Sensory index was not correlated with outcomes. The SPA-Pain index was correlated only with cross-sectional disability and pain outcomes. The SPA-Psych index was the only SPA index significantly correlated with outcomes both cross-sectionally and at three-month follow-up. After controlling for baseline pain/disability and pain catastrophizing, SPA-Psych was no longer a significant prognostic factor for pain, but remained a significant prognostic factor for disability at three-month follow-up (β=0.272, t=2.674, p=0.008, R^2 Δ=5.60%). **Discussion:** This study highlights the importance of conceptualizing and measuring SPA as a biopsychosocial (rather than unidimensional) construct and points toward the added prognostic value of this construct. Implications for future research and practice are discussed.

Key words: Sensitivity to Physical Activity; Biopsychosocial; Longitudinal; Back pain; Prognostic factor

3.2. INTRODUCTION

Non-specific back pain is a leading cause of persistent disability and healthcare expenditure worldwide (1). While activity-based interventions are a central component of clinical practice guidelines for back pain (2-7), there is growing evidence that certain individuals can experience complex, negative responses to engagement in physical activity (8-14). These responses include increased pain intensity (13, 15-23), dysfunction in the endogenous pain-inhibitory system (11, 12, 24, 25), and negative pain-related thoughts and feelings (11, 17, 26). The term sensitivity to physical activity (SPA) is used to broadly capture the full range of these negative multidimensional and biopsychosocial responses to engagement in activity (15-17). Past research has shown that, for musculoskeletal pain conditions, high SPA is uniquely associated with a range of negative pain-related dependent variables, such as increased disability, reduced functional capacity, decreased daily activity, and increased pain severity (15-17, 19-23). This cross-sectional research suggests that biopsychosocial indices of SPA are worthwhile to explore as potential prognostic factors for recovery trajectories, such as treatment outcomes following activity-based rehabilitation programs.

Previous research has primarily focused on three distinct indices of SPA (SPA-Pain, SPA-Sensory, and SPA-Psych) that each target different aspects of the biopsychosocial responses in relation to standardized physical tasks. Figure 3.1 provides an overview of these SPA indices, as well as alternate terminology that has been used to refer to them in past work. What primarily distinguishes SPA indices from conventional pain-related measures is that SPA indices are context specific and aim to capture individual responses to physical activity. For instance, measures of SPA-Pain have been used among people with musculoskeletal pain conditions to evaluate changes in numeric ratings of pain intensity in relation to standardized activities such as lifting tasks (15, 18, 20-23). Similarly, SPA-Sensory measures (also referred to as exercise-induced hypoalgesia) evaluate corresponding pre-to-post activity-related changes in pain threshold levels (11, 12, 24, 25), while measures of SPA-Psych have

been used to evaluate psychological responses (such as situational catastrophizing) (27, 28) to physical tasks (11, 17, 26).

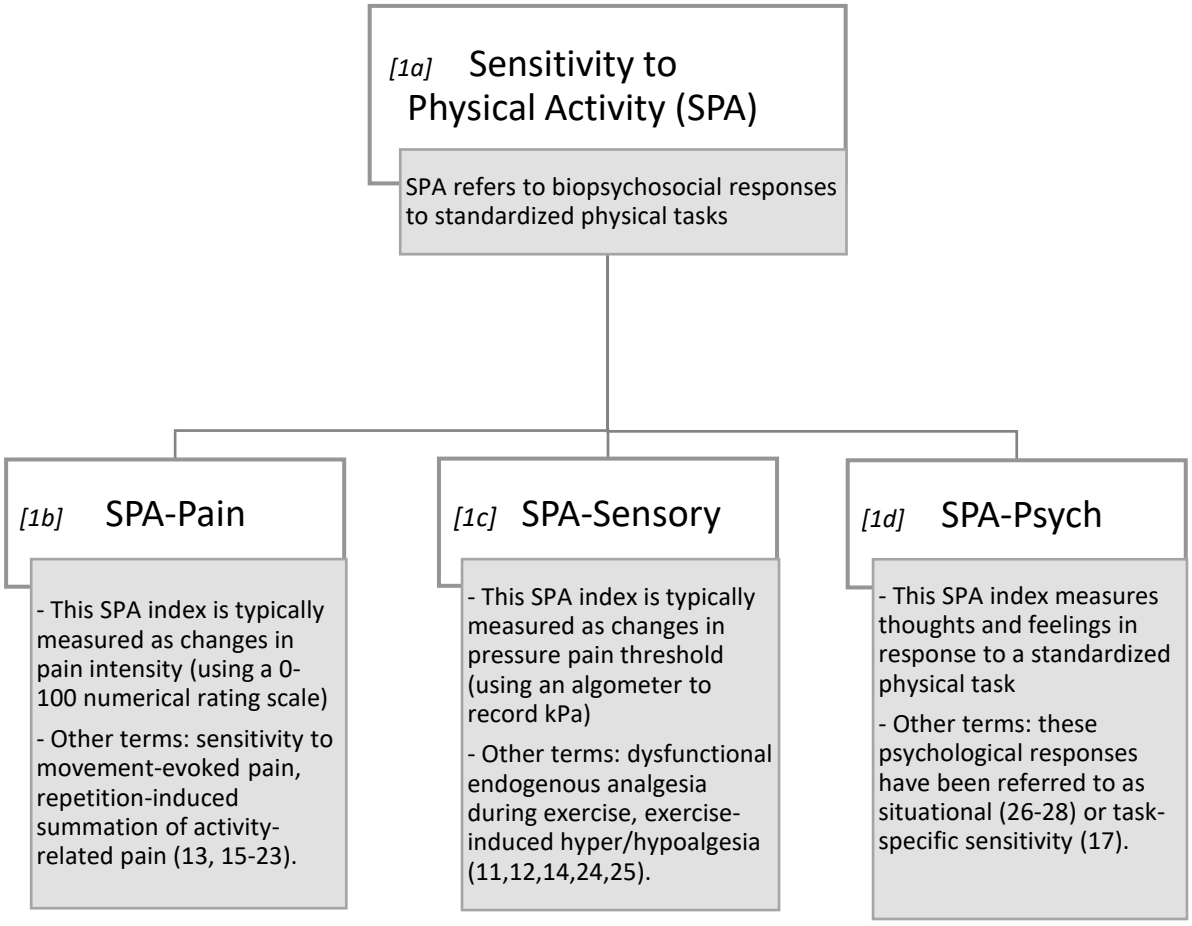

FIGURE 3.1. Operational diagram of sensitivity to physical activity (SPA). Previous research pertaining to sensitivity to physical activity (SPA) has used a variety of terms, definitions, and measurement methods. This operational diagram clarifies our choice of term and definition, and how it relates to measurement methods and other existing terms.

One limitation of previous work in this area is the overarching, unidimensional approach that has been used to investigate SPA. A fundamental aspect of current biopsychosocial models is that pain-related experiences should be evaluated from a multidimensional perspective (29, 30). Yet, the bulk of the previous research in this area has focused on evaluating one, unidimensional index of SPA (i.e. SPA-Pain *or* SPA-Sensory *or* SPA-Psych). Studies that include multidimensional indices of SPA are needed to better understand the inter-relationship between these different responses and their relative influence on pain-related outcomes. A second limitation is that SPA-related research has primarily used cross-sectional designs. Prospective longitudinal studies are needed to better understand the potential role that SPA plays as a prognostic risk factor that influences recovery trajectories. The present study aims to address these gaps by prospectively evaluating how different biopsychosocial indices of SPA predict outcomes among patients with non-specific back pain that are participating in activity-based rehabilitation. Specifically, the objectives of this exploratory study were to determine:

(1) the cross-sectional inter-relationship between three different biopsychosocial indices of SPA (SPA-Pain, SPA-Sensory, SPA-Psych),
(2) the relative prognostic value of these SPA indices for pain and disability outcomes at three-month follow-up, and
(3) the novel added prognostic value of these SPA indices after controlling for baseline clinical measures.

In relation to these objectives, and based on previous work, we hypothesize that all SPA indices would cross-sectionally show significant inter-relationships and would prospectively show significant unique prognostic value.

3.3. MATERIALS AND METHODS

3.3.1. Design

This study used a longitudinal observational design, consisting of an in-person testing session and a three-month follow-up consisting of self-report measures. This study adhered to the STROBE statement guidelines (31) (see Appendix 2 for the completed STROBE checklist for this manuscript) and the PROGRESS framework recommendations for prognostic factor research (exploratory) (32).

3.3.2. Participants and recruitment

Adults who were seeking physical therapy treatment for non-specific back pain were the target population for this study. The inclusion criteria for participant recruitment were: (1) at least 18 years old; (2) less than six months since pain onset; (3) pain location between the gluteal folds and shoulders; and (4) back pain not caused by organic pathology, such as spinal stenosis, spondylolisthesis, and ankylosing spondylitis; and, for data analysis, only participants who participated in both the initial testing session and the follow-up were retained. Participants were excluded from the study if they were not medically stable (serious health conditions, pending surgery or invasive medical procedure, and contra-indication to physical activity). Potential participants were recruited from patients with back pain that were recently enrolled in physical therapy care at one of eight private rehabilitation clinics in the greater Montreal area (in Quebec, Canada). Participants were advised that their decision to participate would have no impact on the treatment that they would receive. The research staff confirmed eligibility and explained what participation in the study entails. Interested patients provided informed consent and research staff completed data collection at the participant's local clinic. While participants were recruited upon enrollment for physical therapy care for their back pain, our analyses were not specifically targeting the outcomes of completed physical therapy care but rather captured the general trajectory of a cohort of people with back pain who were starting physical therapy care.

3.3.3. Procedures

3.3.3.1. Data collection protocol

Research staff (three research assistants) received standardized training for carrying out the recruitment, informed consent, and data collection processes. Standardized training documents for all protocols, one-on-one initial training, and regular check-ins were delivered by the senior investigator or a senior member of the research team. Recruitment and data collection for this study was completed between December 2015 and April 2019. Research staff who collected data did not play a role in the analysis and interpretation of findings.

3.3.3.2. Baseline testing session

Interested and eligible participants were scheduled for an in-person testing session. This consisted of: (1) informed consent, (2) baseline questionnaires including demographic questions, Pain Disability Index (PDI), Brief Pain Inventory (BPI), Pain Catastrophizing Scale (PCS), and (3) completion of a standardized physical task which was used to evaluate biopsychosocial indices of SPA.

Consistent with previous SPA-related research (15), a standardized repeated tailored lifting task was used to evoke SPA responses. This SPA task was selected for use in this study as previous research has shown that, compared to other SPA-related tasks, it is most strongly associated with pain-related dependent variables among people with chronic musculoskeletal pain (15). This task used a specialized lifting apparatus and included two phases.

The lifting task apparatus (15) consisted of a rectangular box (90 cm high×60 cm wide×60 cm deep) resting on the floor. The box contained weights attached by a strap to a height-adjustable handle. The weights could be adjusted to 1.0kg, 2.0kg, 3.0kg, or 3.5kg.

Phase 1 of the SPA task used a tailoring process to determine how to personalize the parameters of the subsequent task. Consistent with previous research, the individual task parameters that evoked pain intensity ratings of ≥ 20 points on a 0-100 scale were then subsequently used to tailor the second phase of the standardized procedure (15). Participants completed a standardized set of lifts that were in

three predetermined positions. The lifting positions were Position 1: standing erect with the elbow of the lifting arm bent at 90 degrees; Position 2: standing erect with lifting arm fully extended; Position 3: standing in a forward flexed position with the lifting arm fully extended. In each of these positions, participants were asked to lift four standardized weights using the height-adjustable handle strapped to the weights. Participants progressed from the lightest to the heaviest weights in lifting position 1, then position 2, followed by position 3. In relation to each lift, participants used a 0-100 verbal numerical rating scale (NRS) to rate their evoked pain intensity, where 0 indicates "no pain" and 100 indicates "the worst pain you can imagine." The lightest weight in the lowest numbered position that evoked ≥20 on the NRS was selected for use in the Phase 2 portion of the task. Phase 2 involved completing a series of repeated lifts using the tailored weight and lifting position that were determined in Phase 1 (15). Participants completed ten, self-paced lifts.

In relation to this standardized task, three biopsychosocial indices of SPA were measured (SPA-Sensory, SPA-Pain, SPA-Psych) and are described in detail in the measures section below. Figure 3.2 provides an overview of the SPA procedures and measures.

3.3.3.3. Follow-up session

Three months after the in-person testing session, participants were contacted for follow-up self-report assessment. The follow-up questionnaires were administered by phone, internet, or in person (according to participant preference), and consisted of the Pain Disability Index (PDI) and Brief Pain Inventory (BPI).

3.3.4. Measures

3.3.4.1. Self-report questionnaires

A list of demographic questions was used to collect information in order to describe the study sample's characteristics (age, sex, height, weight, ethnicity, level of education).

The Pain Catastrophizing Scale (PCS) (33) was used to measure dispositional pain catastrophizing (27, 28, 34). Pain catastrophizing refers to an overly negative cognitive appraisal of

pain, and pain-related stimuli, that includes magnified threat, ruminating thoughts, and feelings of helplessness. A large body of literature links pain catastrophizing with poor pain-related outcomes (28, 34, 35). In contrast to the situational catastrophizing questionnaire (described in detail below), the PCS measures overall dispositional levels of catastrophizing (27, 28). The PCS is composed of 13 items for which a total can be calculated using a sum of the ratings for all the items. Each item is rated on a five-point Likert-type scale in which 0 indicates "not at all" and 4 indicates "all the time". The PCS has good internal reliability (Cronbach alpha = 0.92), test–retest reliability (Spearman rho = 0.88), valid, and widely used measure of pain catastrophizing that is recommended for studies with people with back pain (28, 33, 34).

The Pain Disability Index (PDI) was used to measure self-reported overall disability. The Pain Disability Index is composed of seven items representing seven areas of life activities: family/home responsibilities, recreation, social activity, occupation, sexual behaviour, self-care, and life-support activity. Participants were asked to rate their perceived disability in relation to each item by using a 0-10 scale, where "0 = no disability" and "10 = total disability". Overall self-reported disability was obtained by calculating the sum of all ratings. The PDI is internally consistent (Cronbach alpha = 0.86), valid, and shows good test-retest reliability (intraclass correlation coefficient = 0.91) for people with back pain (36, 37).

The Brief Pain Inventory (BPI) was used to measure self-reported overall pain severity. The pain severity subscale is composed of four items: pain intensity at present and pain intensity (worst, least, average) in the last 24 hours. Pain intensity was rated using an 11-point numerical rating scale in which 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine". An overall pain severity rating was calculated as a mean of the four items on pain intensity. The BPI is an internally consistent (Cronbach alpha = 0.82), reliable, and valid measure for use among people with back pain (38).

3.3.4.2. Biopsychosocial indices of SPA

Three biopsychosocial indices of SPA – SPA-Pain, SPA-Sensory, SPA-Psych – were evaluated in relation to the standardized lifting task. Figure 3.2 includes an overview of the measurement procedures used in relation to each of these indices.

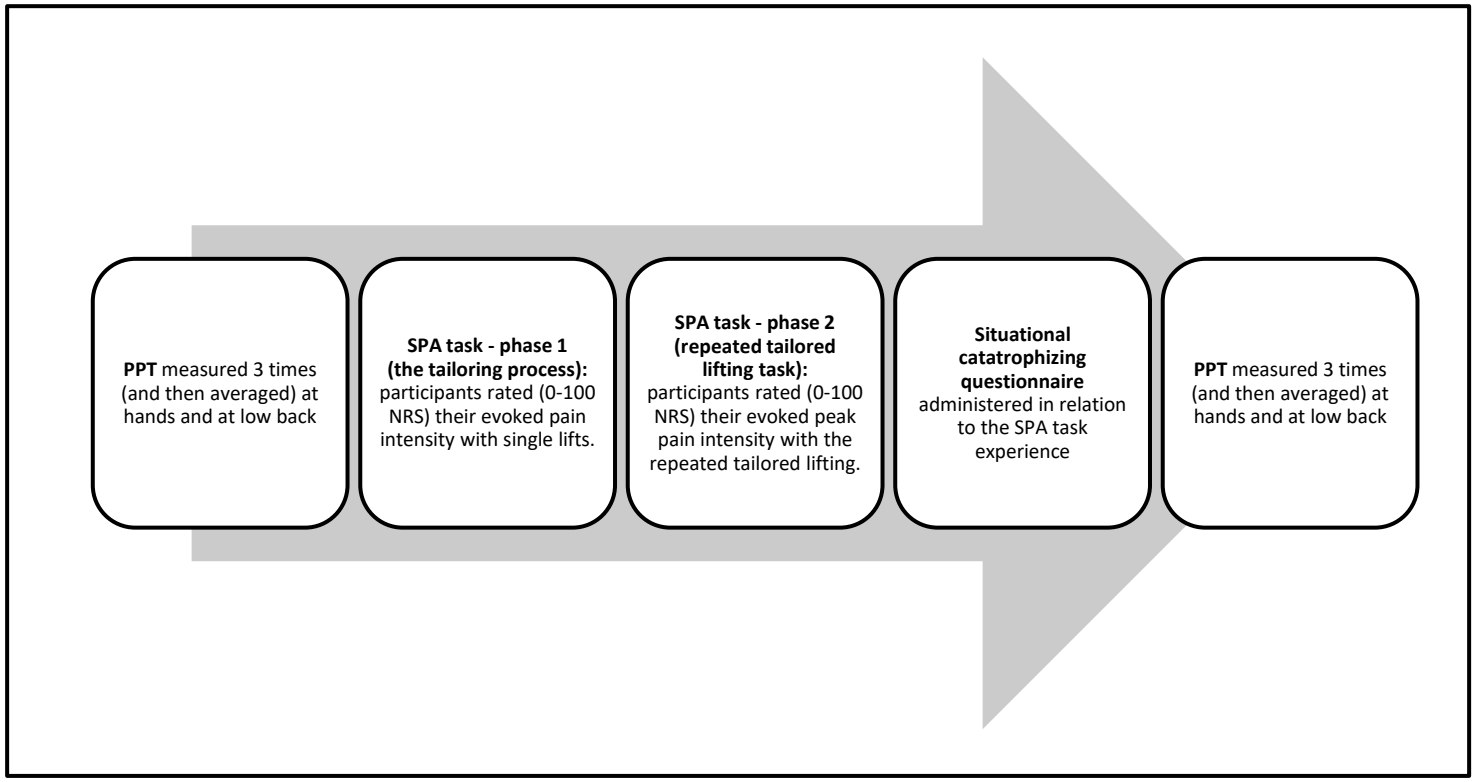

FIGURE 3.2. Overview of the SPA procedures and measures. Three biopsychosocial SPA indices were measured in relation to a standardized physical task (the repeated tailored lifting task is the SPA task). SPA-Pain index is based on changes in evoked pain intensity ratings, SPA-Sensory index is based on pre-post changes in PPT, and SPA-Psych index is based on the situational catastrophizing questionnaire.

SPA = Sensitivity to physical activity; PPT = Pressure pain threshold; NRS = Numerical rating scale.

SPA-Pain index: Consistent with previous approaches (15-17), this index was created by calculating the change in pain intensity between the pain evoked from the single tailored lift (described above in Phase 1) and the ten repeated tailored lifts (described above in Phase 2). After the ten repeated tailored lifts, participants were asked to rate the peak pain intensity evoked during the lifts (15-17). The SPA-Pain index was calculated by subtracting the pain evoked by the single tailored lift from the peak pain intensity evoked during the repeated lifts, such that greater increases in pain indicated higher levels of SPA-Pain.

SPA-Sensory index: Consistent with previous approaches (11, 12, 24, 25), pressure pain thresholds were measured before Phase 1 of the lifting task and then again after Phase 2 of the task. In both cases, thresholds were evaluated using three trials administered bilaterally at the hands (web-space between thumb and index finger) and lower back (five cm laterally from L3 spinous process). Pressure pain threshold was measured in kilopascals using an algometer (FDX 10, Wagner instruments, Greenwich, CT, USA) with a one cm^2 rubber tip that was oriented perpendicular to the skin. Pressure was gradually applied and participants were instructed to indicate when this pressure first became painful. Three trials separated by 30-second breaks were done at each body site. An average was calculated at each body site (11, 12, 24, 25). Change in pressure pain threshold was calculated by subtracting the average pre-lift threshold from the average post-lift threshold, such that lower values of SPA-Sensory indicate greater sensitivity.

SPA-Psych index: After completing the SPA task and relevant pain ratings, participants were asked to fill out the situational catastrophizing questionnaire (SCQ) (27). The situational catastrophizing questionnaire (SCQ) is composed of six items (see Figure 3.3) that ask participants to rate the degree to which they experienced catastrophic thoughts during a specific context. In the context of the present work, the SCQ was used in relation to the standardized lifting task. The SCQ is an adaptation of the Pain Catastrophizing Scale that aims to capture situation-specific (in response to

experimentally evoked pain) pain-related catastrophizing, for which validation work has been initiated (27, 28).

A. PCS:

Directions: Read each of the following statements and then indicate the appropriate value, using the scale below, to the left of the statement to indicate how you felt **during the previous tasks**.

0 - not at all	1 - to a slight degree	2 - to a moderate degree	3 - to a great degree	4 - all the time

1_____I worried about when it would end.
2_____I thought that the pain might overwhelm me.
3_____I felt that I couldn't stand it.
4_____I couldn't stop thinking about how much it hurt.
5_____I kept wishing that it would be over.
6_____I felt that the procedures were awful.

FIGURE 3.3. Situational catastrophizing questionnaire as administered in our study. The situational catastrophizing questionnaire (SCQ) was adapted to be administered in relation to a standardized physical task (repeated tailored lifting task). In our study, this measure provides an index of psychological sensitivity to physical activity (SPA-Psych).

3.3.5. Data analysis

Missing data analysis was conducted to determine the proportion and distribution of missing data, as well as the most likely type of missingness (missing completely at random, missing at random, not missing at random) (39, 40). Participants with complete data were compared to participants with incomplete data using independent-samples t-tests (chi square tests for categorical variables) to determine if there were statistically significant differences (p-value <0.05) on variables used for this study's analyses (outcomes, prognostic factors, covariates); if no differences are found, this would

suggest “missing completely at random” and there is likely no additional bias associated with analyzing only available data (39-41). Alternatively, if differences are found but likely to be explained by our available data (i.e. missing at random), then multiple imputations would be warranted to address the risk of bias associated with analyzing only the available data. If warranted, multiple imputations would be carried out according to recommendations in the literature which suggest five imputations and ten iterations (39-41).

Descriptive statistics (mean, standard deviations, proportions) were calculated for all the variables used in the study’s analyses (outcomes, prognostic factors, and covariates) and for the demographic information collected. Paired t-tests (for the composite measures of SPA-Sensory and SPA-Pain) were computed to determine if there were statistically significant changes in evoked pain intensity and pressure pain threshold, respectively, in relation to the SPA task.

Correlational analyses were conducted to shed light on the inter-relationship between the different SPA indices, as per the first objective listed for this study. Then, correlational analyses were conducted in order to determine if age, sex, BMI, other covariates, and prognostic factors of interest were significantly associated (p-value <0.05) with the outcomes of interest. Specifically, Pearson’s correlations were carried out. In the case of non-normal distributions, Spearman correlations were carried out instead. In the case of sex, an independent samples t-test (Welch t-test reported in case the assumption of equality of variances was violated) was carried out to determine whether there were statistically significant differences in the outcomes of interest due to sex. For all these analyses, statistical assumptions were verified for violations and addressed when necessary. The variables (age, sex, BMI, covariates, predictors), if significantly correlated with the outcomes of interest, were entered into the hierarchical linear regression models.

Two sets of hierarchical linear regression analyses were planned (and implemented as warranted). A first set of hierarchical linear regression analyses were intended to estimate the extent to which SPA indices predicted overall disability and pain at three-month follow-up, beyond age, sex, and

BMI (if significantly correlated with the outcome). The standardized regression coefficients associated with each SPA index were compared in order to determine which SPA index had the most prognostic value. Statistical assumptions were verified for violations and addressed when necessary. A second set of hierarchical linear regression analyses was planned to explore the unique added prognostic value of SPA indices beyond corresponding baseline clinical measures (pain severity, disability). These regression models were similar to the first set but their corresponding baseline clinical measures would now be added in so that the analyses controlled for them as covariates. For instance, baseline pain severity would be controlled for when investigating the prognostic value of SPA indices for pain severity at three-month follow-up, and baseline disability would be controlled for when evaluating the prognostic value for disability at three months. Also, to better expose the added prognostic value of the SPA-Psych index over baseline pain catastrophizing, the Pain Catastrophizing Scale (PCS) would be controlled for in the regression models including the SPA-Psych index. Statistical assumptions were verified for violations and addressed when necessary.

3.3.6. Sample size

This exploratory prognostic factor study was planned to be powered for regression models that can include up to three independent variables, for which a strategy has been described above for using outputs of correlation analyses to reduce the selection of included prognostic factors and covariates. With three independent variables expected per regression model, assuming alpha is set at 0.05 and power is set at 0.80, Green recommends the sample size to be at least 76 in order to detect a medium effect sized relationship (42).

3.4. RESULTS

One hundred twenty-six participants accepted to participate in the study, after providing informed consent. At three-month follow-up, 97 participants completed both outcome measures of interest (Pain Disability Index, BPI-Pain Severity) and therefore made up this study's sample for data analysis. The most common reasons for loss to follow-up were loss of interest/willingness to continue

with participation and not responding to requests for follow-up. The average time between the in-person testing session and the follow-up session was 94.79 days, with a standard deviation of 12.78 days. Table 3.1 summarizes this study sample's characteristics. Our sample's distribution of three-month follow-up scores on the BPI pain severity subscale (0-10 scale) detailed in our Table 3.1 appeared to be broadly consistent with typical distributions in trajectories for people with back pain reported in the literature (43), where roughly 60% of the samples are reported to be in the recovered/minor/mild pain trajectory (0-4 out of 10), 20% in moderate pain (4-6 out of 10), and 20% in severe pain (6-10 out of 10). Also, relative to the distribution of baseline scores on the BPI pain severity subscale, our sample's distribution appeared to shift away from severe pain toward recovered/minor/mild pain.

TABLE 3.1. Sample characteristics (based on available data)

Characteristics	**Mean (SD) or Count (%)**	**Median (IQR)**
Age (years)	44.15 (13.81)	43.00 (22.00)
Sex		
Women	48 (52.75%)	
Men	43 (47.25%)	
BMI (kg/m^2)	28.21 (6.00)	27.38 (6.74)
Ethnicity		
Caucasian	39 (70.90%)	
Other	16 (29.10%)	
Highest level of education		
Elementary school	7 (7.20%)	
High school	43 (44.30%)	
Post-secondary education	47 (48.5%)	
Pain Disability Index (total score, 0-70)		
Baseline	33.00 (15.89)	34.00 (22.00)
3-month follow-up	20.15 (16.84)	18.00 (28.33)
Brief Pain Inventory (Pain Severity subscale, 0-10)		
Baseline	4.35 (1.95)	4.50 (2.75)
Distribution of pain severity subscale scores		
[0-2] out of 10: 12.4%		
]2-4] out of 10: 35.0%		
]4-6] out of 10: 32.0%		
]6-10] out of 10: 20.6%		
3-month follow-up	3.02 (2.24)	2.75 (3.25)
Distribution of pain severity subscale scores		
[0-2] out of 10: 39.2%		
]2-4] out of 10: 28.8%		
]4-6] out of 10: 22.7%		
]6-10] out of 10: 9.3%		
Pain duration at baseline visit (in weeks)	9.59 (6.50)	7.71 (7.00)
Pain Catastrophizing Scale (PCS total, 0-52)	17.71 (11.09)	16.00 (14.75)
SPA indices		
SPA-Sensory at hands (PPT change, kPa)	-18.80 (73.10)	-22.98 (86.37)
Pre SPA task (PPT-Hands, kPa)	292.87 (140.67)	262.26 (207.95)
Post SPA task (PPT-Hands, kPa)	272.98 (152.44)	249.47 (190.90)
SPA-Sensory at low back (PPT change, kPa)	3.97 (97.29)	-14.09 (86.18)
Pre SPA task (PPT-Back, kPa)	310.30 (200.15)	248.73 (230.47)
Post SPA task (PPT-Back, kPa)	303.94 (195.57)	249.10 (287.00)
SPA-Pain (pain intensity NRS 0-100 change)	20.31 (22.17)	15.00 (30.00)
Phase 1: pain evoked w/ single tailored lift (pain intensity NRS 0-100)	22.06 (19.86)	20.00 (22.00)
Phase 2: peak pain evoked w/ ten repeated tailored lifts (pain intensity NRS 0-100)	43.99 (27.86)	40.00 (47.50)
SPA-Psych (0-24)	2.43 (3.97)	1.00 (3.00)

SD indicates Standard Deviation; IQR, interquartile range; BMI, body mass index; NRS, numerical rating scale; SPA, sensitivity to physical activity; PPT, pressure pain threshold; kPa, kilopascal; PCS, pain catastrophizing scale; w/, with.

3.4.1. Missing Data

Data analysis revealed that 27.84% of participants (i.e. 27 out of 97) had incomplete data, however less than 5% (4.36%) of the data was missing overall. The four variables with the highest proportions of missing data were SPA-Psych, PCS, SPA-Pain, and sex (14.4%, 13.4%, 11.3%, and 6.2% respectively). For all other variables, each had less than 5% of missing data. However, no pattern of missing data was shared by more than 5% of participants – that is, the sets of variables with missing data seemed to be unique to each individual in most cases, suggesting that missing data was subject to random chance rather than being systematic.

Comparison of participants with complete data (n=70) and participants with incomplete data (n=27) on variables used for this study's analyses revealed no statistically significant differences for the outcomes of interest (three-month Pain Disability Index, three-month BPI Pain Severity). There were also no statistically significant differences noted for SPA-Sensory at hands, PCS, SPA-Psych, age, sex, or BMI. However, participants with incomplete data appeared to have significantly worse scores ($p<0.05$) for baseline Pain Disability Index ($t=2.836$, $p=0.006$), baseline BPI-Pain Severity ($t=3.201$, $p=0.002$), SPA-Sensory at low back (*Welch* $t=-2.413$, $p=0.018$), and SPA-Pain (*Welch* $t=2.600$, $p=0.018$). These findings suggested that our data's type of missingness was likely "missing at random" and multiple imputations was warranted as a way to reduce the risk of bias associated with analyzing only available data (39-41). While it is not possible to rule out a "missing not at random" pattern with complete certainty, as defined here (39-41), multiple imputations would need to replace less 5% of data (only 4.36% of our data was missing overall), the likelihood of an unaccounted influential factor for missing data is low since no pattern of missing data was shared by more than 5% of participants, and the variables for which differences are noted for participants with incomplete data are actually variables for which other similar or related variables exist in our observed data and likely can adequately inform the computations of our multiple imputations to replace missing data with minimal bias.

3.4.2. Multiple Imputations

Multiple imputations were carried out to address the risk of bias related to our type of missing data ("missing at random") and to avoid the loss of 27.84% of our sample that had incomplete data (39-41). Given that none of our variables exceeded 20% of missing data and that the overall missingness of data was very low (4.36%), five imputations were sufficient (41, 44). Ten iterations achieved FCS (fully conditional specification) model convergence, since FCS charts appeared appropriately random. All the findings presented below are based on pooled data from these multiple imputations (n=97). The same pattern of findings was found when these same analyses were carried out with only available data (complete case analysis according to analysis-by-analysis).

3.4.3. Magnitude of SPA-Sensory, SPA-Pain, and SPA-Psych indices

For the two measures used to calculate SPA-Sensory, paired t-tests revealed a statistically significant pre-post change (in relation to the tailored lifting task) in pressure pain threshold at the hands (t=-2.68, p=0.007), but not at the low back (t=-0.528, p=0.597). In relation to the measures used to calculate SPA-Pain, paired t-tests revealed a statistically significant change in pain intensity evoked from a single lift compared to the repeated lifts (t=9.441, p<0.001). For SPA-Psych (score 0-24, where higher score indicates higher SPA-Psych), descriptive statistics revealed a mean score of 2.43 (SD=3.97). However, 41 out of 97 participants had a score of zero, resulting in a very positively skewed distribution. When only including the 56 participants with a non-zero score, the mean score was 4.81 (SD=4.45).

3.4.4. Correlations

Since the outcome variables (disability and pain at three-month follow-up) were positively skewed and many of the covariates and prognostic factors (BMI, PCS, SPA-Psych, SPA-Pain) were also non-normally distributed, Spearman correlations were considered more appropriate than Pearson correlations. Table 3.2 presents Spearman correlation of all variables of interest for this study, with "r" (correlation coefficient) and "p" (p-value).

TABLE 3.2. Correlation matrix (Spearman's)

		1	2	3	4	5	6	7	8	9	10	11
1. Disability (3-month f/u)	r	1.000										
	p											
2. Pain Severity (3-month f/u)	r	0.782**	1.000									
	p	0.000										
3. Disability (baseline)	r	0.450**	0.391**	1.000								
	p	0.000	0.000									
4. Pain Severity (baseline)	r	0.550**	0.583**	0.678**	1.000							
	p	0.000	0.000	0.000								
5. SPA-Sensory (at hands)	r	-0.067	0.002	0.004	0.128	1.000						
	p	0.515	0.966	0.966	0.211							
6. SPA-Sensory (at low back)	r	-0.109	-0.074	-0.071	0.099	0.478**	1.000					
	p	0.291	0.475	0.493	0.336	0.000						
7. Pain Catastrophizing (PCS)	r	0.363**	0.236*	0.437**	0.375**	-0.029	0.042	1.000				
	p	0.001	0.026	0.000	0.000	0.808	0.591					
8. SPA-Psych	r	0.454**	0.298**	0.435**	0.392**	-0.136	-0.053	0.450**	1.000			
	p	0.000	0.003	0.000	0.000	0.186	0.613	0.000				
9. SPA-Pain	r	0.143	0.178	0.295**	0.352**	0.081	0.122	0.071	0.242*	1.000		
	p	0.166	0.083	0.004	0.000	0.429	0.236	0.505	0.017			
10. Age (in years)	r	-0.106	-0.091	-0.023	-0.069	-0.080	-0.109	-0.052	0.008	-0.138	1.000	
	p	0.311	0.387	0.802	0.522	0.460	0.297	0.644	0.764	0.185		
11. BMI (kg/m^2)	r	-0.013	-0.024	0.119	0.068	0.096	0.111	-0.003	-0.087	0.006	0.094	1.000
	p	0.900	0.817	0.246	0.505	0.349	0.282	0.721	0.414	0.925	0.387	

All correlations are Spearman's r values (pooled multiple imputation data, n=97)
**, p-value < 0.05; **, p-value < 0.01*
F/u, follow-up; SPA, sensitivity to physical activity; BMI, body mass index; PCS, Pain Catastrophizing Scale.

The SPA-Pain index and the SPA-Psych index were significantly correlated ($r_{spearman}$ =0.242, p=0.017). That is, greater activity-related increases in pain were associated with greater activity-related situational catastrophizing. The SPA-Pain index, however, was not significantly correlated with the PCS. The SPA-Sensory index was captured as activity-related changes in pressure pain threshold at the site of pain (low back) and at a remote body site (hands); both measures were significantly correlated to one another ($r_{spearman}$ =0.478, p<0.001). However, neither of the SPA-Sensory index measures were significantly correlated with either SPA-Pain or SPA-Psych.

Among the SPA indices, SPA-Sensory did not yield significant correlations with any of the outcomes (disability, pain severity), both cross-sectionally and at three-month follow-up. As for SPA-Pain, while no significant correlations were found with the three-month outcomes, there were significant cross-sectional correlations with disability ($r_{spearman}$ =0.295, p=0.004) and with pain severity

($r_{spearman}$ =0.352, p<0.001). As for SPA-Psych, significant correlations were found both cross-sectionally and prospectively at three-month follow-up, with both outcomes of interest.

The positively skewed distribution of SPA-Psych (due to the high number of participants with a zero score) may have biased these correlation findings. To explore and potentially mitigate this bias, SPA-Psych was re-analyzed as a binary variable. SPA-Psych was converted to a binary form by categorizing all values as either non-zero (SPA-Psych present) or zero (SPA-Psych absent) values. An independent samples t-test using the binary SPA-Psych yielded a similar pattern of findings as the Spearman correlation using the continuous SPA-Psych. Participants with an absent SPA-Psych had a mean score of 13.22 for disability at three months (SD = 13.95), whereas people with a present SPA-Psych had a mean score of 25.22 for disability at three months (SD = 17.07), resulting in a statistically significant difference (t=-3.690, p<0.001). As for overall pain severity at three months, participants with an absent SPA-Psych had a mean score of 2.48 (SD = 2.32), whereas present SPA-Psych had a mean score of 3.41 (SD = 2.11), resulting in a statistically significant difference (t=-2.044, p=0.041). Thus, regardless of whether SPA-Psych was analyzed as a continuous or binary variable, the same pattern of findings was found in relation to the outcomes of interest. Therefore, SPA-Psych remained as a continuous variable for the regression analyses, as this is the more informative form of the variable.

3.4.5. Prognostic value of sensitivity to physical activity (SPA)

Age, sex, and BMI did not show statistically significant associations (correlations, t-tests) with the outcome variables and therefore were not entered into the hierarchical linear regression analyses. With respect to the disability outcome at three-month follow-up, SPA-Psych was the only SPA index to show a significant correlation. Therefore, SPA-Psych was the only SPA index evaluated for prognostic value in the regression model. In this simple linear regression analysis, SPA-Psych yielded significant prognostic value (β=0.481, t=5.200, p<0.001, R^2=23.24%). With respect to the pain outcome at three-month follow-up, SPA-Psych was again the only SPA index to show a significant correlation. Therefore, only SPA-Psych entered as a prognostic factor for the regression model, yielding again

significant prognostic value (β=0.307, *t*=3.000, *p*=0.003, R^2=9.54%). For the statistical assumptions of linear regression analysis, no violations requiring corrective action were noted and no influential outlier was found (all Cook's Distance values <1 and all standardized DF beta values < |1|).

Among the SPA indices, only SPA-Psych showed significant prognostic value in the first set of regression analyses. Therefore, this second set of regression analyses focused on the unique added prognostic value of SPA-Psych beyond the PCS and the baseline clinical measure corresponding to the outcome (disability, pain severity) included in the regression model.

Table 3.3 presents the final model for the hierarchical regression analysis for disability at three-month follow-up. SPA-Psych remained a significant prognostic factor for disability at three-month follow-up (β=0.272, *t*=2.674, *p*=0.008, R^2 Δ=5.60%), beyond baseline disability and pain catastrophizing. No violations requiring corrective action were noted in relation to the statistical assumptions of hierarchical linear regression analysis and no influential outlier was found (all Cook's Distance values <1 and all standardized DF beta values < |1|). Multicollinearity did not occur, as per Tolerance values which were all > 0.1 (lowest Tolerance value was 0.716) and as per Variance Inflation Factor (VIF) values which were all < 10 (highest VIF value was 1.399) (45).

TABLE 3.3. Hierarchical regression analyses for the outcome: Disability (at 3-month follow-up)

Step Number	Variables	β	*t* (P value)	Collinearity		R^2 Change	F Change (P value)
				Tolerance	VIF		
1	Disability (baseline)	0.333	3.252 (0.001)**	0.716	1.399	0.308	20.992 (<0.001)**
	Pain Catastrophizing	0.145	1.417 (0.158)	0.749	1.341		
2	SPA-Psych	0.272	2.674 (0.008)**	0.745	1.346	0.056	8.269 (0.009)**

All parameter estimates listed are from the final regression model using pooled multiple imputation data (n = 97).
**, p-value < 0.05*
***, p-value < 0.01*

Table 3.4 presents the final model for the hierarchical regression analysis for pain severity at three-month follow-up. SPA-Psych was no longer a significant prognostic factor for pain severity at three-month follow-up when controlling for baseline pain severity and pain catastrophizing. No violations requiring corrective action were noted in relation to the statistical assumptions of hierarchical linear regression analysis and no influential outlier was found (all Cook's Distance values <1 and all standardized DF beta values < |1|). Multicollinearity did not occur, as per Tolerance values which were all > 0.1 (lowest Tolerance value was 0.716) and as per Variance Inflation Factor (VIF) values which were all < 10 (highest VIF value was 1.400) (45).

TABLE 3.4. Hierarchical regression analyses for the outcome: Pain Severity (at 3-month follow-up)

Step Number	Variables	β	*t* (P value)	Collinearity Tolerance	Collinearity VIF	R^2 Change	F Change (P value)
1	Pain Severity (baseline)	0.591	6.125 (<0.001)**	0.751	1.334	0.383	29.162 (<0.001)**
	Pain Catastrophizing	0.061	0.639 (0.523)	0.800	1.254		
2	SPA-Psych	0.008	0.067 (0.947)	0.716	1.400	0.001	0.129 (0.747)

All parameter estimates listed are from the final regression model using pooled multiple imputation data (n = 97).
**, p-value < 0.05*
***, p-value < 0.01*

3.5. DISCUSSION

This is the first study to prospectively explore the potential prognostic value of biopsychosocial indices of SPA and it yielded several surprising results. One unexpected finding was that SPA-Sensory – the index that has likely been the most integrated within previous research – failed to show any significant cross-sectional or prospective associations with pain and disability outcomes. While much of the previous research using the SPA-Sensory index (also referred to as exercise-induced hypoalgesia/hyperalgesia) has helped advance our understanding of the physiological mechanisms underlying activity-related pain (11, 12, 24, 25, 46), it is possible that this index has more modest clinical prognostic value. On the other hand, the SPA-Psych index – which is based on a relatively new approach to measuring situational catastrophizing – emerged as having the most robust prognostic

value of the three SPA indices. Consistent with previous work, SPA-Pain showed significant cross-sectional associations with pain severity and disability; however, the corresponding prospective relationships were non-significant in our analysis. Of the three indices, SPA-Psych was the only index that demonstrated both cross-sectional and prospective associations with the pain and disability outcomes. Thus, our findings partially support our hypothesis that SPA has unique prognostic value, but unexpectedly only for the SPA-Psych index. Together, these findings have important implications for clinical practice and future research.

The bulk of previous research addressing the SPA-Pain index has evaluated cross-sectional associations with pain severity and disability (15-17, 20-23). We were only able to identify one additional study that used this index within a longitudinal design; at odds with our findings, this study demonstrated that the SPA-Pain index was a significant prognostic factor for both pain and disability outcomes at three-month follow-up (47). This discrepancy highlights the potential impact of variations in SPA measurement methodology. In Trolle et al.'s study, the SPA-Pain index was measured in relation to a 45-minute, high-intensity battery of physical tasks (47, 48). In contrast, our ten-repetition lifting task was brief and likely of only moderate intensity, as a result of being tailored to evoke a minimally clinically important pain on the first of ten lifts. Despite the shorter duration and lower intensity, our SPA task was sufficient to evoke significant mean changes in both pain intensity as well as pressure pain threshold levels (when measured at the hands). The lack of statistically significant change in pressure pain threshold at the lower back suggests, however, that our SPA task was specific to evoking self-reported pain intensity, but did not substantially evoke change in our sensory measure (pre-post pressure pain threshold, i.e. SPA-Sensory index). Thus far, little research has focused on the duration and nature of physical activity used to evoke SPA. While a shorter SPA task may be more feasible to implement with respect to the time constraints of clinical practice, it may also have less prognostic value. Future research should explore sources of methodological variations affecting prognostic value, such as the parameters of physical tasks for SPA assessment (painful vs. non-painful

task, intensity/duration/type of the task, etc.), yet attempt to maintain clinical feasibility – that is, taking into account factors that may affect willingness to participate in the testing procedures such as too much pain evoked, factors affecting implementation in day-to-day clinical practice such as too much time or resources required.

Future research should also explore whether lab-based measures of SPA (as was used in this study as well as the Trolle et al. study) are the best strategy for evaluating this phenomenon. While previous research addressing SPA has broadly focused on using lab-based standardized physical tasks, there may be important advantages to using emerging assessment techniques that aim to capture in vivo responses to physical activity, such as Ecological Momentary Assessment (EMA) (13, 49-51). EMA consists of taking repeated measures as a person goes through their day-to-day life using momentary prompts such as with a mobile phone application (49-51). This helps to limit recall bias due to the momentary nature of the prompts, and it also allows to capture fluctuations due to taking repeated measures. Also, each prompt can contain sets of questions that assess multidimensional responses, such as pain intensity as well as pain-related thoughts and feeling. Since the biopsychosocial expression of SPA is context-dependent and likely subject to fluctuations in daily life, future research on SPA should consider using EMA.

Our findings suggest that SPA-Psych may contribute novel added prognostic value for disability outcomes. The SPA-Psych index added unique prognostic value for the 3-month disability outcome, even when accounting for baseline levels of disability and PCS; this finding suggests that adding this measure to a battery of existing clinical assessment tools is likely to contribute further prognostic value. While many studies have investigated the prognostic value of psychological factors (28, 52, 53), few have considered situational psychological measures in the context of painful activity (17, 26). SPA-Psych evaluates the psychological response *evoked* by a standardized painful activity. SPA-Psych may add important value in helping to identify patients that are most likely to benefit from psychologically-informed physical therapy and/or activity-based interventions (54-57). This approach to treatment

consists of asking patients to systematically and progressively engage in painful (or potentially painful) activities of daily living, while employing various psychologically-informed strategies (e.g. reassurance, pain neuroscience education, cognitive-behavioural interventions) to help mitigate the increased negative thoughts and feelings associated with physical activity (i.e. increased SPA-Psych) (54-57). Despite the centrality of SPA-Psych to these clinical approaches, this construct is rarely measured directly. It is important to note that, although the baseline pain catastrophizing (PCS) levels were moderate in our sample, we obtained low mean and median scores for the SPA-Psych variable even when considering only the non-zero scores. It may be that our SPA task had a low threat value. However, a higher threat value may elicit avoidance behaviour and the participant may hold back from actively engaging in the physical task, which would limit the ability to assess a sensitizing response (58). Future research should explore how the threat value of a task influences the prognostic value of a SPA task. Future research should explore the added value of SPA-Psych in stratifying patients for psychologically-informed physical therapy and, potentially, for guiding patient progress and evaluating patient outcomes.

Our findings highlight some of the biopsychosocial inter-relationships related to SPA. For instance, SPA-Psych and SPA-Pain were significantly correlated with one another, such that greater activity-related catastrophizing (SPA-Psych) was associated with greater activity-related pain (SPA-Pain). This is consistent with past research that found situational catastrophizing was associated with QST-evoked pain intensity (27) and with exercise-evoked pain intensity (26). On the other hand, we found that SPA-Sensory was not significantly correlated with either SPA-Psych or SPA-Pain, suggesting that SPA-Sensory may be a distinct dimension of sensitized responses to activity. Together, these findings highlight the importance of using a multidimensional approach to SPA assessment. Including different biopsychosocial indices of SPA will permit a more robust understanding of the mechanisms and processes underlying SPA and thus help direct its management.

It is important to consider our study's findings in light of its limitations. The inclusion criteria for our study were broad by design to facilitate recruitment and increase generalizability of our findings to typical clinical populations of back pain. Also, the specific components of the physical therapy care were not standardized but rather left to the discretion of the treating physical therapist. This may have introduced more heterogeneity in our study's sample and their treatment responses, thus potentially reducing estimates of prognostic value and explained variance. Moreover, research staff were not formally evaluated over the course of this study regarding their application of the data collection methods. However, to support the consistency in the application of the data collection methods, standardized training documents for all protocols, one-on-one initial training, and regular check-ins were delivered by the senior investigator or a senior member of the research team, consistent with past SPA research (15, 18-23, 47) – a lack of formal inter-rater reliability testing, however, represents a limitation in this area of research which should be addressed in future work. Also, although the format of SPA index measurement was consistent with past research (i.e. evaluating pressure pain threshold pre-post a standardized pain-evoking physical task, recording evoked pain as it was occurring during the task, and administering the Situational Catastrophizing Questionnaire immediately after the task), applying these measurement procedures in a set order for all participants may have induced an order effect whereby the experience and self-report associated with each measurement component may have influenced one another. We suspect, however, that the influence of each of these measurement components on one another is likely minor given that pressure pain threshold only induces a minimal amount of pain and that the other measures were simply self-report questions to describe the lived experience during the pain-evoking physical task. Finally, given the exploratory nature of this prognostic factor study (32), future research should replicate and confirm the added prognostic value of biopsychosocial indices of SPA by using a larger sample size which, in turn, would allow for regression analyses to control for a more comprehensive set of established prognostic factors. Despite

these limitations, these methodological characteristics are broadly reflective of clinical reality where patients can experience individualized treatments without artificial restrictions.

In conclusion, this work revealed the surprising finding that psychological responses to physical activity (SPA-Psych) play a more influential role in shaping longitudinal disability outcomes, than traditionally studied indices of SPA (i.e. SPA-Sensory or SPA-Pain). Future research should build on these findings by investigating how SPA assessment can be further optimized, either by clarifying the ideal parameters for lab-based physical tasks or exploring the potential value of using daily-living EMA to assess this construct. Future clinical research should explore the potential value of SPA-Psych measures to help stratify and evaluate patient responses to psychologically-informed physical therapy. Using a biopsychosocial approach to assess SPA appears to be a promising strategy for shedding further light on why certain patients have sensitized responses to physical activity and how their recovery can be facilitated.

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PREFACE TO CHAPTER 4 (STUDY 3)

The introduction of this thesis described ecological momentary assessment (EMA) and highlighted that an important aspect of SPA assessment that was not yet explored was whether these lab-based SPA measures (administered in clinic) map onto corresponding daily life measures as intended. Study 3 aimed to address this gap. It will be the first study to investigate the relationship of SPA with daily life using EMA. To do so, Study 3 used *dataset #2* which included a subset of 67 participants who participated in both the baseline in-person testing session and a subsequent nine days of smartphone-based EMA. The individually tailored lifting SPA task used in Studies 1 and 2 will be used here as well. Also, the multidimensional range of SPA indices (evoked pain intensity, sensory changes, and situational catastrophizing) explored in Study 2 will continue to be investigated as part of Study 3.

While Studies 1 and 2 advanced research on SPA assessment, it was done with a focus on prognostic value; Study 3, on the other hand, advances research on SPA assessment with a focus on validity. Study 3 aimed to contribute preliminary empirical support for the ecological validity of SPA assessment, as well as supporting its construct validity, by estimating the extent to which the lab-based SPA measures (administered in clinic) are associated with momentary pain and mood in daily life. This was an exploratory study, but it was expected that corresponding constructs would be associated: the SPA index based on evoked pain intensity or sensory changes with daily-life momentary pain and the SPA index based on situational catastrophizing with daily-life momentary mood. Although ecological validity has been previously mentioned in SPA research when discussing its assessment design, Study 3 will be the first to investigate this.

CHAPTER 4: TASK-BASED MEASURES OF SENSITIVITY TO PHYSICAL ACTIVITY PREDICT DAILY LIFE PAIN AND MOOD AMONG PEOPLE LIVING WITH BACK PAIN (STUDY 3)

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4.1. ABSTRACT

Background: Clinical interventions aim to improve the daily-life experiences of patients. However, past research has highlighted important discrepancies between commonly used assessments (e.g., retrospective questionnaires) and patients' daily-life experiences of pain. These gaps may contribute to flawed clinical decision-making and ineffective care. Recent work suggests that real-time, task-based clinical assessments may help reduce these discrepancies by adding predictive value in explaining daily-life pain experiences. This study aimed to investigate these relationships by evaluating whether task-based measures of sensitivity to physical activity (SPA) predict daily-life pain and mood, beyond traditional pain-related questionnaires. **Methods**: Adults with back pain (<six-month onset) answered pain-related questionnaires and completed a standardized lifting task. SPA-Pain, SPA-Sensory, and SPA-Mood were respectively assessed as task-evoked changes in pain intensity, pressure pain threshold (back, hands), situational catastrophizing. Over the next nine days, daily-life pain and mood were assessed using smartphone-based ecological momentary assessment (EMA-Pain and EMA-Mood, respectively) with stratified random sampling. Data analyses estimated fixed effects (*b*) using multilevel linear modelling with random intercepts. **Results**: Median EMA completion per participant was 66.67% (n=67 participants). After controlling for covariates, SPA-Pain was associated with EMA-Pain (b=0.235, p=0.002) and SPA-Psych approached significance with EMA-Mood (b=-0.159, p=0.052). **Conclusions**: Task-based assessment of SPA helps explain daily-life pain and mood among adults with back pain, beyond traditional questionnaires. Adding task-based assessment of SPA may achieve a more complete picture of pain and mood in daily life, offering clinicians better guidance when prescribing activity-based interventions that are designed to modify daily life behaviour, such as graded activity. **Significance:** This study found that, among people with back pain, task-based measures of sensitivity to physical activity contribute additional predictive value for daily-life pain and mood beyond self-report questionnaires. Findings suggest that real-time, task-based measures may help mitigate some of the shortcomings that are commonly associated with retrospective questionnaires.

4.2. INTRODUCTION

Most clinical pain interventions aim to improve the daily-life experiences of people living with pain. Clinicians have predominantly relied upon clinically-administered measures to infer their patient's lived experiences of pain. However, past research suggests that there are important gaps between clinically-administered pain assessments, such as self-report questionnaires, and daily-life experiences of pain (1-6). For instance, a study by Stone et al. found that a weekly retrospective pain questionnaire explained approximately 50% of the variance of pain ratings captured in real-time during everyday life (5). This leaves room for questionnaires to misrepresent the real-life experience of patients, which in turn, can contribute to flawed clinical decision-making and ineffective care.

Recent research suggests that real-time, task-based clinical assessments may offer added value in predicting daily life experiences of pain. For instance, sensitivity to physical activity (SPA) is evaluated with pain-related negative reactions to a standardized task representative of physical activity typically encountered in daily life, and thus is expected to map well onto real-life pain-related experiences (7-13). As repetitions or continued engagement in a task are maintained at stable intensity, task-related changes in pain intensity are recorded as an index of SPA. Other dimensions of the task-related reactive pain experience (SPA indices) may also be captured such as pre-post changes in pressure pain thresholds or task-specific situational pain catastrophizing (7-11).

This study aims to investigate the added predictive value of functional task-based SPA assessment for daily-life pain and mood ratings among patients with back pain, beyond corresponding retrospective questionnaires. The Brief Pain Inventory's pain severity subscale (BPI-Pain) and the Pain Catastrophizing Scale (PCS) are retrospective questionnaires that are commonly used to provide important insights into daily-life pain and mood. SPA assessment, however, has features that more closely align with real-life experiences of pain and mood encountered in daily living, or at least may represent a distinct aspect (14). Also, since SPA is tested in real-time with a functional task, it avoids

memory bias issues characteristic of retrospective questionnaires (1-3). If the predictive value of SPA for daily-life pain and mood is shown, then this will provide preliminary evidence in support of the ecological validity of task-based SPA assessment.

4.3. METHODS

4.3.1. Design

This observational study used an intensive longitudinal design (4, 6, 15, 16), consisting of an in-person testing session followed by nine days of ecological momentary assessment (EMA). This study respected the Declaration of Helsinki and was approved by the research ethics committee of McGill University's Faculty of Medicine and Health Sciences. This study adhered to the STROBE statement guidelines (17) (see Appendix 3 for the completed STROBE checklist for this manuscript), as well as the procedural and reporting recommendations for EMA studies (4, 6, 16).

4.3.2. Participants and recruitment

This study recruited adults (at least 18 years old) living with back pain (less than six months since onset). The six-month threshold was selected in order to facilitate the recruitment of participants with back pain who were starting physical therapy treatment, which may extend beyond the typical three-month threshold for acute pain. The back pain was considered eligible if located between the gluteal folds and shoulders, and was not caused by any known organic pathology (examples of excluded conditions: spinal stenosis, spondylolisthesis, ankylosing spondylitis). Participants also needed to be medically stable (serious health conditions, pending surgery or invasive medical procedure, and contra-indication to physical activity).

The recruitment source were eight private rehabilitation clinics in the greater Montreal area (in Quebec, Canada). Upon starting physical therapy treatment for their back pain, physical therapists handed out recruitment flyers to potentially eligible participants. It was explained that their decision to

participate or not in the study was considered completely separate from their care and would have no bearing on the clinical services received.

The recruitment flyers directed interested potential participants to contact our lab's research assistants, who in turn confirmed eligibility, provided additional details on the study, and offered to schedule an in-person session to sign an informed consent form and initiate data collection. No special COVID-19 related considerations were needed, since all recruitment and data collection for this study was completed between December 2015 and April 2019.

4.3.3. Procedures

4.3.3.1. In-person testing session

Data collection was carried out by research staff (three research assistants) who received standardized training by the senior investigator, through protocol documents, one-on-one training, and regular check-ins. Data collection consisted of an in-person testing session, immediately followed by nine days of smartphone-based EMA. The in-person testing session started with obtaining informed consent and then administering a battery of questionnaires (demographic, pain-related, psychological).

Afterwards, SPA assessment was carried out. It required participants to complete a pain-provoking lifting task, for which a standardized procedure was used to individually tailor the difficulty (10, 11). Specifically, the lifting task consisted of the following elements:

(1) A custom-made lifting apparatus. This consisted of a rectangular box (90 cm high×60 cm wide×60 cm deep), which concealed weights (adjustable to 1.0kg, 2.0kg, 3.0kg, or 3.5kg). The weights were attached to a strap with a height-adjustable handle, relative to three standardized positions: *easy* (participant standing erect with dominant hand holding the handle with a pronated grip, 90 degrees elbow flexion, zero degrees of shoulder flexion), *medium* (participant standing erect with dominant hand holding the handle with a pronated grip at the same height as the "easy" lifting position, but with an outstretched arm), *hard* (same as the "medium" lifting position, but with a forward lean equivalent to approximately

45 degrees of trunk flexion). These standardized lifting positions are illustrated in Figure 2, page 969 of an earlier study (18).

(2) The standardized individualized tailoring procedure. This consisted of a series of single lifts in the "easy" lifting position, starting with the lightest weight (1.0kg) and progressively increasing the weight (2.0kg, 3.0kg, 3.5kg). This was repeated in the "medium" lifting position, and then in the "hard" lifting position. Thus, the standardized individualized tailoring procedure was organized from the least biomechanically demanding lifting position to the most demanding. However, participants did not complete all combinations of lifting positions and weights. Participants were asked to report how much pain was evoked by each lift, using a 0-100 numerical rating scale (NRS) of pain intensity (0 is "no pain at all", 100 is "the worst pain you can imagine"). As soon as a combination of lifting position and weight was sufficient to evoke a clinically important pain (≥20 out of 100), the tailoring procedure was stopped for that individual.

(3) Using the individually determined pain-provoking lifting position and weight, participants were asked to do ten repeated lifts.

(4) Participants were asked to report their evoked reactions to these ten repeated lifts, using three SPA indices (SPA-Sensory, SPA-Pain, SPA-Psych) which are described in the "Measures" section below and consistent with past work (10).

4.3.3.2. Ecological Momentary Assessment (EMA)

After the SPA assessment, EMA was initiated by way of installation and instructions for a customized smartphone application (MetricWire Inc, v.3.2.0, Kitchener, ON, Canada). EMA is a measurement method that samples a person's everyday experience, by collecting repeated "in the moment" measures as a person engages in their usual daily life activities in their own natural environment and social contexts (e.g., at home with their family, at work with their coworkers, etc.) (4,

6, 15). EMA was conducted using random stratified sampling (4). The first EMA prompt was manually initiated at the conclusion of the in-person testing session, and then, for the next nine days, the EMA smartphone application sent a prompt three times per day, each prompt sent with random timing within predetermined timeframes (8am to 12pm, 12pm to 4pm, 4pm to 8pm). Nine days were selected for the EMA duration, consistent with the typical EMA durations in the literature (6), recommendations to limit excessive length of EMA to support response rates (19), and expert advice that EMA beyond two weeks has the potential of creating a data trend similar to regression to the mean.

4.3.4. Measures

4.3.4.1. In-person testing session

During the in-person testing session, participants completed a battery of questionnaires. Of interest for this study's analyses were the demographic questions (age, sex, height, weight, ethnicity, level of education), the Brief Pain Inventory (BPI), and the Pain Catastrophizing Scale (PCS). They also completed a SPA assessment.

The BPI has two main subscales, the pain severity subscale and the pain interference subscale (20, 21). The BPI's pain severity subscale was of interest for this study. It averages the score from four items (pain intensity at present, on average, as well as the worst and least pain intensity in the last 24 hours) that are rated using a numerical rating scale (NRS) from 0 "no pain" to 10 "pain as bad as you can imagine". The use of the BPI's pain severity subscale is consistent with recommendations for pain research (22). It has supporting evidence for its internal consistency (Cronbach alpha = 0.82), reliability, and validity for people with back pain (20). The PCS has 13 items that reflect different aspects of pain catastrophizing (rumination, magnification, helplessness), but for which a total score can be calculated as a sum of all items (0-52) (23-25). Pain catastrophizing refers to having pain-related thoughts that are disproportionately negative relative to the actual threat value of the pain. It is a key psychological factor to consider in pain research (24-26). Higher scores indicate higher frequency of pain catastrophizing related thoughts, with each item rated on a Likert scale ranging from 0 "not at all"

to 4 “all the time”. The PCS is commonly used to assess catastrophic thinking in pain research, with evidence supporting internal consistency (Cronbach alpha = 0.92), reliability (test-retest Spearman rho = 0.88), and validity for people with back pain (23-25).

In relation to the individually tailored repeated lifting task for the SPA assessment (lifting procedures described above), participants were asked to report their evoked reactions using three SPA indices (SPA-Sensory, SPA-Pain, SPA-Psych) (10).

(1) SPA-Sensory: The lifting task evoked changes in pressure pain threshold were measured at the lower back (five cm laterally from L3 spinous process) and at both hands (web-space between thumb and index finger), using a one cm^2 rubber tip algometer (FDX 10, Wagner instruments, Greenwich, CT, USA). Specifically, three measures in kilopascals were taken at each body location before the lifting task’s difficulty tailoring procedures and after the lifting task’s tailored ten repetitions. The three measures were separated by 30-second breaks and averaged at each body site (8, 27-29). The algometer was applied with a slow, gradual pressure perpendicular to the skin, and participants were instructed to voice as soon as the pressure first became painful. This pre-post approach to measuring task-evoked changes in pressure pain threshold is consistent with past work (8, 27-29). The SPA-Sensory index was calculated as “post-task pressure pain threshold” minus “pre-task pressure pain threshold” (10); thus, a lower value of the post-task pressure pain threshold compared to the pre-task threshold indicates that the pain threshold has lowered and sensitization has occurred. The lower the SPA-Sensory index, the greater the sensitivity to physical activity.

(2) SPA-Pain: The lifting task evoked pain intensity was rated on a 0 “no pain at all” to 100 “the worst pain you can imagine” NRS. The SPA-Pain index was calculated as “the evoked peak pain intensity experienced during the ten repeated tailored lifts” minus “the evoked pain intensity with the first of ten repetitions of tailored lifts” (7, 9-11); thus, a higher value

means that greater pain summation has occurred. The higher the SPA-Pain index, the greater the sensitivity to physical activity.

(3) SPA-Psych: The lifting task evoked situational pain catastrophizing was measured using the Situational Catastrophizing Questionnaire (SCQ) (30), administered once immediately after the SPA lifting task. The six items of the SCQ ask about the extent to which pain-related catastrophizing thoughts were experienced (rated from 0 "not at all" to 4 "all the time") in relation to a specific context, which in this study was the repeated lifting task. Pain catastrophizing evoked by a specific context (e.g., SCQ) is purported to be potentially different from non-specific disposition to pain catastrophizing (e.g., PCS), a distinction which is receiving preliminary empirical support (10, 25, 30). The SCQ total score is a sum of the six items (0-24); thus, a higher value indicates that greater pain catastrophizing has been evoked by the task. The higher the SPA-Psych index, the greater the sensitivity to physical activity.

4.3.4.2. Ecological Momentary Assessment (EMA)

In relation to the EMA data collection procedures described above, the following measures were collected. Each EMA prompt included the following questions:

(1) Please rate your present pain intensity: 0=no pain, 100=worst pain imaginable (participants were presented a sliding scale which displayed the number value, or they could enter a number value to rate their present pain intensity); see Figure 4.1. Similar to an important proportion of pain research using EMA (6), the use of a 101-point numerical rating scale (NRS) was selected to best allow for capture of moment-to-moment variability in pain intensity reporting (15). Compared to the recommended 11-point NRS (22), the 101-point NRS is considered equivalent; moreover, using an NRS remains a preferred choice over other pain intensity measurement scales due to better completion rates and responsiveness (31, 32).

(2) Please rate your present mood: -5=very bad, -4, -3=bad, -2, -1=fairly bad, 0=neutral, +1=fairly good, +2, +3=good, +4, +5=very good (participants were presented these multiple choice response options); see Figure 4.1. Emotional functioning (or psychological functioning) is an important outcome that is recommended in pain research (22) and is the second most commonly tracked variable after pain intensity in pain research using EMA (6). To reduce respondent burden associated with EMA repeated measures and to improve completion rates (19), a single-item momentary mood question was developed in a way that is similar to other EMA studies tracking mood (33-35). One study showed that use of a similar single-item mood rating scale achieved a comparably satisfactory level of discriminatory validity as multi-item questionnaires in the context of depression, and cites previous work supporting its test-retest reliability (36); whereas another study using a similar single-item mood rating supported its validity by finding prognostic value for future outcomes in the context of depression (37).

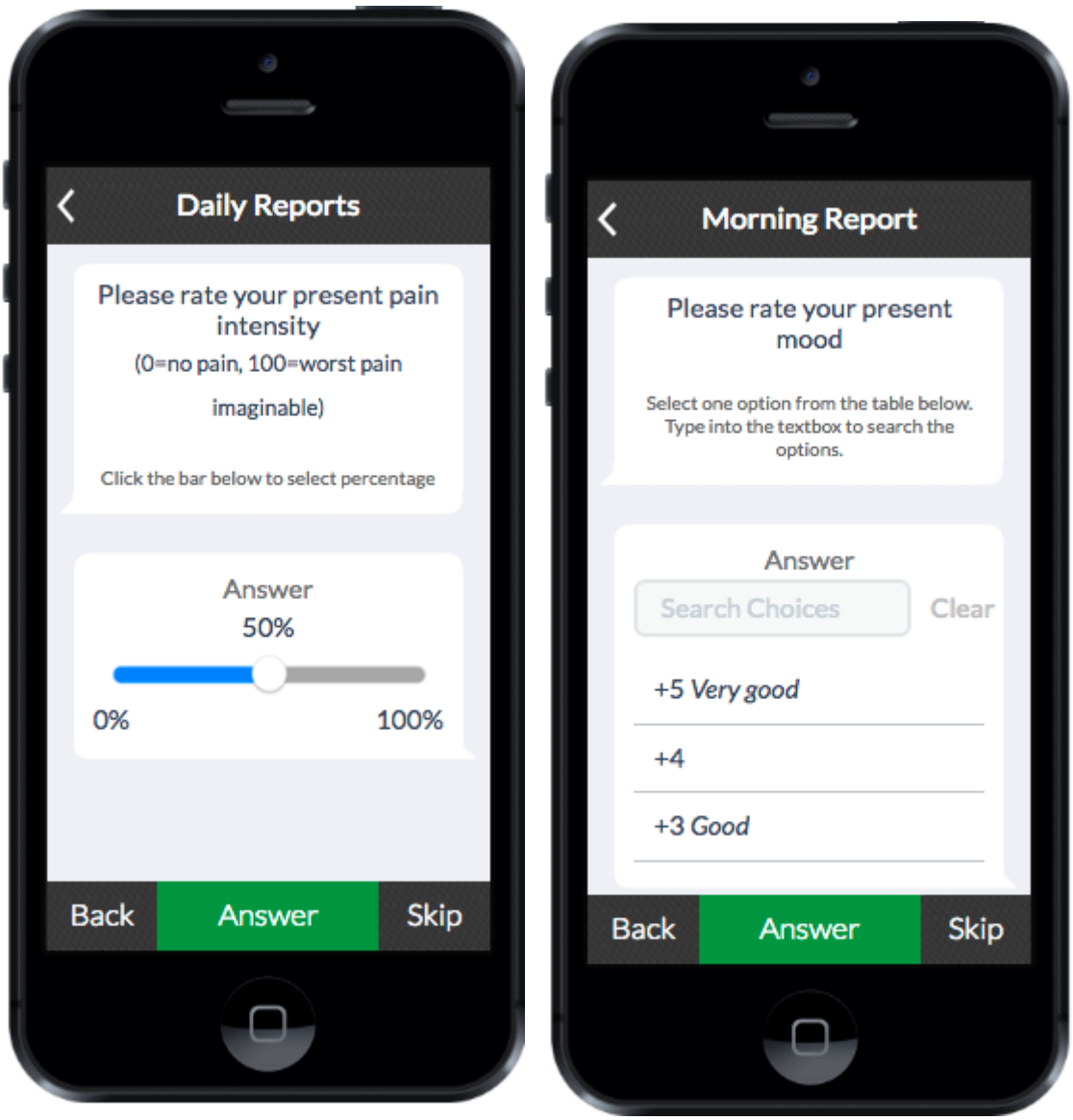

FIGURE 4.1: Ecological momentary assessment (EMA) using the smartphone application Metricwire (v.3.2.0, Kitchener, ON, Canada). These images illustrate how our EMA questions for momentary pain intensity (left) and momentary mood (right) displayed on participants' smartphones (exact appearance varied between different smartphone operating systems). These EMA questions were customized for our study, using the Metricwire application (v.3.2.0, Kitchener, ON, Canada). Permission was granted by e-mail to use these images.

4.3.5. Data analysis

All analyses were carried out using IBM SPSS Statistics version 26.

4.3.5.1. Descriptive statistics

Descriptive statistics were carried out at the participant level (level three or aggregated level one moments) to characterize the study sample at baseline in terms of age, gender, body mass index (BMI), ethnicity, level of education, back pain duration, Brief Pain Inventory subscale on pain severity (BPI-Pain), Pain Catastrophizing Scale (PCS), SPA indices (SPA-Sensory, SPA-Pain, SPA-Psych), aggregated momentary pain intensity, and aggregated momentary mood. Furthermore, descriptive statistics were carried out to characterize the EMA completion rates (e.g., the mean, standard deviation, median, and interquartile range of the percentage of prompts that were answered per participant), as recommended in the literature (6, 16). Participants were not asked for their reasons for not completing EMA prompts.

4.3.5.2. Multilevel linear model (MLM) analyses

Hierarchical data structure

The data were organized in relation to their hierarchical data structure, which was verified using the calculation of the intraclass correlation (ICC) and the design effect statistics as recommended in this MLM methodological review paper (38):

(1) level one is composed of the randomized EMA prompts (referred to as "moments") for which three are clustered per day,

(2) level two is composed of the days of EMA for which nine are clustered per participant,

(3) level three is composed of the participants and their time invariant data collected during the in-person baseline testing session.

Independent variables of interest

MLM analyses were carried out, taking into account the three-level hierarchical data structure composed of EMA moments (level one) nested within EMA days (level two) which in turn were nested

within participants (level three). In other words, the participant-level variables are labelled "level three" since it is within each participant that all the two-level EMA data is nested. Specifically, we conducted multilevel linear regression analyses, modelled with random intercept to estimate fixed effects ("*b*", unstandardized regression coefficients), using a maximum-likelihood (ML) parameter estimation method (38-41). The literature supports using ML since it takes into account all of the available data (complete and incomplete) to then estimate parameters (e.g., fixed effect estimates or *b*) using an iterative process that results in parameter estimates that have the highest probability of producing the sample data, and ML is less affected by potential bias found in more traditional approaches which tend to either underestimate error or excessively delete data using listwise deletion (41, 42). MLM is well-suited to accept data from all participants, even in cases of unequal data points due to missing data and does not require any data imputation methods, therefore all participants from our sample can be directly entered in our analyses (38, 40, 41). The first series of MLM analyses were conducted to determine: (1) the extent to which SPA indices are associated with momentary pain intensity, and (2) the extent to which SPA indices are associated with momentary mood. Specifically, all SPA indices variables were considered as the independent variables of interest and thus were transformed using grand mean centering (38, 40, 41). Momentary pain intensity and momentary mood were considered the outcome variables of interest and were kept in their raw form as repeated measures ("moments"). In this first series of MLM analyses, each SPA index was considered individually in relation to each outcome of interest (momentary pain intensity, momentary mood). The variables that were statistically significantly ($p<.05$) associated were retained for a second series of MLM analyses.

Covariates

For this second series of MLM analyses, we controlled for covariates and determined the extent to which the previously identified significant associations still held. Age, gender, BMI, back pain duration, BPI-Pain, and PCS were considered as potential covariates and all were transformed using grand mean centering. MLM was first carried with each covariate individually in relation to an

outcome of interest (momentary pain intensity, momentary mood). The statistically significantly ($p<.05$) associated covariates were retained for the final MLM analyses.

Final models

Thus, the final MLM analyses were multivariable, whereby significant SPA indices and covariates were entered simultaneously in relation to each outcome of interest (momentary pain intensity, momentary mood). The statistical significance of these final models of MLM was tested in relation to a null model, using the likelihood ratio model test (which is analogous to using an omnibus F-test for final regression models) as described here (38, 40, 41).

Moreover, for these final MLM models, a pseudo-R^2 (specifically, the "proportional reduction in variance" or PRV statistic) was calculated, in accordance with expert recommendations (38, 41). The PRV is a local effect size estimate that is akin to the R^2 change statistic that is uniquely attributable to each independent variable added into a multiple regression model. Aligned with previous pain research that used MLM (43, 44), the beta or the estimate of fixed effect (i.e., "*b*", unstandardized regression coefficient) is not typically transformed into a standardized form; in fact, it is typically recommended against trying to standardized the estimate of fixed effect due to complications in determining a clear basis for standardization as a result of the outcome variance being partitioned in MLM to multiple piles of variance (38, 41). The aforementioned PRV calculation for a pseudo R^2 is recommended instead if one wishes to clarify the effect size of one predictor relative to another (38, 41). This pseudo-R^2 is calculated as the reduction in variance individually contributed by an independent variable, relative to a null MLM model (i.e. a model with no independent variables entered):

$$PRV = (variance_{No\ IV} - variance_{IV\ of\ interest}) / variance_{No\ IV}$$

Where $variance_{No\ IV}$ refers to the variance in a model with no independent variables (IV) entered, and $variance_{IV\ of\ interest}$ refers to the variance in a model with one independent variable (IV) of interest entered (to expose the individual contribution of each independent variable towards reducing the variance in the null MLM model). Since the pseudo-R^2 is calculated individually as PRV for each

independent variable, one at a time rather than as part of a group of independent variables, no adjustments are required in relation to the number of independent variables in the final model. It is important to note that our MLM models only include time-invariant person-level (i.e. level three) independent variables, therefore it is only appropriate to calculate the PRV in relation to the corresponding pile of variance (i.e., the level three, person-level random intercept variance) instead of the total outcome variance (41).

4.4. RESULTS

4.4.1. Descriptive statistics

After providing informed consent, 67 individuals participated in the full study (both the in-person testing session and the following nine days of EMA). Table 4.1 summarizes the descriptive statistics, including the EMA completion rates for our study sample (6, 16).

TABLE 4.1. Sample characteristics

Characteristics	Mean (SD) or Count (%)	Median (IQR)
Baseline visit		
Age (years)	44.74 (13.83)	45.00 (23.25)
Gender		
Women	30 (61.70%)	
Men	50 (37.00%)	
Other	1 (1.20%)	
BMI (kg/m^2)	28.07 (6.05)	27.75 (7.14)
Ethnicity		
Caucasian	20 (44.40%)	
Other	25 (55.60%)	
Highest level of education		
Elementary school	8 (9.10%)	
High school	23 (26.10%)	
Post-secondary education	57 (64.80%)	
Back pain duration at baseline visit (in weeks)	11.29 (6.77)	9.21 (10.07)
Brief Pain Inventory (Pain Severity subscale, 0-10)	4.67 (1.87)	4.63 (2.75)
Pain Catastrophizing Scale (PCS total, 0-52)	16.38 (10.98)	15.00 (15.00)
SPA indices		
SPA-Sensory[a] at hands (PPT change, kPa)	-20.60 (88.00)	-28.73 (85.72)
Pre SPA task (PPT-Hands, kPa)	299.80 (142.97)	275.05 (211.66)
Post SPA task (PPT-Hands, kPa)	276.49 (156.42)	248.73 (236.96)
SPA-Sensory[a] at low back (PPT change, kPa)	-1.62 (87.23)	-20.39 (78.96)
Pre SPA task (PPT-Back, kPa)	309.09 (205.40)	240.20 (310.63)
Post SPA task (PPT-Back, kPa)	293.84 (194.93)	242.06 (295.07)
SPA-Pain (pain NRS 0-100 change)	21.53 (23.12)	15.00 (29.00)
First repetition of tailored lifts (evoked pain intensity NRS, 0-100)	24.86 (23.26)	20.00 (23.50)
Ten repeated tailored lifts (peak evoked pain intensity NRS, 0-100)	46.75 (28.84)	50.00 (45.00)
SPA-Psych (0-24)	2.42 (3.93)	0.00 (3.00)
Ecological Momentary Assessment (EMA)		
EMA completion rates (%)		
EMA-Pain	55.61 (26.30)	66.67 (37.04)
EMA-Mood	55.89 (26.38)	66.67 (37.04)
EMA aggregated[b] ratings		
Momentary pain intensity (NRS 0-100)	42.64 (19.72)	37.50 (26.45)
Momentary mood (Likert-scale, -5, very bad to +5, very good)	1.56 (2.13)	1.75 (2.87)

SD indicates Standard Deviation; IQR, interquartile range; BMI, body mass index; PCS, pain catastrophizing scale; SPA, sensitivity to physical activity; PPT, pressure pain threshold; kPa, kilopascal; NRS, numerical rating scale; EMA, Ecological Momentary Assessment.

[a] For the SPA-Sensory indices, a lower value indices greater the sensitivity to physical activity, because the post-task PPT is lowered compared to the pre-task PPT indicating that sensitization has occurred due to the SPA task.

[b] Aggregated indicates that EMA within-person repeated data were averaged for each listed measure in order to provide descriptive statistics at the person-level (i.e., MLM level three).

4.4.2. Multilevel linear model (MLM) analyses

4.4.2.1. Hierarchical data structure

In support of our data's three-level hierarchical structure, ICC calculations revealed that 72.03% of momentary pain intensity variation occurred across participants (with 11.10 as a design effect estimate), and 23.24% variation occurred across EMA days (with 1.15 as a design effect estimate). For momentary mood, ICC calculations revealed that 18.74% of variation occurred across participants (with 3.64 as a design effect estimate), and 49.51% variation occurred across EMA days (with a 1.34 design effect estimate). As reported by Peugh (38), ICC values where MLM application is indicated are commonly above 40% for longitudinal studies, and between 5% and 20% for cross-sectional studies; whereas design effects estimates above 2.0 suggest a need for MLM. Taking into consideration all of these ICC and design effect estimates together, as well as considering that traditional regression analyses would in this case be subject to violations of assumptions of multicollinearity and independence of residuals, it is justified to proceed with three-level MLM analyses.

4.4.2.2. Independent variables of interest

In the first series of MLM analyses, we found the following results. For the momentary pain intensity outcome, higher SPA-Pain ($b = 0.34$, $p < 0.01$) was associated with higher momentary pain intensity. Higher SPA-Psych ($b = 1.48$, $p = 0.01$) was associated with higher momentary pain intensity. SPA-Sensory at hands and SPA-Sensory at low back were not significantly associated with momentary pain intensity.

For the momentary mood outcome, higher SPA-Psych ($b = -0.21$, $p = 0.01$) was associated with worse momentary mood. SPA-Pain, SPA-Sensory at hands, and SPA-Sensory at low back were not significantly associated with momentary mood.

4.4.2.3. Covariates

In the second series of MLM analyses, we found the following results. For the momentary pain intensity outcome, higher BPI-Pain ($b = 8.28$, $p < 0.01$) was associated with higher momentary pain

intensity. Higher PCS ($b = 0.69$, $p < 0.01$) was associated with higher momentary pain intensity. Age, gender, BMI, and back pain duration were not significantly associated with momentary pain intensity (all p's > 0.05).

For the momentary mood outcome, higher age ($b = 0.05$, $p = 0.04$) was associated with better momentary mood. Higher BPI-Pain ($b = -0.48$, $p < 0.01$) was associated with worse momentary mood. Higher PCS ($b = -0.07$, $p = 0.02$) was associated with worse momentary mood. Gender, BMI, and back pain duration were not significantly associated with momentary mood.

4.4.2.4. Final models

For the final models of MLM, we found the following results. Table 4.2 shows the MLM analyses using momentary pain intensity as the outcome. Of note, in this final MLM, even after controlling for significantly associated covariates identified earlier (BPI-Pain and PCS), higher SPA-Pain remained significantly associated with higher momentary pain intensity. In terms of the pseudo-R^2, SPA-Pain explained a 13.97% proportion of variance reduction (PRV) for the person-level random intercept variance compared to the null MLM model for momentary pain intensity. However, SPA-Psych was no longer significantly associated with momentary pain intensity in this final model. This final model of MLM for momentary pain intensity was a better fit to the data over the null model, as per the likelihood ratio model test (χ^2 (4) = 1976.194, p <0.01).

TABLE 4.2. Final MLM for the outcome: **momentary pain intensity in daily life**

Variable	*b*	Standard Error	Degrees of freedom	*t*	*p*	95% Confidence interval		Pseudo-R^2 (PRV)
						Lower bound	Upper bound	
Intercept	**39.89**	**1.48**	**44.88**	**27.03**	**<0.01**	**36.92**	**42.86**	–
BPI-Pain	**6.21**	**1.02**	**45.03**	**6.11**	**<0.01**	**4.16**	**8.26**	**70.82%**
PCS	0.23	0.16	44.15	1.45	0.15	-0.09	0.54	21.10%
SPA-Pain	**0.24**	**0.07**	**49.88**	**3.19**	**<0.01**	**0.09**	**0.38**	**13.97%**
SPA-Psych	0.63	0.36	44.88	1.76	0.09	-0.09	1.35	27.78%

MLM indicates multilevel linear model (random intercept); b, estimate of fixed effect (unstandardized regression coefficient); BPI-Pain, Brief Pain Inventory (Pain Severity subscale, 0-10); PCS, Pain Catastrophizing Scale (total, 0-52); SPA-Pain, evoked pain response index of sensitivity to physical activity (0-100); SPA-Psych, evoked psychological response index of sensitivity to physical activity (0-24); PRV, Proportional Reduction in Variance statistic is analogous to an r-square change (pseudo-R^2) statistic attributed uniquely to each independent variable.

All participant-level independent variables (BPI-Pain, PCS, SPA-Pain, SPA-Psych) are grand mean centered.

Statistically significant results ($p < 0.05$) are shown in bold.

Table 4.3 shows the MLM analyses using momentary mood as the outcome. Of note, in this final MLM, after controlling for significantly associated covariates identified earlier (Age, BPI-Pain, and PCS), SPA-Psych was no longer significantly associated with momentary mood but approached significance ($p = 0.052$, with alpha set at <0.05) with $b = -0.16$, such that higher SPA-Psych showed a trend for worse momentary mood. In terms of the pseudo-R^2, SPA-Psych explained a 17.81% proportion of variance reduction (PRV) for the person-level random intercept variance compared to the null MLM model for momentary mood. This final model of MLM for momentary mood was a better fit to the data over the null model, as per the likelihood ratio model test (χ^2 (4) = 2497.836, p<0.01).

TABLE 4.3. Final MLM for the outcome: **momentary mood in daily life**

Variable	*b*	Standard Error	Degrees of freedom	*t*	*p*	95% Confidence interval		Pseudo-R^2 (PRV)
						Lower bound	Upper bound	
Intercept	**2.27**	**0.38**	**47.53**	**5.93**	**<0.01**	**1.50**	**3.04**	–
Age	0.05	0.03	47.06	1.62	0.11	-0.01	0.11	19.05%
BPI-Pain	**-0.47**	**0.21**	**52.26**	**-2.18**	**0.03**	**-0.90**	**-0.04**	**23.76%**
PCS	-0.03	0.03	47.60	-0.84	0.41	-0.09	0.04	11.42%
SPA-Psych	**-0.16**	**0.08**	**47.81**	**-1.99**	**0.052**	**-0.32**	**0.001**	**17.81%**

MLM indicates multilevel linear model (random intercept); b, estimate of fixed effect (unstandardized regression coefficient);Age (in years); BPI-Pain, Brief Pain Inventory (Pain Severity subscale, 0-10); PCS, Pain Catastrophizing Scale (total, 0-52); SPA-Psych, evoked psychological response index of sensitivity to physical activity (0-24); PRV, Proportional Reduction in Variance statistic is analogous to an r-square change (pseudo-R^2) statistic attributed uniquely to each independent variable.

All participant-level independent variables (Age, BPI-Pain, PCS, SPA-Psych) are grand mean centered.

Statistically significant results ($p < 0.05$) are shown in bold.

4.5. DISCUSSION AND CONCLUSIONS

This is the first study to investigate the predictive value of task-based assessment of SPA for subsequent momentary measures (EMA) of pain and mood experienced in daily life among people with back pain. Consistent with past research (5), BPI-Pain unsurprisingly contributes a large proportional reduction in variance (pseudo-R^2=70.82%) of momentary pain intensity in daily life and significantly contributes to momentary mood in daily life (pseudo-R^2=23.76%). While much of the variance is explained, not all of it is and this leaves room for misrepresentation of the real-life experience of patients, which in turn, can contribute to flawed clinical decision-making and ineffective care. Our study did find that SPA indices uniquely contribute a proportional reduction in variance, indicating that SPA indices seem to tap into a distinct aspect of the everyday life experience of pain and mood (pseudo-R^2=13.97% and 17.81%, respectively). Indeed, SPA-Pain maintained a unique association

with momentary pain, even after controlling for covariates such as age, gender, body mass index, back pain duration, BPI-Pain, and PCS. Similarly, after controlling for covariates, SPA-Psych was significantly associated with momentary mood in the univariate MLM, and showed a trend for maintaining a unique association ($p=0.052$) in the final MLM.

This unique association contributed by SPA, beyond BPI-Pain, may reflect some of the distinction between the two types of assessments. For instance, SPA assessment aims to align with real-life experiences by using a functional task that is typically encountered in everyday life. Also, because SPA assesses task-related reactions in real-time, it circumvents the inherent memory-experience gap of self-report questionnaires (7-11, 14). The memory-experience gap refers to the discrepancies that may occur between memory and experience (2, 3). Retrospective questionnaires are subject to recall bias, particularly of a negative memory such as pain which tend to be exaggerated due to peak and end effects, and may be further influenced by other factors such as the retention interval as well as the patient's state-related and trait-related characteristics (1-3). These differences may have contributed to the added predictive value of the SPA measures.

Our study findings on the predictive value of specific SPA indices are broadly consistent with previous findings (10). SPA-Sensory (i.e. based on pre-post task-related changes in pressure pain threshold) did not show a significant association with our outcomes of interest yet the other SPA indices did. Indeed, previous research on SPA-Pain found cross-sectional associations with clinical outcome variables such as pain and disability assessed by questionnaires (7, 9, 11, 18, 45-47), but revealed mixed findings in relation to longitudinal prognostic value for pain and disability (10, 12, 48). This study found that SPA-Pain maps onto the subsequently EMA-measured everyday pain experience of patients with back pain even when controlling for covariates, consistent with the cross-sectional findings of previous research on SPA-Pain and providing preliminary evidence for ecological validity. As for research on SPA-Psych, it is significantly more sparse than its counterparts, but initial findings

appear to support its prognostic value (10, 49) though to a varying degree (9). In this study, we found that SPA-Psych is significantly associated with its corresponding construct in EMA, that is, momentary mood in everyday life; thus, it provides preliminary evidence for ecological validity. In the final MLM, SPA-Psych's association with momentary mood nearly maintained significance (p=0.052) after controlling for personal and pain-related factors (BPI-Pain, PCS, age, gender, body mass index, and back pain duration). The PCS, on the other hand, was non-significant (p=0.405). Whereas SPA-Psych is a "state" pain catastrophizing measure focused on the transient "state" evoked by the SPA task, the PCS was designed to measure the "trait" expression of pain catastrophizing (though may capture a mix of "state" and "trait") (25, 50). It thus appears from our findings that having an elevated level of state-oriented pain catastrophizing (SPA-Psych) seems to be more predictive for subsequent ratings of negative mood in daily life than trait-oriented pain catastrophizing. This may help to explain previous findings of SPA-Psych's prognostic value for pain and disability outcomes (10, 49) – SPA-Psych may help to identify individuals who habitually tend to be more state-oriented for catastrophizing thoughts and feelings evoked by painful daily activities and, therefore, hypervigilant to pain and discouraged from activity engagement (51).

Our findings suggest that SPA indices may prove to be helpful in informing activity-based interventions designed to be integrated within daily life. For instance, much of the research on graded activity (52, 53) and pacing (54, 55) demonstrate limited or no additional benefit beyond a simple recommendation to stay active. This may be in part due to dosage prescriptions that are too conservative and inadvertently too close to natural avoidance behaviours (54, 55). On the other hand, while being active or exercising into pain appears to be as effective or superior to doing so without pain (56), evidence suggests that exacerbating too much pain with activity is detrimental for both pain-related outcomes (55) and for adherence (57, 58). The prescription of activity-based interventions would thus likely benefit from being informed by more precise estimates of actual pain levels experienced in daily-life, which currently rely on retrospective self-report of pain (e.g., BPI-Pain) and

do not typically also consider functional task-related pain measures such as SPA. This study's findings have shown that while retrospective self-report of pain (e.g., BPI-Pain) are good predictors of daily-life pain, SPA indices provide additional predictive value that complement clinically-administered measures in representing the daily-life experience. Using SPA additionally to current clinical pain assessment methods would be particularly useful upon the initial prescription and progression of activity-based interventions, since experiencing too little benefit or too much pain from the prescribed physical activity may discourage patients from continued engagement (58, 59). Future research should investigate whether SPA indices can provide added precision for the dosage of activity-based interventions such as graded activity, and whether this translates into improved effectiveness.

The findings of this study should be interpreted in light of the following limitations. Our EMA completion rates, as reported in the Results section (mean is approximately 56%), are below the 84% mean completion rate that was obtained from the review by May et al. which averaged completion rates across all EMA pain studies published to date (6). Our relatively low EMA completion rates occurred despite following recommendations by the review paper by Morren et al. (19) such as minimizing the number of questions (e.g., our EMA assessment of mood was reduced to one item), using push-notifications, and having a standard set of instructions conveyed by the research assistant (including an in-person practice prompt and a telephone follow-up call). However, our EMA completion rate is still higher than other previously published EMA pain studies, which had approximately 50% mean completion rates of EMA (6). It is also worth noting that approximately a third of all EMA pain studies in the May et al. review paper (and that were included to generate the benchmark levels of completion) did not report their EMA completion rates (6). It is therefore possible that several other studies had relatively low EMA completion rates but did not report them; thus, May et al.'s reported 84% mean completion rate is potentially inflated. Another potential limitation to consider is that our SPA assessment was based on a single task for all participants rather than personalizing the task selection for optimal relevance to their daily life experience. However, this use of a single task for all reflects an

effort to standardize the SPA assessment to allow between-person comparisons, as done in previous SPA research (7, 9-13), and it is also reflective of the relatively early stage of development of this measure. Future research should consider developing preference-based methodology for standardized yet personalized SPA assessment and evaluate it for psychometric properties, as well as for its association with daily life measures.

In conclusion, we found that SPA-Pain was uniquely associated with momentary (EMA) pain and that SPA-Psych trended for a unique association with momentary mood, even after controlling for BPI-Pain, PCS, and other personal characteristics (age, gender, body mass index, and back pain duration). Thus, using real-time task-based SPA assessment in addition to retrospective questionnaires would likely provide clinicians with a better picture of their patient's daily life experiences, such as their pain and mood. This, in turn, is expected to enable clinicians to optimally tailor the prescription of treatment interventions that are integrated into daily life, such as graded activity and pacing. Future research will need to determine if this helps to strengthen the effectiveness of those interventions, whilst mitigating the risk of negative reactions such as flare-ups which can discourage further engagement. Furthermore, the alignment in associations between corresponding constructs (SPA-Pain with momentary pain, and SPA-Psych with momentary mood) may serve as preliminary support for ecological validity; in other words, these SPA indices appear to indeed map onto real-life pain-related experiences as per their intended design (i.e., using a standardized task that is typically encountered in daily life). The findings of this study thus add to the growing literature on SPA indices, which to date has focused on underlying processes and prognostic value but lacked direct investigation in relation to their association with daily life (EMA) pain-related measures as done in this study.

4.6. ACKNOWLEDGMENTS

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PREFACE TO CHAPTER 5 (STUDY 4)

The introduction of this thesis discussed the importance of considering daily-life outcomes that occur in the days following an in-person assessment, in addition to traditional prognostic outcomes that occur further into the future (e.g., three-month follow-up of pain and disability such as in Study 2). Daily life outcomes can include, for instance, indices of intraindividual pain variability (within-person fluctuations in pain) such as pain flare-ups. Past research has found that pain flare-ups are particularly disruptive in one's life when they lack predictability, and can contribute to greater pain, disability, and distress. Therefore, Study 4 aimed to address this issue of predictability of pain flare-ups by considering the prognostic value of SPA assessment.

While Study 3 explored the relationship of SPA with daily life from an ecological validity standpoint, Study 4 explores the prognostic value of SPA for daily-life outcome variables (pain fluctuations and flare-ups). This adds insight into yet another facet of potential prognostic value of SPA assessment, which builds on the findings of SPA's prognostic value for pain and disability cross-sectionally (Study 1) and at three-month follow-up (Study 2). Indeed, there is little research investigating prognostic factors for pain fluctuation and flare-ups, and none has investigated SPA as a potential prognostic factor. Therefore, Study 4 aimed to address this gap. Study 4 used the same *dataset #2* as in Study 3 consisting of a sample of 67 individuals recruited upon seeking care for back pain, who completed both an in-person testing session and nine days of EMA. Also, as in the previous studies of this thesis, the individually tailored lifting SPA task and the multidimensional range of SPA indices (evoked pain intensity, sensory changes, and situational catastrophizing) were used. Study 4 is the final study of this thesis.

CHAPTER 5: DYSFUNCTIONAL EXERCISE-INDUCED HYPOALGESIA PREDICTS PAIN FLARE-UPS IN DAILY LIFE AMONG PEOPLE WITH BACK PAIN (STUDY 4)

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5.1. ABSTRACT

Objectives: Pain fluctuations and flare-ups are very disruptive to daily life for people living with back pain. Making pain-related disruptions more predictable can help both clinicians and patients manage pain better. Past research has suggested that dysfunctional exercise-induced hypoalgesia (EIH), and other dynamic measures of sensitivity to physical activity (SPA), may be particularly well-suited to predicting daily pain-related fluctuations and flare-ups. EIH evaluates how pain thresholds change in relation to standardized physical activity; dysfunctional EIH indicates that there is increased sensitivity (lower pain thresholds) following physical activity. Recent work has framed dysfunctional EIH within a broad collection of measures that can be used to evaluate SPA. For instances, previous work has used EIH to evaluate sensory-related changes in relation to physical activity, while other work has used situational catastrophizing or pain intensity to target other biopsychosocial responses to physical activity. No study to date has investigated whether SPA measures can predict the degree of pain fluctuations and flare-ups experienced by people with back pain as they go about their daily life activities. Therefore, this study aimed to address this gap. The predictive value of more commonly used assessments (Brief Pain Inventory, Pain Catastrophizing Scale) was also considered.

Methods: This observational study used a short-term longitudinal design, for which 67 participants from private physical therapy clinics completed an in-person testing session including questionnaires and SPA assessment, followed by nine days of daily-life ecological momentary assessment of pain and mood. The latter served to generate indices of pain-related fluctuations and flare-ups.

Results: Dysfunctional widespread EIH (increased sensitivity following physical activity) was a risk factor for pain flare-ups in daily life in two analyses (Spearman's correlation found r=-0.338, p=0.012; multilevel logistic regression analyses with random intercept modelling found *odds ratio*=0.997, p=0.020). No prognostic value was found for the other predictors or outcomes of interest.

Conclusion: Our study is the first to demonstrate the prognostic value of dysfunctional EIH for pain flare-ups and has important implications for risk-stratifying activity-based treatments.

Key words: Sensitivity to Physical Activity; Exercise-induced hypoalgesia; Movement-evoked pain; Intraindividual pain variability; Flare-ups

5.2. INTRODUCTION

Pain fluctuations are typically transient but can be very disruptive to a person's daily life, especially if they are unexpected (1-10). Particularly disruptive pain fluctuations, if meeting certain pre-determined criteria such as concurrently worsened mood, may be qualified as pain flare-ups (1-3, 5, 7). Pain fluctuations and flare-ups may complicate recovery and rehabilitation processes, discourage consistent adherence to activity-based treatment recommendations, and may explain why pain and disability persist in some cases (1-6, 11-13). Thus, in line with IMMPACT recommendations (14), there is a growing recognition for investigating these daily-life pain fluctuations and flare-ups, in addition to traditional future outcomes (e.g., three-month follow-up) of pain and disability (1-6, 13, 15).

Individuals with back pain experience pain fluctuations and flare-ups to varying degrees and would benefit from better predictability (5, 15, 16). Addressing the predictability of these pain fluctuations and flare-ups helps to inform treatment, makes them less disruptive to a person's daily life (4), and reduces their effect on overall pain severity (8-10). Emerging research has identified some time-varying predictors (i.e., momentary measures taken during daily life), including momentary pain intensity or sleep quality in the last 24 hours (16), or prolonged sitting (> six hours) or having either stress or depression in the last 24 hours (17). However, research on time-invariant predictors (i.e., taken at baseline in clinical or lab settings, such as through questionnaires or physical evaluation) remains scarce despite their practical value (15).

Dysfunctional exercise-induced hypoalgesia (EIH), and other dynamic measures of sensitivity to physical activity (SPA), may be particularly well-suited to predicting daily pain-related fluctuations and flare-ups. EIH evaluates how pain thresholds change in relation to standardized physical activity;

dysfunctional EIH indicates that there is increased sensitivity (lower pain thresholds) following physical activity (12, 18-20). Recent work has framed dysfunctional EIH within a broad collection of measures that can be used to evaluate SPA (21, 22). For instances, previous work on SPA has used dysfunctional EIH to evaluate sensory-related changes in relation to physical activity, while other work has used situational catastrophizing (21, 23, 24) or pain intensity (also referred to as movement-evoked pain (25, 26)) to target other biopsychosocial responses to physical activity. Thus, SPA is a type of sensitization measure that includes a broad range of activity-evoked reactions, which can be sensory (e.g., pain intensity or sensitivity) or psychological (e.g., situational pain catastrophizing) (21, 22). Previous research has developed standardized task-based measures of SPA, which use tasks that reflect activities typically encountered in daily life (e.g., lifting tasks) (18, 21, 22, 27-29). Although SPA is specifically tied to physical activity, it may nonetheless explain a meaningful proportion of variance in daily-life pain fluctuations and flare-ups, since research has shown a high prevalence of activity-related pain among people living with pain conditions such as back pain (30, 31). Empirical support is emerging for the broader prognostic value of SPA for pain-related outcomes at future follow-up periods (21, 25, 32-34), but no study to date has considered the prognostic value at the closer range of daily-life pain fluctuations and flare-ups.

Therefore, the purpose of this study was to explore whether clinical indices of SPA have predictive value for pain fluctuations and flare-ups in the daily lives of patients with back pain. The predictive value of commonly used pain-related questionnaires such as the Brief Pain Inventory (BPI) and the Pain Catastrophizing Scale (PCS) were also explored for this study, to contextualize the findings on the predictive value of SPA indices.

5.3. METHODS

5.3.1. Design

The design of this short-term longitudinal study was observational, using a combination of an in-person testing and a subsequent nine-day ecological momentary assessment (EMA) (5, 6, 13, 35, 36). Reporting followed recommendations for EMA studies (6, 13, 35) and STROBE statement guidelines (37) (see Appendix 4 for the completed STROBE checklist for this manuscript). Ethics approval was obtained for this study through a local research ethics board.

5.3.2. Participants and recruitment

Upon starting physical therapy in one of eight collaborating local private rehabilitation clinics, patients with back pain were invited to take part in this study via a pamphlet with a brief description and contact information for our lab's research staff. The intention was to have a study sample that is representative of the typical back pain patient encountered in clinical practice; the physical therapy treatments themselves were not a focus of our analyses. Upon giving the study information pamphlet, the treating physical therapist clarified that the decision to participate had no bearing on the quality of care provided. If interested, these patients contacted the lab's research staff, who then verified the following eligibility criteria: (1) at least 18 years old, (2) less than six months since onset of back pain, (3) back pain located between the gluteal folds and shoulders, (4) back pain was non-specific, that is not caused by any known organic pathology (e.g., spinal stenosis, spondylolisthesis, ankylosing spondylitis), (5) medically stable (absence of serious health conditions, pending surgery or invasive medical procedure, and contra-indication to physical activity). If eligibility criteria were met, interest in study participation was verified after clarifying what participation in the study entailed and answering any questions. Interested participants were then scheduled for an in-person testing session to fill out informed consent forms and collect data. Data analyses for this study were carried out on the participants who did both the in-person testing session and the subsequent nine-day EMA.

5.3.3. Procedures

All data collection was completed between December 2015 and April 2019, and took place at the clinic where the patient was recruited. Specifically, a research assistant administered informed consent forms, questionnaires, and SPA assessment (details below), and ended the in-person testing session by initiating a nine-day span of smartphone-based EMA. EMA was a core component of the study design, since it is best suited for capturing pain-related fluctuations and flare-ups (5, 6, 13). EMA repeatedly collects "in the moment" ratings as a person goes about their activities of daily living, thus allowing for dynamic assessments of pain (5, 6, 13).

To support optimal EMA completion rates, two days into the EMA, the research assistant made a follow-up telephone call to troubleshoot any issues and to provide encouragement. Additional strategies, such as an initial practice session for answering the first EMA prompt (at the end of the in-person testing session), using push notifications, and minimizing the number and length of questions, were used to maximize EMA completion rates (38). EMA was administered using a smartphone application known as "Metricwire" (Kitchener, Canada), with a customized set of questions which participants were prompted to answer using stratified random sampling (random times within three pre-programed timeslots, 8am to 12pm, 12pm to 4pm, 4pm to 8pm) over the course of nine days (see "Measures" section for the EMA questions posed).

SPA was assessed using a standardized lifting procedure, in relation to which pain-related, sensory, and psychological reactions were measured as indices of SPA (21, 28). This standardized lifting procedure was as follows. A custom-made lifting apparatus was used, such that weights (1.0kg, 2.0kg, 3.0kg, or 3.5kg) were concealed in a rectangular box (90 cm high×60 cm wide×60 cm deep) and attached to a height-adjustable strap. Participants were first instructed to adopt the following lifting position: standing erect with dominant hand holding the handle with a pronated grip, 90 degrees elbow flexion, zero degrees of shoulder flexion (the "easy" lifting position). Using this "easy" lifting position, participants were asked to hold onto the handle and lift the weight up to a marked height on the handle

strap (approximately five cm lift). Thus, participants did a series of single lifts and reported on how much pain was evoked by the lift. The lifts were organized from easiest to hardest, starting with the lightest weight and incrementally increasing the weights. If the heaviest weight was used (3.5 kg) and no clinically important pain was evoked (less than 20 on a 0-100 numerical rating scale [NRS] of pain intensity), the lifting position was modified. Thus, the participants did another series of single lifts, again starting with the lightest weight and incrementally progressing to heavier weights, except this time the "easy" lifting position was modified to now have an outstretched arm (i.e., "medium" difficulty lifting position). Again, if no clinically important pain was evoked by the time the heaviest weight was used, then the "medium" lifting position was further modified (i.e., now with a forward lean equivalent to approximately 45 degrees of trunk flexion) to be of "hard" difficulty. The purpose of these series of single lifts was to identify the minimum level of lifting difficulty (in terms of weights and lifting position) which evoked a clinically important pain (≥20 out of 100 pain intensity NRS).

Using this individually tailored level of difficulty, participants were subsequently instructed to perform ten repetitions of that lift, and report on their pain-related, sensory, and psychological reactions (see "Measures" section for SPA indices' description).

5.3.4. Measures

5.3.4.1. In-person testing session

For this study, participants completed the Brief Pain Inventory, the Pain Catastrophizing Scale, the clinical assessment of SPA, and the EMA-based indices of pain-related fluctuations and flare-ups.

Pain intensity was measured using the Brief Pain Inventory's pain severity subscale (BPI-Pain), which averages 11-point numerical rating scale (NRS) scores for present, average, 24-hour worst, and 24-hour least pain intensity (39, 40). This questionnaire is commonly used to assess pain intensity, with research demonstrating its internal consistency (Cronbach alpha = 0.82), reliability, and validity for people with back pain (39). Higher scores (0-10) indicate more severe pain intensity.

Pain catastrophizing was measured using the Pain Catastrophizing Scale's total score (PCS), which sums up the five-point Likert scale scores for the questionnaire's 13 items (41-43). This questionnaire is commonly used to assess pain catastrophizing, with research demonstrating its internal consistency (Cronbach alpha = 0.92), reliability (test-retest Spearman rho = 0.88), and validity for people with back pain (41-43). Higher scores (0-52) indicate more severe pain catastrophizing.

Based on reactions to the SPA assessment's standardized lifting task described above, four SPA indices were measured (SPA-Sensory widespread and localized, SPA-Pain, and SPA-Psych) as in previous work (21):

(4) SPA-Sensory (widespread and localized): Consistent with the exercise-induced hypoalgesia (EIH) literature (18, 19, 44, 45), three pressure pain threshold (PPT) measures in kilopascals were taken with an algometer (FDX 10, Wagner instruments, Greenwich, CT, USA) before and after the SPA lifting task. Specifically, the algometer's one cm^2 rubber tip was applied with a slow, perpendicular pressure until a participant determined that the pressure became painful. A 30-second break was incorporated in-between repeated PPT measures. Given our back pain study sample, the SPA-Sensory body site representing widespread EIH was the hands (web-space between thumb and index finger) and would indicate if central sensitization processes are potentially involved; the body site representing localized EIH was the low back (five cm laterally from L3 spinous process) and would indicate if peripheral sensitization processes are potentially involved (19, 46, 47). Similar to EIH studies (18, 19, 21, 44, 45), SPA-Sensory was calculated as "the average of the three PPT measures post-task" minus "the average of the three PPT measures pre-task", at each body site. Dysfunctional EIH was indicated by a lower post-task PPT than pre-task PPT, therefore a negative SPA-Sensory value. Conversely, a higher post-task PPT than the pre-task PPT gives a higher positive SPA-Sensory value and indicates that EIH took place (18, 19).

(5) SPA-Pain: Consistent with the SPA and the movement-evoked pain literature (21, 22, 25-28), SPA-Pain was based on task-evoked changes in pain intensity. Specifically for this study, the evoked pain intensity measures (NRS, 0 “no pain at all” to 100 “the worst pain you can imagine”) were taken at the start of the lifting task (first tailored lift) and at end of the lifting task (peak pain with the ten repeated tailored lifts). The SPA-Pain index was calculated as “peak pain evoked with the ten repeated tailored lifts” minus “pain evoked with the first tailored lift”. Higher sensitivity was indicated by a higher peak pain value relative to the pain with the first tailored lift, therefore a greater SPA-Pain value.

(6) SPA-Psych: While SPA-Psych indices can include various task-evoked psychological reactions, this study focused on Campbell et al.’s Situational Catastrophizing Questionnaire (SCQ) (23). Consistent with the situational catastrophizing literature (21, 23, 24, 43, 48), the SCQ in this study had a specified referent event – the SPA lifting task – as opposed to the more traditional Pain Catastrophizing Scale, which is intended to evaluate general disposition and does not explicitly specify a referent event (43, 48). The SCQ has a total score (0-24) calculated as sum from six items asking participants to rate the extent (0 “not at all” to 4 “all the time”) to which they had pain-related catastrophic thoughts during the SPA lifting task. Higher sensitivity was indicated by a higher SCQ score, therefore a greater SPA-Psych value.

5.3.4.2. Ecological Momentary Assessment (EMA)

As per the procedures described above, study participants responded to three prompts per day for nine days, using push notifications on the smartphone application “Metricwire” (Kitchener, Canada). The questions were customized for this study as follows:

(3) EMA-Pain: “Please rate your present pain intensity: 0=no pain, 100=worst pain imaginable” (responses could be entered directly by typing or by using a sliding scale which displayed the

number value). NRS, such as this one, have better completion rates compared to other pain intensity measurement scale (49, 50). While an 11-point NRS is more commonly used and recommended (14), the 101-point NRS is not considered inferior and may improve the granularity of the variance that can be captured (49, 50). This in turn supports the subsequent calculations of indices of pain-related fluctuations and flare-ups (5).

(4) EMA-Mood: "Please rate your present mood: -5=very bad, -4, -3=bad, -2, -1=fairly bad, 0=neutral, +1=fairly good, +2, +3=good, +4, +5=very good" (responses were entered in a multiple-choice response format by simply selecting an answer option). This item served as part of the calculation to generate the multidimensional pain flare-up variable (described below). Single-item rating of momentary mood has been used in other EMA studies (51-53), and despite more tenuous empirical support for reliability (54) and validity (55), it is typical of EMA studies to write custom single-item ratings to reduce the burden of answering multiple questions and improve response rates (13, 38).

5.3.4.3. Intraindividual pain variability

Pain-related fluctuations and flare-ups can be represented as indices of intraindividual pain variability (IPV) (5). Figure 5.1 illustrates this study's IPV indices. Using the EMA raw data described above, IPV indices were calculated according to the formulas in Mun et al.'s review paper (5):

(1) iSD (intraindividual standard deviation): using an individual's raw repeated EMA-Pain data, a standard deviation can be calculated as an IPV index of the magnitude of fluctuations. High iSD indicates a high average magnitude of EMA-Pain fluctuations.

(2) iAC (intraindividual autocorrelation): using an individual's raw repeated EMA-Pain data, a correlation can be calculated between sequential (i.e., "lag 1") EMA-Pain prompts as an IPV index of temporal dependency (i.e., autocorrelation)– the extent to which pain intensity at one EMA moment influences the pain intensity at the subsequent EMA moment. An iAC value close to 1 indicates a maintained similar trend (e.g., a high value remains high, or a

low value remains low at the next EMA moment); an iAC value close to -1 indicates predictable fluctuation to the other extreme (e.g., a high value will be low, or a low value will be high at the next EMA moment); and an iAC value close to 0 indicates low temporal dependency between EMA-Pain momentary ratings.

(3) iMSSD (intraindividual mean square successive difference): using an individual's raw repeated EMA-Pain data, the squared differences between successive EMA moments can be squared to calculate an IPV index of temporal instability. High iMSSD indicates a high magnitude of fluctuations when considering change from one EMA-Pain rating to the next, in contrast to the iSD which considers the magnitude of fluctuations across all EMA-Pain ratings without taking into account the temporal order.

(4) iPAC (intraindividual probability of acute change): using an individual's raw repeated EMA-Pain data, the differences between successive EMA moments can be considered in relation to evidence-informed criteria for pain flare-ups (1-3). Depending on the analyses, iPAC can be considered as a percentage of EMA-Pain prompts qualifying as pain flare-ups relative to the total number of answered EMA-Pain prompts (i.e., which aggregates this level-one hierarchical data to a participant-level variable, adequate for exploratory correlation analyses) or as a level-one binary variable of pain flare-ups (i.e., yes/no pain flare-up occurred, adequate for multilevel logistic regression analyses based in generalized linear mixed modelling as described below). In both case, two types of pain flare-ups were calculated as indices of IPV:

    a. A "pain-only flare-up" was deemed to have occurred when at least a 10-point increase in EMA-Pain occurred from one EMA moment to the next, indicating a minimal detectable change (MDC) in pain intensity (56-58). This flare-up index was intended to capture any noticeable sudden increases in pain.

b. A “pain-mood flare-up” was deemed to have occurred when the condition for a “pain-only flare-up” was fulfilled *and* it was associated with a decrease in EMA-Mood that was at least half a standard deviation (a proxy for MDC (59)) lower than the individual’s within-person average for that EMA variable, which was approximately a one-point decrease in EMA-Mood. Thus, this flare-up index was intended to capture flare-ups that were potentially more meaningful to the person experiencing them, since the sudden increases in pain were accompanied with worsened mood (1-3).

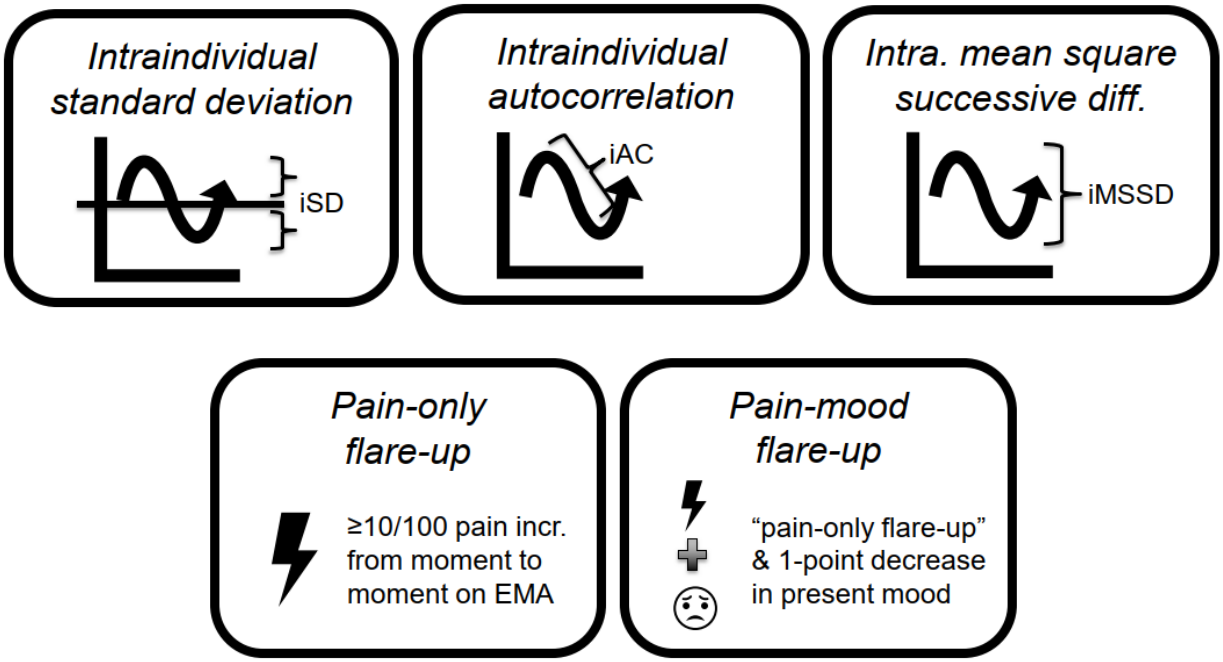

FIGURE 5.1. Intraindividual pain variability (IPV) indices. Intraindividual pain variability (IPV) indices are visually represented in this figure. These IPV indices represent pain-related fluctuations (iSD, intraindividual standard deviation; iAC, intraindividual autocorrelation; iMSSD, intraindividual mean square successive difference) and flare-ups (also referred to as iPAC, intraindividual probability of acute change). Details provided in the Methods section.

5.3.5. Data analysis

All analyses were carried out using IBM SPSS Statistics version 26, using a stacked format that takes into consideration the hierarchical data structure (36, 60, 61). The EMA moments (level one) were nested in EMA days (level two), which in turn were nested within each participant (level three, time invariant data). Of note, the IPV indices (iSD, iAC, iMSSD, and the two types of iPAC pain flare-ups) result from computations that effectively aggregate the level one EMA data to participant-level, time-invariant variables.

Descriptive statistics focused on participant-level variables (demographics, pain characteristics, SPA indices, EMA aggregated variables and IPV indices), as well as the EMA completion rates (13, 35). This also included graphs to display the proportion of EMA prompts that qualified as pain flare-ups throughout the nine days of EMA (62), both at the participant level and at the sample level.

Exploratory correlation analyses were carried out with either Pearson's correlations or Spearman's correlations, depending on the presence of skewed distributions for the variables of interest (SPA indices, BPI-Pain, PCS, and IPV indices). Given the exploratory nature of these analyses and the large number of pairings that would be considered (four SPA indices, BPI-Pain, PCS and five IPV indices result in 30 correlations), no significance threshold adjustments were made for multiple comparisons (maintained at $p<0.05$).

Generalized linear mixed model (GLMM) analyses (36), specifically multilevel logistic regression analyses with random intercept modelling, were also used to explore for potential associations of the in-clinic SPA indices, BPI-Pain, and PCS in relation to the two types of IPV indices of pain flare-ups (pain-only flare-up and pain-mood flare-up). The IPV indices for pain flare-ups were amenable to multilevel logistic regressions, since they could be seen as a series of binary pain flare-up outcome units (i.e., yes/no fulfilled criteria for that type of pain flare-up) at the hierarchical data level one. The predictors of interest (SPA indices, BPI-Pain, PCS) were grand mean centered and their fixed effect (probability for pain flare-ups in daily life) were individually estimated as odds ratios using

multilevel logistic regression (GLMM, random intercept, logit link function, binomial distribution, marginal maximal likelihood estimation) (36); in other words, one predictor at a time was investigated in relation to one outcome at a time. This analytical approach thus assesses the outcome data at its original hierarchical data level, rather than aggregating it to participant-level percentage-based indices for the two pain flare-up types (iPAC, proportion of answered EMA prompts that count as a flare-up given specific criteria). Similar to the aforementioned correlation analyses, these multilevel logistic regression analyses were exploratory and considered a rather large number of pairings (four SPA indices, BPI-Pain, PCS, and two types of IPV indices of pain flare-ups result in 12 associations to investigate); as such, no adjustments were made to the significance threshold ($p<0.05$).

5.4. RESULTS

Table 5.1 presents the descriptive statistics of our study's 67 participants, including EMA completion rates statistics as recommended in the literature (13, 35). Figures 5.2 and 5.3 present graphs that display the proportion of EMA prompts that qualified as pain flare-ups throughout the nine days of EMA, at the participant level and at the sample level respectively.

TABLE 5.1. Sample characteristics (n=67)		
Characteristics	**Mean (SD) or Count (%)**	**Median (IQR)**
Baseline visit		
Age (years)	41.19 (12.29)	41.00 (20.00)
Gender		
Women	38 (56.70%)	
Men	22 (32.80%)	
Other	1 (1.50%)	
Preferred not to answer	6 (9.00%)	
BMI (kg/m^2)	28.18 (6.53)	27.27 (7.99)
Ethnicity		
Caucasian	16 (23.88%)	
Other	18 (26.87%)	
Preferred not to answer	33 (49.25%)	
Highest level of education		
Elementary school	6 (9.00%)	
High school	16 (23.90%)	
Post-secondary education	45 (67.10%)	
Back pain duration at baseline visit (in weeks)	11.37 (7.01)	9.14 (10.57)
Brief Pain Inventory (Pain Severity subscale, 0-10)	4.75 (1.89)	4.50 (2.50)
Pain Catastrophizing Scale (PCS total, 0-52)	16.93 (11.36)	15.00 (16.50)
SPA indices		
SPA-Sensory widespread (dysfunctional EIH at hands, PPT change, kPa)	-18.87 (83.86)	-31.69 (69.87)
Pre SPA task PPT at hands	287.04 (141.61)	259.48 (223.89)
Post SPA task PPT at hands	265.93 (164.02)	212.96 (212.03)
SPA-Sensory localized (dysfunctional EIH at low back, PPT change, kPa)	-11.58 (63.02)	-20.39 (57.46)
Pre SPA task PPT at low back	283.57 (194.41)	235.39 (205.73)
Post SPA task PPT at low back	259.46 (180.01)	214.26 (196.46)
SPA-Pain (pain NRS 0-100 change)	23.92 (24.29)	20.00 (32.75)
First repetition of tailored lifts (evoked pain intensity NRS, 0-100)	25.60 (23.50)	20.00 (20.00)
Ten repeated tailored lifts (peak evoked pain intensity NRS, 0-100)	49.61 (28.58)	50.00 (43.75)
SPA-Psych (SPA task-evoked pain catastrophizing, 0-24)	2.74 (4.20)	0.50 (3.25)

Ecological Momentary Assessment (EMA)		
EMA completion rates per participant (%)		
EMA-Pain	55.61 (26.30)	66.67 (37.04)
EMA-Mood	55.89 (26.38)	66.67 (37.04)
EMA daily life aggregated repeated measures		
EMA-Pain (NRS 0-100)	42.64 (19.72)	37.50 (26.45)
EMA-Mood (Likert-scale, -5, very bad to +5, very good)	1.56 (2.13)	1.75 (2.87)
EMA-based IPV indices		
iSD	11.94 (5.41)	11.03 (6.31)
iAC	0.11 (0.23)	0.09 (0.29)
iMSSD	263.10 (264.61)	187.31 (260.36)
Pain-only flare-up (iPAC, %)	25.19 (14.00)	25.00 (16.67)
Pain-mood flare-up (iPAC, %)	8.61 (8.84)	6.90 (14.29)

SD indicates Standard Deviation; IQR, interquartile range; BMI, body mass index; PCS, pain catastrophizing scale; EIH, exercise-induced hypoalgesia; SPA, sensitivity to physical activity; PPT, pressure pain threshold; kPa, kilopascal; NRS, numerical rating scale; EMA, Ecological Momentary Assessment; IPV; intraindividual pain variability (including indices of pain fluctuations and flare-ups); iSD, intraindividual standard deviation; iAC, intraindividual autocorrelation; iMSSD, intraindividual mean square successive difference; iPAC, intraindividual probability of acute change.

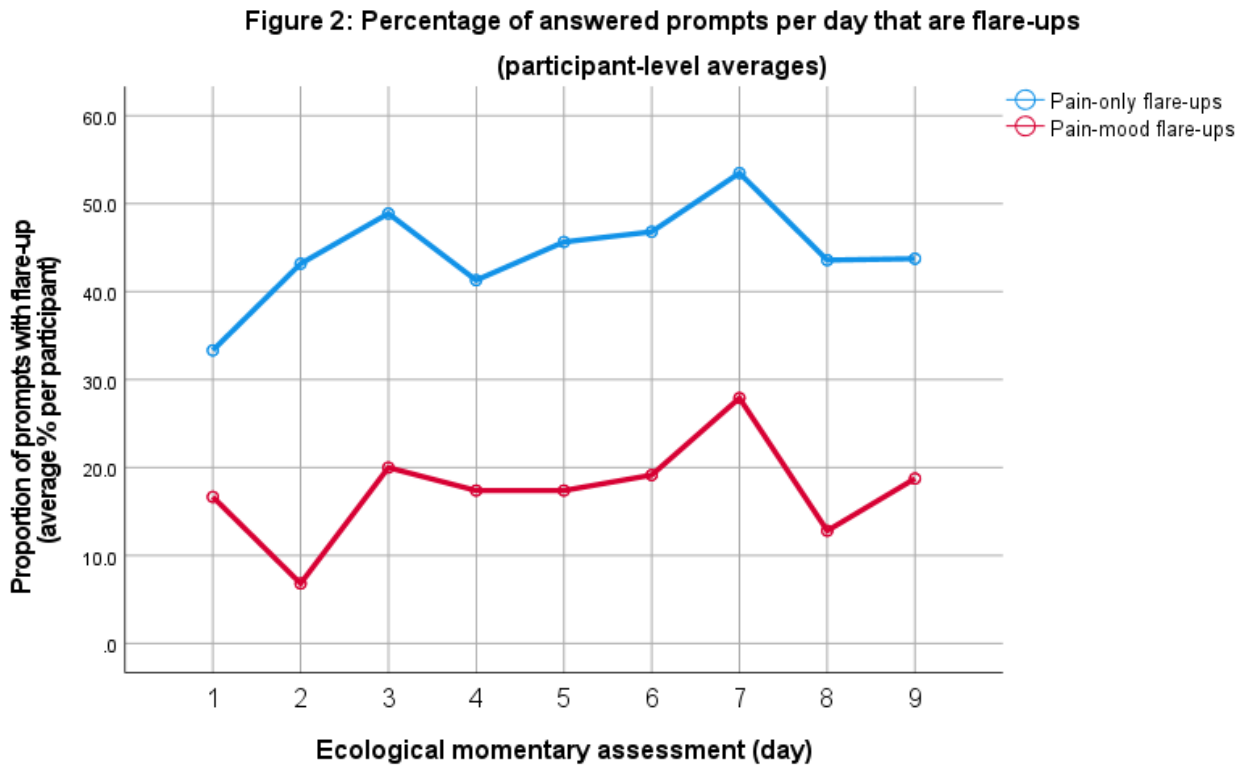

FIGURE 5.2. Percentage of answered prompts per day that are flare-ups (participant-level averages). This figure represents the daily-life prevalence of flare-ups experienced by a participant on average throughout the nine days of ecological momentary assessment (EMA). Specifically, for every participant, the percentage of answered EMA prompts per day which qualified as flare-ups was computed. The mean was then calculated across all participants, for each day, and then graphed according to pain flare-up types (as defined in the Methods section).

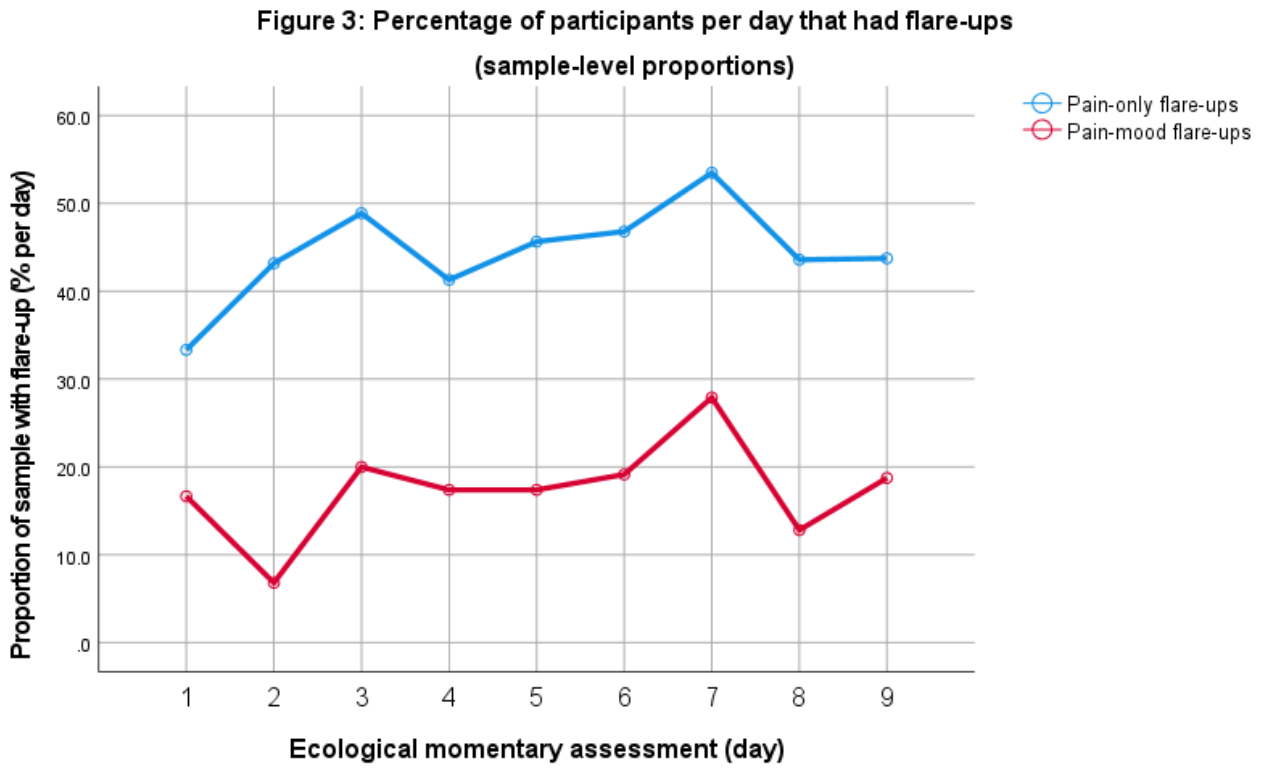

FIGURE 5.3. Percentage of participants per day that had flare-ups (sample-level proportions). This figure represents the daily-life prevalence of flare-ups experienced by this sample of study participants throughout the nine days of ecological momentary assessment (EMA). Specifically, from the number of participants who answered at least one EMA prompt per day, the proportion of participants with at least one flare-up per day was calculated and converted into a percentage. This was graphed according to pain flare-up types (as defined in the Methods section).

5.4.1. Exploratory correlations

Since several variables had a skewed distribution, Spearman's correlations were carried out to explore for potential associations. Between the predictors of interest (four SPA indices, BPI-Pain, and PCS) and the outcomes of interest (five IPV indices: iSD, iAC, iMSSD, iPAC pain-only flare-up, and

iPAC pain-mood flare-up), 29 out of 30 pairings were not significantly associated ($p>0.05$) despite the fact no significance threshold adjustments were made for multiple comparisons. That said, the one potentially significant correlation found was between widespread SPA-Sensory and pain-mood flare-ups, such that a post-task lowered remote pain threshold (i.e., dysfunctional widespread EIH) was associated with greater intraindividual frequency of pain-mood flare-ups ($r_{spearman}$ =-0.338, p=0.012).

5.4.2. Exploratory GLMM (multilevel logistic regressions)

Exploratory GLMM (multilevel logistic regressions) between the predictors of interest (four SPA indices, BPI-Pain, and PCS) and the two IPV indices for pain flare-ups (pain-only flare-up, pain-mood flare-up) revealed the following: 11 out of 12 pairings were not significantly associated ($p>0.050$). However, an association was found between widespread SPA-Sensory and pain-mood flare-ups (odds ratio=0.997, p=0.020), such that a post-task lowered remote pain threshold (i.e., dysfunctional widespread EIH) was associated with greater odds of pain-mood flare-ups.

5.5. DISCUSSION

This is the first study to prospectively explore the predictive value of clinical indices of SPA for pain-related fluctuations and flare-ups in the daily lives of people with back pain. Surprisingly, the only predictor of interest to show prognostic value was widespread SPA-Sensory (dysfunctional EIH). While previous research found that SPA-Pain and SPA-Psych indices have prognostic value for daily-life pain and mood ratings respectively (63) as well as for three-month pain-related outcomes (21, 25, 32), we did not find any predictive value for SPA-Pain and SPA-Psych in relation to any IPV indices. Also, localized SPA-Sensory seemed a likely candidate since the localized EIH response that it tracks is focused on the patient's primary area of pain complaints (i.e., the low back for patients with back pain)–yet no such prognostic value was found.

Similarly, neither BPI-Pain nor PCS demonstrate predictive value–this, however, is less surprising. There have been mixed findings in the literature. While daily-life pain intensity has been previously found to predict intraindividual standard deviation of pain (64) and momentary pain

exacerbations (16), it has also been found that daily-life pain intensity does *not* show a clear association with multidimensional pain flare-ups (16). Of particular interest, our findings are consistent with a study with low back pain patients that specifically used clinically administered patient-level measures (e.g., BPI and PCS) as predictors instead of daily-life measures, and similar to our results did *not* find any association with their daily-life IPV indices (15). Moreover, although the presence of momentary stress or depression have been found to predict risk of flare-ups in some studies (17, 64), our lack of predictive value for SPA-Psych (situational catastrophizing) and PCS is consistent with other research that failed to find predictive value when using psychological variables regardless of whether the measure was EMA-administered such as daily pain catastrophizing (16) or clinically-administered such as the PCS (15). Thus, using clinically-administered patient-level measures to predict IVP in daily life is a challenging area of research in need of further investigation.

Nonetheless, we did find prognostic value for the widespread SPA-Sensory index. This prognostic value for the frequency or odds of pain-mood flare-ups showed up in *both* the exploratory Spearman's correlations *and* the exploratory multilevel logistic regression analyses. Moreover, although this is the first study investigating whether a measure of dysfunctional EIH (increased sensitivity following physical activity) predicts flare-ups, previous research did find prognostic value of dysfunctional EIH for other clinical outcomes (33, 34). Also, past studies found an association between greater sensory hypersensitivity measured by PPT and clinical pain intensity among people with back pain (65) as well as other research showing that remote site sensory hypersensitivity is a PPT feature that distinguishes people with back pain from healthy controls (47). Thus, our results for the prognostic value of widespread SPA-Sensory appear to be broadly aligned with the EIH and PPT literature.

Moreover, the multilevel logistic regression analyses found that for every one kPA decrease in post-task pain threshold (i.e., dysfunctional EIH), the odds of experiencing a pain-mood flare-up in daily life increased by 0.3% ($p=0.020$). While this might not seem like much, the mean and median post-SPA task decreases in PPT in our sample were 18.87 kPa and 31.69 kPa, respectively, which

translate to a 5.66% and 9.51% increase in odds of experiencing a pain-mood flare-up. In exploring the quartiles, a quarter of our participants experienced a 60.79 kPa or greater post-task decrease in PPT which translates to an 18.24% or greater increase in odds of experiencing a pain-mood flare-up. Thus, the widespread SPA-Sensory index (dysfunctional EIH) may help to identify a proportion of patients with back pain that have an important increase in odds of experiencing pain-mood flare-ups in their daily life. It is interesting to note that these findings relate to the more clinically meaningful pain-mood flare-ups, and not the unidimensional pain-only flare-ups. According to consensus among patients, clinicians, and researchers, flare-ups that are truly disruptive in daily life are multidimensional–as opposed to unidimensional pain-only flare-ups or pain-only defined fluctuations indices for IPV which are not necessarily distressing or disruptive (1-3, 16).

This study's results have important clinical implications. Simply making flare-ups more predictable can be helpful in itself for patients, since it can improve the sense of control over one's pain condition in daily life and may attenuate the interruptive power of unexpected flare-ups (4). Left unaddressed, research has found that the greater the unpredictability of pain, the greater the pain intensity, disability, and distress (8-10, 66). Otherwise, since exercise therapy has been consistently recommended by clinical practice guidelines for the care of people with back pain (67-72) and since it is also showing up consistently as the top recommended treatment intervention for SPA itself (29, 73), greater predictability of dysfunctional EIH-related flare-ups may help to inform clinicians on the use of risk stratification to prescribe exercise therapy more gradually and to identify when added support is warranted (12, 18, 74, 75). In fact, Suri et al.'s 2018 study found that physical therapy is a protective factor against the odds of experiencing pain flare-ups in daily life (17). Thus, widespread dysfunctional EIH may indicate the need for mitigation strategies such as risk-stratification, conservative exercise prescription, and added physical therapy support. The mitigation of the odds of pain-mood flare-ups can in turn improve not just the quality of day-to-day life, but it can also help to support adherence to physical activity-based treatment interventions and rehabilitation (12, 18, 74, 75).

Furthermore, the prognostic value of widespread SPA-Sensory suggests that central sensitization processes are relevant for multidimensional pain flare-ups (18, 19, 45, 47). In particular, as described in the dysfunctional EIH literature, dysfunctional conditioned pain modulation or other central mechanisms (e.g., greater release of proinflammatory than anti-inflammatory mediators by the immune system) which sensitize central nociceptive processing of sensory input may be at play here (18, 19, 45, 73, 76). However, further research is needed to clarify which distinctive features of dysfunctional widespread EIH are in fact contributing to its predictive value for multidimensional pain flare-ups. This, in turn, may indicate the use of centrally targeted treatment interventions.

The findings of this study should be interpreted considering the following limitations. Given the exploratory nature of these analyses and the large number of potential associations that were investigated, no significance threshold adjustments were made for multiple comparisons (maintained at $p<0.05$) and as such the risk of type I error (false positive) was elevated. Furthermore, most of the investigated associations were non-significant. It is possible that more associations would have been detected as significant had our sample size of n=67 been larger or our EMA completion rate of a mean of 55.61% and 55.89% per person for momentary pain and mood, respectively, been greater. That being said, May et al. conducted a systematic review of pain studies using EMA and found that the average sample size of such studies was n=62.7 (median of n=42) (13). They also found that the mean EMA completion rate was 84%, with a few studies at approximately 50%, and a third of the studies included in this systematic review did not report their EMA completion rates (13). Finally, it is worth noting that although the IVP indices were computed with our EMA data based on evidence-informed recommendations (5), this remains a relatively new approach. In particular, despite being developed based on the findings from the consensus of experts and people living with back pain as well as from empirical research (1-3, 16), this study's pain-mood flare-up variable was operationalized and calculated with our EMA data in a way that was not previously done and has yet to be validated in future research.

In conclusion, the SPA-Sensory index (dysfunctional widespread EIH) was the only predictor of interest to show prognostic value for daily-life IPV. It did so consistently across two different types of analyses and in relation to the same outcome measure, pain-mood flare-ups. This outcome measure is a proxy for multidimensional flare-ups, which is arguably the most meaningful pain variability measure for patients. Making these flare-ups more predictable is helpful in itself for patients but may also further serve to inform clinicians on risk-stratified dosage of exercise therapy and when to employ additional physical therapy support.

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CHAPTER 6: GENERAL DISCUSSION

6.1. OVERALL SUMMARY OF FINDINGS

This thesis set out to advance the assessment of pain-related sensitivity to physical activity (SPA) among adults with chronic musculoskeletal pain and adults with back pain by addressing a number of gaps in the literature. These gaps included determining which research-based method of SPA assessment is superior, whether SPA maps onto daily life as intended, and what is the prognostic value for pain-related outcomes at a cross-sectional level, immediate short-term (subsequent nine days), and longer term (three-month follow-up). Study 1 found that, compared to the existing SPA measures found in the literature (self-paced walking SPA task and the standardized canister lifting SPA task), the novel individually tailored lifting SPA task was most effective at evoking pain and it was the only SPA measure to be associated with pain-related outcomes and measures of temporal summation of pain. At the outset, it was hypothesized that all three SPA tasks would show associations with pain-related outcomes and sensory and psychological measures, but only the tailored SPA task did so and none of the psychological measures came up in the significant associations. Study 3 found that clinically administered SPA measures are indeed associated with corresponding constructs in daily life, and that this association contributed explained variance even when controlling for commonly used pain and catastrophizing questionnaires. This supports the hypotheses for this study, with the exception that neither of the SPA sensory indices (task-evoked pressure pain threshold changes) showed an association with daily life momentary pain nor with any other of the SPA indices. Finally, Studies 1, 2, and 4 contributed evidence in support of SPA's prognostic value for pain-related outcomes at the cross-sectional, three-months, and immediate short-term, respectively. This supports the hypotheses associated with those studies, but only partially since there was at least one (but not all) SPA measure showing prognostic value for at least one (but not for all) outcome of interest for each study.

Altogether, the studies of this thesis reveal certain patterns of consistency in findings and others of inconsistency. Among the SPA indices, SPA-Pain (task-evoked pain intensity) consistently showed cross-sectional associations with self-reported pain severity and disability across Study 1 (chronic musculoskeletal pain) and Study 2 (back pain). Similarly, in Study 3, SPA-Pain was associated with momentary pain intensity in daily life. However, this cross-sectional association between SPA-Pain and pain-related outcomes did not carry over to longitudinal prognostic value. When looking at three-month outcomes in pain and disability, only SPA-Psych (task-evoked situational pain catastrophizing) showed prognostic value. When controlling for the baseline clinical measure corresponding to the outcome (disability, pain severity) and for baseline pain catastrophizing, SPA-Psych was only predictive of disability. SPA-Psych did not come up again as a predictor in the subsequent studies. From the standpoint of ecological and construct validity though, SPA-Psych did show consistency with SPA-Pain in Study 3, in that SPA-Psych showed a near-significant association with its corresponding construct of momentary mood in daily life. Finally, a surprising inconsistency between Study 4 and the three earlier studies, is that SPA-Sensory (dysfunctional widespread exercise-induced hypoalgesia measured as task-evoked pressure pain threshold change at a body site distal from the clinical back pain) showed prognostic value for flare-ups in daily life. This was surprising since neither of the SPA-Sensory indices (whether measured at a local or distal site from the clinical back pain) showed any associations with pain-related outcomes of interest in the earlier studies of this thesis. Moreover, when considering the interrelations between SPA-Pain, SPA-Psych, and SPA-Sensory, the SPA-Sensory indices were not associated with either of SPA-Pain and SPA-Psych. Yet, SPA-Pain and SPA-Psych were correlated with one another. Future research needs to build on these exploratory studies in order to elucidate what may be the reasons for these inconsistencies or to bring to light further consistencies in findings. It is worth noting, however, that these findings highlight the important value in adopting a multidimensional framework when investigating SPA. Without this multidimensional range of SPA indices, the extent of the findings in this thesis would have been greatly reduced. Furthermore,

acknowledging the multidimensional complexity of possible sensitized responses to physical activity is aligned with ecological validity recommendations that push against oversimplifying constructs (1, 2).

Although the Studies in this thesis were predominantly exploratory in nature, they yield a first set of findings that provide guidance on which methods of SPA assessment to use moving forward in research as well as justifying the continued use of SPA measures with supporting evidence for prognostic value as well as ecological and construct validity. In this general discussion section, the implications of these findings will be discussed within the broader contexts of SPA assessment development, clinical implications, and theoretical implications. However, these downstream implications are understood to be contingent on future larger and more robust studies that replicate and confirm the exploratory findings from this thesis, which will be discussed in the limitations section.

6.2. IMPLICATIONS FOR THE DEVELOPMENT OF SPA ASSESSMENT

The studies presented in this thesis have advanced SPA assessment, but several other considerations have yet to be investigated. First, a more detailed summary of our Study findings relevant to advancing SPA assessment will be provided here, then the gaps and other considerations will be discussed.

The first advance made by this thesis was in Study 1 (Chapter 2) where the individually tailoring the difficulty of the SPA task to each participant, resulted in the greatest amount of pain on average (24.46/100), evoked at least a minimally clinically important intensity of pain (≥20/100) in the greatest proportion of participants (57.76%), and showed the best prognostic potential (cross-sectional association with pain-related outcomes). The tailoring procedure was modelled from quantitative sensory testing (QST) protocols for temporal summation of pain and ensured that the starting point of the SPA task was similarly provocative for all participants (3, 4). This is likely the differentiating factor from the other SPA measures which did not correlate with the pain-related outcomes. In the self-paced walking SPA task, participants may be reluctant to reach a walking intensity that can provoke pain and therefore may perform at a reduced capacity (5, 6). In the standardized canister lifting SPA task, the

pre-determined difficulty level is the same for all and is not adjusted to match the baseline level of participants' sensitivity, thus possibly undershooting or overshooting the extent of pain provocation. The discussion section associated with Study 1 (Chapter 2, section 2.5) further explores the potential reasons why these SPA tasks from past literature did not correlate with pain-related outcomes in Study 1; such as that the statistical significance threshold was possibly raised too high for our modest sample size due to the highly heterogenous study population (adults with a range of chronic musculoskeletal pain conditions, as opposed to targeting a single pain condition). Thus, Study 1 has shed light on the relative advantages of using an individually tailored paradigm for setting the difficulty of a SPA task, over self-paced or standard pre-determined difficulty approaches. This is the first study that concurrently compared different task-based SPA measures. While future studies would need to verify the replicability and generalizability of these findings, the Study 1 findings have nonetheless provided initial support to move forward in future research with an individually tailored approach to task-based SPA assessment.

A more contentious issue is whether SPA-Pain is associated with underlying psychological factors such as pain catastrophizing or pain-related fear. Our Study 1 did not find such associations and discusses (Chapter 2, section 2.5) the mixed state of the literature on this topic. This was also discussed in the introduction of this thesis (Chapter 1, section 1.4.1.4), recognizing that one systematic review supported that pain catastrophizing, pain-related fear and other psychological factors are associated with SPA among musculoskeletal pain conditions (7) but that two other reviews mostly failed to find such associations in their included studies (8, 9). It may be that psychological factors are potentially relevant for SPA-Pain but not a consistently integral part of the SPA-Pain experience. Alternatively, the selection of factors underlying SPA-Pain may be highly individual, and certain individual associations may be hidden when considering associations at a group level. Another way to look at the potential role of psychological factors in relation to SPA is to consider them as an index of SPA rather than an underlying process. When Study 2 broadened SPA assessment to include a multidimensional range of

indices, including a psychological one (SPA-Psych, i.e. a task-specific situational pain catastrophizing index), the descriptive statistics revealed that 41 out of 97 participants had a score of zero for the SPA-Psych index. Thus, there may be an important psychological aspect to multidimensional SPA but not in all cases. It was also found in Study 2 that SPA-Psych was correlated with SPA-Pain, further suggesting role for psychological factors as an index of SPA. Also, it is worth mentioning that other SPA task-related situational psychological responses have yet to be investigated in future research since the studies in this thesis only used situational catastrophizing as part of its SPA-Psych index.

An important recommendation made in Study 2 for the design of SPA assessment in future studies, is to cast the net broadly using a multidimensional approach to SPA assessment that monitors a variety of sensitized reactions to physical activity. In this way, the most important form of sensitized response to physical activity can be identified for each individual. An important aim with SPA assessment should be to identify any negative immediate response to physical activity that impacts an individual's function, overall pain experience, and engagement with prescribed physical activity-based treatment interventions. Limiting SPA assessment to a unidimensional approach, such as evoked pain intensity, has advantages in terms of providing deep insights on a specific facet of SPA but it restricts its clinical usefulness in trying to identify salient barriers to the rehabilitation goals of an individual living with disabling pain. Also, reducing SPA to a unidimensional response may reduce ecological validity due to a concern of oversimplification, in terms of Holleman et al.'s simplicity-complexity consideration of "real-world" experiences (1, 2). Thus, future research is encouraged to use a multidimensional approach to SPA assessment.

Other ways in which the studies in this thesis advanced the assessment of SPA include support for the construct validity of SPA in relation to underlying sensory processes. Study 1 (Chapter 2) found that TSP explained variance in SPA-Pain, but pressure pain threshold did not. Other studies, which similarly measured SPA-Pain by tracking pain-related changes in relation to a physical activity of stable intensity, also support TSP as an underlying process of SPA-Pain (3, 10-13). TSP (also referred

to as “wind up” pain) refers to the “progressively increasing activity of dorsal horn neurons” in response to repetitive noxious stimuli (14). This is consistent with the construct that this SPA-Pain measure seeks to capture, namely a dynamic state of sensitization specific to physical activity as a repetitive noxious stimulus. Since SPA assessment is designed as a dynamic pain-related sensitivity measure (contextualized to physical activity), this may be why no association was found with baseline pressure pain threshold measures which can be considered as static pain sensitivity measures (13). In fact, a study conducted among people with back pain found that static pain sensitivity measures such as pressure pain threshold were associated with resting pain but not SPA, and that dynamic pain sensitivity measures such as temporal summation of pain were associated with SPA but not resting pain (13).

Another point to consider for SPA assessment is that Study 3 provides preliminary support that the lifting SPA task is representative of daily life as intended (i.e., ecological validity (2)). Indeed, the design of the lifting SPA task sought to emulate a painful functional task that is likely encountered in daily life. By using ecological momentary assessment (EMA), Study 3 demonstrated that the clinically administered SPA-Pain index predicts its corresponding daily life construct of momentary pain, and that SPA-Psych predicts momentary mood in daily life. Alignment between these SPA indices and their corresponding constructs also supports construct validity. Although SPA is focused on the context of physical activity, SPA-Pain is nonetheless expected to be a significant part of the daily life pain experience and SPA-Psych is expected to be a significant part of the daily life mood experience. Showing these associations therefore helps support construct validity of these different SPA indices.

6.2.1. Gaps in standardized SPA assessment research

Overall, this thesis advanced SPA assessment from the standpoint of certain design considerations and various types of validity (construct, ecological). However, an important gap that remains in the research area of SPA assessment is the psychometric consideration of reliability (8). This has only been evaluated in healthy (pain-free) participants so far (15, 16). These SPA studies

considered baseline pressure pain threshold (PPT) done prior to aerobic cycling exercises and found excellent within-session (ICC=0.86-0.95) and between-session (ICC=0.84-0.89) reliability for these baseline PPT measures (15, 16); but when these PPT measures were considered as pre-post changes relative to a cycling exercise (i.e., SPA) then the between-session reliability found was fair for absolute change scores (ICC=0.40-0.54) and poor for percent change scores (ICC ≤ 0.40) (15, 16). Thus, the reliability appears lower when considering change scores of test-stimuli than the raw measure of an individual test-stimulus. It would be interesting to see in future research whether there is a similar drop in test-retest reliability when pre-post change in other SPA indices are considered; for instance, it can be hypothesized that for SPA using evoked pain intensity as an index, the test-retest reliability will be lower than for the numerical rating scale of pain intensity which has been found to be moderate to high, ranging from 0.67 to 0.96 (17). Also, no study to date has evaluated the test-retest reliability of SPA in a musculoskeletal pain population, which may potentially further reduce the reliability given that SPA responses are quite variable within musculoskeletal pain conditions (8, 18). Moreover, there may be limits on the extent to which SPA measures can show test-retest reliability since it is not known whether the construct of SPA is stable enough over time to support its test-retest reliability. Nonetheless, evaluating the stability of the SPA construct and its test-retest reliability are important gaps in the SPA literature that this thesis did not address. Future research is needed on this topic.

When considering the points that this thesis did explore, it is important to point out that the studies in this thesis were predominantly exploratory in nature and require larger studies to revisit their conclusions more robustly. For instance, future research has yet to compare an individually tailored approach, a self-paced approach, and a standard pre-determined difficulty approach to SPA assessment by using the exact same physical task. Study 1 considered SPA tasks (and their associated manner of setting the task difficulty) by using existing SPA task procedures from the literature and a novel one that was described in a past study but not yet tested—this served as a form of *in vivo* literature review of SPA tasks. However, the SPA tasks differed not only in the manner in which the task difficulty was

set (self-paced, pre-determined, or individually tailored) but also in the SPA task itself (six-minute walking, 18-canister lifting, 10-repetition custom weight-plate lifting apparatus). The variability in SPA tasks is a confounding factor. Therefore, for a true "apples-to-apples" comparison in future research, a single task should be selected (e.g., the 10-repetition custom weighted lifting apparatus) and the three aforementioned ways of setting the task difficulty should be compared using this same task.

There are other task-related considerations for SPA assessment that have yet to be explored in future research. For instance, it is not yet known whether there is additional value in including more than one SPA task. All the studies in this manuscript focused on a single SPA task at a time, yet a battery of SPA tasks may prove more valuable. It must be taken into consideration, however, whether the benefit of additional SPA tasks outweighs the additional burden on the patient and the clinician. Another aspect which the studies in this thesis did not explore is the selection of the SPA task. More research is needed to clarify what can guide the decision-making process for SPA task selection. While a repeated lifting task is arguably highly relevant for a back pain population, other tasks may also be relevant to test under the SPA paradigm for people with back pain. Naturally, this needs to also be explored in other patient populations. Moreover, even within the same patient population, there can be important variability for what is most relevant from one individual to the next. In the next section, the question of standardized versus personalized approaches to SPA assessment will be discussed.

6.2.2. Standardized versus personalized SPA assessment

An important consideration for SPA assessment that is yet to be explored is whether to adopt a standardized or personalized approach. This likely depends on the desired application, as there are pros and cons to either approach. An important advantage in favour of adopting a standardized approach to assessing SPA is that it facilitates group comparisons as well as synthesizing research findings (5). On the other hand, personalizing the SPA task (determining which physical activities to test) and SPA index (determining which task-evoked reactions to track) to each participant introduces a higher degree of difficulty in analyzing the sample's distribution in evoked pain-related responses, in determining the

prognostic value of SPA, and in determining the underlying mechanisms of SPA. That being said, there are important advantages to personalizing SPA assessment in terms of identifying the task(s) and task-related SPA reactions that interfere the most with the daily life of a particular individual, as well as, setting the task difficulty and duration according to this individual's daily-life needs. This personalized approach has the potential to increase prognostic value as well as patient engagement. Thus, standardized SPA assessment seems best suited for research applications, whereas personalized SPA assessment seems advantageous for clinical applications. Future research should consider using preference-based assessment methodologies to develop ways of standardizing the decision-making process of incorporating individual patient preferences in the administration of an assessment. This can be modelled after the methodology of the Patient Generated Index used in the area of health-related quality of life research (19, 20). The Patient Generated Index allows for an individualized assessment of health-related quality of life by asking patients to identify the top five areas of their lives affected by a specified health condition, rating the severity using a 0-10 scale, and weighing the relative importance of each of those areas using a points system (19, 20). Future research may consider similarly developing a patient-generated SPA index by breaking down parts of the SPA assessment where preferences can be expressed, rated, and weighted for a composite score (e.g., selection of SPA task to evaluate, its parameters, and the task-evoked reactions to track).

6.3. CLINICAL IMPLICATIONS FOR SPA

The clinical implications for SPA will be discussed in terms of the potential role of SPA as a prognostic factor, process variable, and outcome variable.

6.3.1. Can SPA assessment help to enhance activity-based treatment interventions?

The studies in this thesis have advanced SPA assessment by being among the first to contribute evidence on prognostic value. Study 1 pointed to the potential prognostic value of the SPA tailored lift task, due to cross-sectional associations with self-reported pain and disability. Study 2 demonstrated that SPA-Psych (situational pain catastrophizing) evoked by the tailored lift task has prognostic value

for pain-related disability at three-month follow-up. Study 4 showed that SPA-Sensory index, measured as widespread dysfunctional exercise-induced hypoalgesia in relation the tailored lift task (pre-post changes in pressure pain threshold at a distal site from the back pain), has prognostic value for flare-ups in daily life. Altogether, the studies in this thesis suggest that SPA may be an important prognostic factor to add to routine clinical assessments of musculoskeletal pain. Future research needs to determine whether SPA adds value to current prognostic models for musculoskeletal pain conditions such as back pain (21-23). If yes, then SPA assessment is likely to be most helpful in informing how to personalize the prescription of physical activity-based treatment interventions such as graded activity, which may in turn enhance the effectiveness of those interventions.

For instance, SPA-Pain may shed light on whether activity-based interventions should be performed without any increase in pain or if it is acceptable to have some increase in pain during the intervention (6). The systematic review by Smith et al. demonstrated that exercising into pain for the management of chronic musculoskeletal pain conditions may provide small additional benefits in the short term but is equivalent to exercising without pain in the medium and long term (24). Smith et al.'s review (24) did not take SPA-Pain into consideration. Perhaps greater benefits of exercising into pain may be achieved among individuals with low levels of SPA-Pain, since low SPA-Pain indicates that the pain evoked with initiation of activity is expected to remain relatively stable or reduces with continued engagement. In other words, since there is little concern associated with pain during activity for individuals with low levels of SPA-Pain, they may initiate and progress an intervention such as graded activity at a higher intensity and dosage which may help obtain therapeutic benefits faster.

On the other hand, for individuals with high levels of SPA-Pain, it could be important to limit as much as possible any increases in pain with activity since the high SPA-Pain levels suggest that pain can not only be easily evoked by activity but may also summate quite rapidly. In these cases, high SPA-Pain is likely to be an especially important barrier to initiation and continued engagement in activity-based treatment interventions (6, 25, 26). Specifically, the risk associated with high SPA-Pain

may be mitigated by initiating and progressing with a more conservative intensity and dosage of activity-based interventions (6, 8, 27, 28). Indeed, related research found that exercise parameters can be adjusted to lower intensity and volume than is typically required for fitness-based improvements and yet still achieve clinical outcomes such as improved pain and activity limitations among people with chronic musculoskeletal pain (27, 29). Another strategy is to strategically adjust the activity-based treatment intervention to target specific body parts or to use a specific type of exercise, and then gradually progress to challenge what is more closely associated with SPA. If pain is localized, research has found that a useful strategy is to initially prescribe exercise to body parts distal to the clinical pain site since it is likely to evoke a non-sensitized response as opposed to a SPA response (6, 8, 18, 27, 28), and exercises directly engaging the localized pain site may be incorporated later as a progression. If pain is widespread, then starting off with a self-paced intensity aerobic exercise (low-to-moderate intensity) is least likely to evoke a SPA response (6, 8, 18, 27, 28), and resistance exercises may be incorporated later as a progression. Moreover, patients with high SPA-Pain may also benefit from educational forewarning of the likelihood for increases of pain with the intervention but with reassurance and explanation that these increases of pain are not dangerous (6, 8, 27, 28, 30). Finally, another SPA mitigation strategy would be to assist patients at risk with additional physical therapy or analgesic support (26, 28, 31). For instance, transcutaneous nerve stimulation may be combined with an activity-based intervention to reduce the amount of SPA experienced (32-37). Other non-pharmacological interventions, such as manual therapy, have been found to reduce central nociceptive excitability and improve central nociceptive inhibition which ultimately may attenuate the extent to which SPA is experienced during an activity-based intervention (37-39). Similarly acting pharmacological interventions, which appear in research to be relevant for reducing SPA (5, 40, 41), may also be considered as additional support for individuals with high SPA who will be engaging with activity-based treatment interventions.

In addition to SPA-Pain helping clinicians anticipate whether a patient is at risk of experiencing increases in pain during an activity-based intervention, the SPA-Sensory index (indicating dysfunctional widespread exercise-induced hypoalgesia) may also provide helpful insights. Study 4 found that this SPA-Sensory index has prognostic value for flare-ups, adding to the emerging body of literature that explores the prognostic factors for daily-life pain fluctuations and pain flare-ups (42, 43). Making flare-ups more predictable has been found to be helpful in itself, with studies showing a positive impact the overall pain intensity, disability, and distress of a patient (44-46), as well as reducing the interruptive effect on participation in everyday activities (47). For an activity-based intervention such as graded activity, SPA-Sensory might help to warn clinicians when a patient is more prone to flare-ups that may occur in the days following the intervention. In anticipation of this higher risk of flare-ups, past research has found a protective effect from added physical therapy support (26, 31). Clinicians should also considering trying the same SPA risk mitigation strategies as described above in the previous paragraph, such as prescribing and progressing the activity-based intervention more conservatively, providing reassuring education warning that flare-ups may occur but are not dangerous, and considering additional non-pharmacological and analgesic support (6, 8, 27, 28, 30, 37).

Moreover, individual with high levels of SPA-Psych (e.g., using a situational catastrophizing questionnaire in association with a SPA assessment, though it could also be situational fear or other task-specific psychological measures) may indicate a need for activity-based interventions that include explicit consideration of the thoughts and feelings that may occur during that prescribed physical activities, such as Cognitive Functional Therapy (48, 49) or Graded Exposure to feared movements (50, 51).

6.3.2. SPA assessment may help future research to evaluate certain mechanisms of action of activity-based interventions

In the previous section, the clinical implications of using SPA as a prognostic factor were discussed. SPA may also serve as a process variable to evaluate certain mechanisms of action of

activity-based interventions. For instance, for the graded activity intervention, it could be useful for future research to monitor whether SPA-Pain remains at a manageable level during the intervention and whether it improves over time as intended. This may provide new insights, since most research on graded activity has focused on end-point results in pain-related outcome variables rather than on evaluating mechanisms of action with process variables (50, 52). Also, future research may investigate whether the effectiveness of graded activity differs between individuals that have significant SPA reactions during the activity bouts of the intervention versus individuals for whom these SPA reactions remain at a low level. This may help to explain why research currently shows limited treatment effectiveness with graded activity (50, 52). Similarly, SPA-Psych can be a valuable process variable for determining whether activity-based interventions that incorporate psychological process interventions more explicitly, such as Cognitive Functional Therapy (48, 49) or Graded Exposure to feared movements (50, 51), have the intended effect on the negative thoughts and feelings experienced during painful movements and physical activities. SPA-Psych evaluates situational psychological responses occurring in the context of physical activity. Therefore, SPA-Psych may potentially also serve to identify individuals who are most likely to benefit from such psychologically-informed activity-based interventions. Future research is needed to investigate these topics.

6.3.3. SPA as a treatment target

SPA itself may also be a treatment target and therefore serve as an important end-point outcome variable. The systematic review by Leemans et al. (53) found that the most effective treatment for SPA is using a physical activity-based intervention such as exercise therapy. Mechanisms-based research supports that greater physical activity levels may address SPA by improving the dysfunctional endogenous pain modulation processes affected by sedentarism (54). For instance, transitioning to a more physically active lifestyle has been found to increase the proportion of M2 macrophage phenotype relative to the M1 macrophage phenotype which would appear to lead to anti-inflammatory cytokines dominating the muscle fatigue metabolite cascade (54-56). Also, systemically, the immune

system has been found to produce greater proportion of anti-inflammatory cytokines than pro-inflammatory cytokines after an exercise program (57, 58). Moreover, regular physical activity is thought to lead to increased expression of the endogenous opioid system, which would inhibit phosphorylation of the NR1 subunit of the NMDA (N-methyl-D-aspartate) receptor in the brainstem, and reduce serotonin transporter expression (54). Furthermore, Lima et al. review several studies which indicate that physical activity can lead to reduced temporal summation of pain, improved conditioned pain modulation, as well as better function of endogenous opioid, serotonergic, endocannabinoid systems (59). Physical activity-based interventions also improve physical strength and endurance (60), which reduces the risk of experiencing excessive load demand (61) which would potentially contribute to SPA via risk of suprathreshold mechanical stimuli, muscle fatigue metabolites, delayed onset muscle soreness, inflammation, and/or tissue injury.

Thus, physical activity-based treatment interventions such as exercise therapy appear to reduce SPA over time by positively affecting a variety of sensitization mechanisms underlying SPA. However, SPA itself is an important barrier for engaging in these physical activity-based treatment interventions (6, 25, 26). This creates a somewhat circular problem. Therefore, the SPA risk mitigation strategies discussed earlier for enhancing activity-based interventions (section 6.3.1.) are also important for the treatment of SPA itself: managing the prescribed intensity and dosage of a physical activity-based intervention at initiation and progression, strategically choosing which body parts to target first and which type of exercise to start with before progressing to all body parts and types of exercises, preparing the patient with pre-emptive education and reassurance about the potential likelihood of experiencing a SPA response or a flare-up, concomitantly using non-pharmacological and pharmacological analgesic interventions, or to simply provide closer supervision and physical therapy support (6, 8, 27, 28, 30).

6.4. THEORETICAL IMPLICATIONS FOR SPA

The studies in this thesis have important downstream theoretical implications for SPA. While several theoretical models could be discussed, this section will focus on theory related to pain-related activity coping behaviours since it is particularly clinically relevant for SPA. Pain-related activity coping behaviour may inadvertently perpetuate or maintain SPA, but it is also plausible that SPA may influence these activity coping behaviours as well.

Pain-related activity coping behaviour can be understood through the following two complementary theoretical models. The Fear-Avoidance Model (FAM) is supported by research and thoroughly explores the underlying processes associated with avoidance behaviour, which is characterized by avoiding or disengaging from activities that one fears may evoke pain or cause injury (62-64). Supported by an emerging body of research (65-70), the Avoidance-Endurance Model (AEM) builds on the FAM in order to emphasize not only avoidance but also persistence behaviour (originally referred to as "endurance"). Persistence behaviour refers to activity engagement despite the presence of pain, or SPA (65-67). While a certain degree of persistence behaviour may be needed to lower pain and disability levels, excessive persistence behaviour has been linked with worse pain and disability (65-69). The AEM has been expanded to propose four main subgroups of pain-related activity coping behaviours (65-68, 70):

(1) Avoidance (also referred to as fear-avoidance or excessive avoidance).

(2) Persistence (also referred to as endurance copers or overactivity).

(3) Pacing (also referred to as functional performers or adaptive copers), which can be described as having both low persistence and low avoidance since activity engagement is not avoided but is often stopped early so that there is not excessive persistence.

(4) Mixed, which can be described as having both high persistence and high avoidance depending on the activity at hand as well as other possible reasons.

The presence of these patterns of pain-related activity coping behaviour have been found in past studies conducted among people with chronic musculoskeletal pain, which gives an idea of how people cope with SPA for their activity-related behaviours (66-69). According to the AEM theory (65) and its extended motivational perspective (70), it may be suggested that a person with SPA will tend to adopt either a consistent activity pattern (avoidance, persistence, pacing) or a context-specific one (mixed). The AEM suggests that this is influenced by a variety of factors, such as cognitive-affective factors (e.g. pain catastrophizing, pain-related fear) and motivational factors (e.g. self-regulation, goal conflict). Ultimately, pain-contingent interruption of activities will tend to occur when the importance of pursuing the pain relief goal supersedes the activity-related goal (47, 71), though this may be influenced by other contextual or personal factors such as mood (72). If these pain-related interruptions occur frequently and lead to fluctuation in activity levels, this has been linked with increased levels of activity limitations (73). Excessive avoidance and excessive persistence have also been associated with increased levels of activity limitations (69). However, functional pacing that engages in task-limited (not excessive) persistence in spite of pain, in a consistent manner (74), has been characterized with having lower levels of activity limitations (65-68). Future research is needed to investigate whether SPA has an influence on whether an individual will gravitate towards one or another of these activity-related coping behaviours. For instance, it would be interesting to determine whether individuals with high levels of SPA tend to adopt avoidance predominantly as an activity-related coping behaviour. Also, future research has yet to explore whether these pain-related activity coping behaviours affect the relationship between SPA and pain-related outcomes. It seems plausible that the association between SPA and overall pain severity is stronger when an individual adopts a persistence or mixed coping behaviour but that SPA might no longer be well correlated with overall pain severity if an individual tends to engage in pacing or avoidance behaviours. Similarly, it seems likely that the association between SPA and disability is stronger with avoidance or mixed coping behaviour but that this association is weaker with persistence or pacing. Future research has yet to investigate this.

In addition to better understanding the interrelationships between SPA and the AEM pain-related activity coping behaviours, it will also be important to shed light on the clinical recommendations made to patients on how to adjust their activity coping behaviours with respect to their SPA level. Meeus et al. recommend adapting the prescription of physical activity-based treatment interventions according to both the patient's predominant activity coping behaviour and SPA (6). Thus, if a patient's behaviour is characterized by excessive persistence, then an activity pacing intervention would likely work best but some allowances may be made if SPA levels are low. Activity pacing aims to avoid excessive pain exacerbations associated with excessive persistence by modifying daily life activities to be performed in several bouts or reduced to do less overall (69). However, a systematic review found that activity-pacing tends to be prescribed too conservatively and inadvertently approximates avoidance behaviour, resulting in keeping increased activity limitations (69). Activity-pacing needs to keep a high enough activity level and to consistently aim to increase that activity level, though a high level of SPA may indicate a need to nonetheless go about it conservatively (67, 69). Interventions for avoiders emphasize increasing activity despite pain but again this may need to be approached cautiously in the presence of high SPA. Ultimately, the aim is to bring patients from one extreme of pain-related activity coping behaviour to the middle, a functional pacing behaviours that is either cautious for high SPA or more intense for low SPA (65, 66). This, in turn, can facilitate the return to previously limited activities and reduces the amount of trail-and-error guesswork that would otherwise have to happen naturally through personal experimentation with SPA (75).

Thus, there appears to be a natural fit between SPA and theoretical models of pain-related activity coping behaviours such as the FAM and AEM. Although these theoretical models do not explicitly use SPA in their terminology, they discuss pain with activity and how this is responded to in terms of predominant activity-related coping behaviors. It would be interesting, however, if future developments of FAM and AEM more explicitly incorporate SPA as part of its discussions. Also, it

would be interesting to see FAM and AEM go beyond simply talking about pain with activity but also to consider how coping behaviours are influenced by how quickly pain summates with activity as well as considers other multidimensional sensitized reactions to physical activity. The studies in this thesis provided guidance on which methods of assessing SPA have prognostic value for pain-related disability and flare-ups, as well as support for ecological and construct validity. Therefore, it seems reasonable to suggest using SPA assessment as described in this thesis for future studies that would investigate the proposed theoretical implications discussed above.

6.5. LIMITATIONS

The findings from this thesis and the discussion that ensued need to be interpreted in light of some limitations. As mentioned earlier in this thesis, the studies in this thesis were predominantly exploratory in nature. There need to be studies with larger sample sizes that replicate and confirm the findings, in particular in relation to prognostic value (76). Sample sizes were adequate from an exploratory standpoint, and the effect of missing data was addressed by using multiple imputations for linear regression analyses and maximum-likelihood parameter estimation for multilevel linear analyses. However, there is a need for studies with larger sample sizes in order to better mitigate the risk of a Type 2 error. It could be that additional associations would have been uncovered in the studies of this thesis with a larger sample size. That being said, small sample sizes are still useful in finding associations that are strong enough to be detected in spite of being less statistically powered. This helps to guide the expensive resources of larger studies towards signals found in exploratory studies.

Moreover, while Study 1 uses a mixed sample of adults with chronic musculoskeletal pain, Studies 2-4 had a sample of adults with back pain recruited upon seeking physical therapy care. The findings of those studies need to be replicated in other patient populations. Study 1 may benefit also from a more homogenous sample in order to better bring out the relevant associations; it could be that the noise associated with having such a heterogenous sample may have led to a Type 2 error. This may

be why Study 1 did not find associations between existing SPA measures and pain-related outcomes, and this may also be why no associations were found between any of the SPA measures and the psychological factors (catastrophizing, fear). For Studies 2-4, in addition to a larger sample size and exploring other patient populations, it would also be interesting to explore whether the same findings are found among individuals with back pain who are *not* seeking physical therapy care.

My supervisor's research lab experienced some technical issues that affected the design of the studies in this thesis. For instance, some unexpected issues occurred with international customs that prevented access to accelerometry devices which were supposed to be used in combination with EMA data. As a result, Study 3 could only look at self-reported EMA data such as momentary pain or mood. However, if future research would have access to both self-reported EMA and accelerometry, then SPA may be directly computed from daily life data. This would open up the possibility of a more robust exploration of the extent to which lab-based SPA measures are representative of how SPA is experienced in daily life rather than looking at adjacently corresponding constructs such as momentary pain and mood. The availability of accelerometry alongside self-reported EMA data would also benefit Study 4 in generating more robust indices of pain flare-ups that are characterized not only by impact on mood but also impact that reduces activity levels, as per the proposed definition of flare-ups by Costa et al. (77). Similar to the unexpected issues that prevented the use of accelerometry, Study 2 was affected by technical issues that prevented the use of temporal summation of pain measures. This restricted the ability for Study 2 to investigate whether the SPA measures were associated with temporal summation of pain measures, as was done in Study 1.

6.6. CONCLUSIONS AND SUMMARY

The studies conducted as part of this thesis have advanced the assessment of SPA by addressing gaps in the literature pertaining to methodology for the assessment of this construct, its prognostic value, and its construct and ecological validity. The methodology for the assessment of SPA was advanced in Study 1 by demonstrating the superior value of the novel individually tailored repeated

lifting SPA task compared to other SPA tasks from the literature (self-paced walking, standardized canister lifting) in terms of evoking pain, showing associations with pain and interference and temporal summation of pain. Moreover, Studies 2-4 together support the importance of using a multidimensional range of SPA indices (SPA-Pain: task-evoked pain intensity, SPA-Sensory: task-evoked pre-post sensory changes in pressure pain threshold, and SPA-Psych: task-related situational pain catastrophizing). As for the prognostic value of SPA, Study 1 pointed to SPA-Pain using a tailored lifting task as a potential prognostic factor, but Study 2 found SPA-Psych instead to be predictive of self-reported disability at three-month follow-up and Study 4 found SPA-Sensory to be predictive of pain flare-ups in daily life. In terms of validity, Study 1 supported construct validity by showing that the SPA tailored lifting task was associated with temporal summation of pain and Study 3 supported ecological validity by showing that SPA-Pain and SPA-Psych were associated with momentary pain and mood in daily life, respectively.

The findings of this thesis support the continued investigation of SPA in favour of shedding more light on its prognostic value, validity, and potential clinical and theoretical implications. In addition to conducting larger, more robust studies to address the limitations discussed above, future research needs to also evaluate the proposed clinical implications for SPA-informed prescription of physical activity-based treatment interventions to mitigate risks of SPA and flare-ups. Similarly, future research needs to explore the theorized relationships and interactions between SPA, activity-related coping behaviours, and pain-related outcomes. Overall, although more research still needs to be conducted, the assessment of SPA appears to have the potential to provide important support for physical activity-based interventions for the treatment and rehabilitation of people living with musculoskeletal pain conditions such as back pain.

6.7. REFERENCES FOR CHAPTER 6

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APPENDIX 1: STROBE CHECKLIST FOR STUDY 1 (CHAPTER 2)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract: Yes, see abstract (identifies current paper as "cross-sectional study")
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found: Yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported: Yes
Objectives	3	State specific objectives, including any prespecified hypotheses: Yes, but use of hypotheses is limited due to the emerging nature of this line of research which lead to the original intention of this study to be mainly exploratory in nature.
Methods		
Study design	4	Present key elements of study design early in the paper: Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants: Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group: Yes
Bias	9	Describe any efforts to address potential sources of bias: Yes
Study size	10	Explain how the study size was arrived at: Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding: Yes

		(*b*) Describe any methods used to examine subgroups and interactions: Yes
		(*c*) Explain how missing data were addressed: Yes
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses: Yes
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed: Yes
		(b) Give reasons for non-participation at each stage: Yes
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders: Yes
		(b) Indicate number of participants with missing data for each variable of interest: Yes (overall)
Outcome data	15*	Report numbers of outcome events or summary measures: Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included: Yes
		(*b*) Report category boundaries when continuous variables were categorized: Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses: All analyses reported.
Discussion		
Key results	18	Summarise key results with reference to study objectives: Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias: Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence: Yes

Generalisability	21	Discuss the generalisability (external validity) of the study results: Yes
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based: Yes

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

APPENDIX 2: STROBE CHECKLIST FOR STUDY 2 (CHAPTER 3)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Yes
Objectives	3	State specific objectives, including any prespecified hypotheses Yes
Methods		
Study design	4	Present key elements of study design early in the paper Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Yes
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Yes

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Yes
Bias	9	Describe any efforts to address potential sources of bias We do not perceive to have any important sources of bias in our study.
Study size	10	Explain how the study size was arrived at Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Yes
		(*b*) Describe any methods used to examine subgroups and interactions Yes
		(*c*) Explain how missing data were addressed Yes
		(*d*) If applicable, explain how loss to follow-up was addressed Yes
		(*e*) Describe any sensitivity analyses Yes
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Yes
		(b) Give reasons for non-participation at each stage Yes
		(c) Consider use of a flow diagram

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Yes
		(b) Indicate number of participants with missing data for each variable of interest Yes
		(c) Summarise follow-up time (eg, average and total amount) Yes
Outcome data	15*	Report numbers of outcome events or summary measures over time Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Yes
		(*b*) Report category boundaries when continuous variables were categorized Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Yes
Discussion		
Key results	18	Summarise key results with reference to study objectives Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Yes

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results Yes
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Yes

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

APPENDIX 3: STROBE CHECKLIST FOR STUDY 3 (CHAPTER 4)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Yes
Objectives	3	State specific objectives, including any prespecified hypotheses Yes
Methods		
Study design	4	Present key elements of study design early in the paper Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Yes
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Yes

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Yes
Bias	9	Describe any efforts to address potential sources of bias We do not perceive to have any important sources of bias in our study.
Study size	10	Explain how the study size was arrived at Our studies sample size was comparable to most other pain studies using ecological momentary assessment. May et al.'s 2018 systematic review on pain studies using ecological momentary assessment found that, when excluding pharmaceutical clinical trials, the average sample size was n=62.7, with a median of n=42. Our study had n=67. May, M., Junghaenel, D. U., Ono, M., Stone, A. A., & Schneider, S. (2018). Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. The Journal of pain, 19(7), 699-716. https://doi.org/https://doi.org/10.1016/j.jpain.2018.01.006
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Yes
		(*b*) Describe any methods used to examine subgroups and interactions Yes
		(*c*) Explain how missing data were addressed Yes
		(*d*) If applicable, explain how loss to follow-up was addressed Yes
		(*e*) Describe any sensitivity analyses Yes
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Yes

		(b) Give reasons for non-participation at each stage Yes
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Yes
		(b) Indicate number of participants with missing data for each variable of interest Multilevel linear modelling is well-suited to accept data from all participants, even in cases of unequal data points due to missing data and does not require any data imputation methods, therefore all participants from our sample can be directly entered in our analyses (Field, 2013, pp.814-865; Hoffman, 2015, pp. 3-27, 281-326; Peugh, 2010). Furthermore, the average completion rates for ecological momentary assessment per participant is provided in the manuscript. Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. Sage. Hoffman, L. (2015). *Longitudinal analysis: Modeling within-person fluctuation and change*. Routledge. Peugh, J. L. (2010, Feb). A practical guide to multilevel modeling [Review]. *Journal of School Psychology, 48*(1), 85-112.
		(c) Summarise follow-up time (eg, average and total amount) Yes (ecological momentary assessment completion rates statistics are provided)
Outcome data	15*	Report numbers of outcome events or summary measures over time Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Yes
		(*b*) Report category boundaries when continuous variables were categorized Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Yes
Discussion		
Key results	18	Summarise key results with reference to study objectives Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results Yes
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Yes

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

APPENDIX 4: STROBE CHECKLIST FOR STUDY 4 (CHAPTER 5)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Yes
Objectives	3	State specific objectives, including any prespecified hypotheses Yes
Methods		
Study design	4	Present key elements of study design early in the paper Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Yes
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Yes

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Yes
Bias	9	Describe any efforts to address potential sources of bias We do not perceive to have any important sources of bias in our study.
Study size	10	Explain how the study size was arrived at Our studies sample size was comparable to most other pain studies using ecological momentary assessment. May et al.'s 2018 systematic review on pain studies using ecological momentary assessment found that, when excluding pharmaceutical clinical trials, the average sample size was n=62.7, with a median of n=42. Our study had n=67. May, M., Junghaenel, D. U., Ono, M., Stone, A. A., & Schneider, S. (2018). Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. The Journal of pain, 19(7), 699-716. https://doi.org/https://doi.org/10.1016/j.jpain.2018.01.006
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Yes
		(*b*) Describe any methods used to examine subgroups and interactions Yes
		(*c*) Explain how missing data were addressed Yes
		(*d*) If applicable, explain how loss to follow-up was addressed Yes
		(*e*) Describe any sensitivity analyses Yes
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Yes

		(b) Give reasons for non-participation at each stage Yes
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Yes
		(b) Indicate number of participants with missing data for each variable of interest Generalized linear mixed modelling, a form of multilevel linear modelling, is well-suited to accept data from all participants, even in cases of unequal data points due to missing data and does not require any data imputation methods, therefore all participants from our sample can be directly entered in our analyses (Field, 2013, pp.814-865; Hoffman, 2015, pp. 3-27, 281-326; Peugh, 2010). Furthermore, the average completion rates for ecological momentary assessment per participant is provided in the manuscript (Table 1). Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. Sage. Hoffman, L. (2015). *Longitudinal analysis: Modeling within-person fluctuation and change*. Routledge. Peugh, J. L. (2010, Feb). A practical guide to multilevel modeling [Review]. *Journal of School Psychology, 48*(1), 85-112.
		(c) Summarise follow-up time (eg, average and total amount) Yes (ecological momentary assessment completion rates statistics are provided)
Outcome data	15*	Report numbers of outcome events or summary measures over time Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Yes
		(*b*) Report category boundaries when continuous variables were categorized Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Yes
Discussion		
Key results	18	Summarise key results with reference to study objectives Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results Yes
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Yes

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