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Central Sensitization, Muscle Function, and Knee Kinematics in Females with Patellofemoral Pain

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CENTRAL SENSITIZATION, MUSCLE FUNCTION, AND KNEE KINEMATICS IN FEMALES WITH PATELLOFEMORAL PAIN

by

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ABSTRACT

CENTRAL SENSITIZATION, MUSCLE FUNCTION, AND
KNEE KINEMATICS IN FEMALES WITH PATELLOFEMORAL PAIN

by

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Under the Supervision of Associate Professor Jennifer Earl-Boehm, PhD, ATC

Context: Females with patellofemoral pain (PFP) are at higher risk, have higher rates, and experience worse long-term outcomes than males. Structural and functional changes have been observed in pain networks and neuromuscular systems in individuals with PFP. Central sensitization describes dysfunctional pain modulation which could lead to altered neuromuscular control. Evidence examining relationships between central sensitization and muscle function in PFP is lacking.

Objective: The purpose of this study is to determine whether females with PFP exhibit signs of central sensitization compared to pain-free females. Then, after grouping each individual based on her quantitative sensory test results into a centrally sensitized (CS) and non-centrally sensitized (NS) groups, we will determine whether quadriceps muscle function is altered during a static task, and whether quadriceps muscle function and knee kinematics are altered during a functional task.

Participants: Thirty-three total females participated. For the first aim, a PFP and pain-free healthy control (CON) group were compared. For the second and third studies, the PFP group was further divided based on their quantitative sensory test (QST) results into the CS and NS groups and the CON group was maintained.

Main Outcome Measures: QST measures included local and remote pressure pain thresholds (PPTs), conditioned pain modulation (CPM), and temporal summation of pain (TSP). Surface electromyography (EMG) was used to collect the time of vastus medials (VM) and vastus lateralis (VL) onset activation in response to an auditory stimulus (SRT) and peak activation response to a stimulus (PRT) during a maximal voluntary isometric contraction and stair descent tasks. Inertial measurement unit motion analysis was also used to collect peak knee flexion and peak knee abduction angles during stair descent.

Results: Females with PFP exhibited impaired CPM and facilitated TSP relative to the CON group. No differences in PPTs at local or remote sites were observed. Once grouped by central sensitization status, no differences in VM and VL SRT or PRT were observed between- or within- groups during the static task. During the functional task, PRT for both muscles was later in the CS group compared to the CON group ($p<0.001$), but no differences in SRT or knee kinematics were observed between groups.

Conclusions: Females with PFP exhibit enhanced pain facilitation with impaired pain inhibition compared to pain-free females. Quadriceps muscle function was not altered during a static task. Peak VM and VL activation during stair descent occurred later in the CS group compared to the

CON group. Peak activation occurred just prior to maximum knee flexion and later than maximum knee abduction in the CS group, indicating the potential for reduced control during stair descent. However, similar activation onset times, and knee flexion and abduction angles were observed regardless of group. Altered muscle function may occur in females with centrally-sensitized PFP during a functional, weight-bearing task without changes in peak knee angles. Muscle function is not altered between groups during static non-weight-bearing task when grouped by central sensitization. Pain facilitation and pain inhibition mechanisms can be restored, but current treatment models and practice guidelines do not account for central sensitization. Clinicians should consider assessing signs of central sensitization during clinical examination of females with PFP.

To my husband and partner, Michael,

my children, my parents,

and the friends who supported me along the way.

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2D	Two-Dimensional
3D	Three-Dimensional
bpm	beats per minute
CS	Centrally Sensitized PFP Group
CON	Control Group
CPM	Conditioned Pain Modulation
EMG	Electromyography
FABQ-K	Fear-Avoidance Beliefs Questionnaire for the Knee
fMRI	Functional Magnetic Resonance Imaging
GMax	Gluteus Maximus
GMed	Gluteus Medius
ICC	Intraclass Correlation Coefficient
IPAQ	International Physical Activity Questionnaire
kg	kilograms
KOOS	Knee Injury and Osteoarthritis Outcome Score
KOOS-PF	Knee Injury and Osteoarthritis Outcome Score- Patellofemoral Subscale
kPa	kiloPascal
mm	millimeters
ms	milliseconds
MVIC	Maximal Voluntary Isometric Contraction
NS	Non-Centrally Sensitized PFP Group
QST	Quantitative Sensory Testing

PCS	Pain Catastrophizing Scale
PFJ	Patellofemoral Joint
PFP	Patellofemoral Pain
PPT	Pressure Pain Thresholds
PRT	Peak Activation Response Time
PSEQ	Pain Self-Efficacy Questionnaire
s	seconds
SRT	Stimulus Response Time
TSP	Temporal Summation of Pain
VAS	Visual Analog Scale
VL	Vastus Lateralis
VM	Vastus Medialis

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Chapter I

Introduction

Patellofemoral pain (PFP) is a common chronic lower extremity condition characterized by retro- and/or peri-patellar pain (Willy et al, 2019). It is estimated that PFP affects about 25% of the population (Willy et al, 2019) and females are 2.2 times more likely to experience the condition than males (Boling et al, 2010; Smith, Selfe, et al, 2018). Current etiological theories propose elevated patellofemoral joint (PFJ) loading as a nociceptive event (Powers, Witvrouw, Davis, & Crossley, 2017). Treatment strategies aimed at reducing PFJ loading appear to provide short-term relief, however, prospectively, PFP becomes recurrent in 70-90% of cases (Stathopulu & Baildam, 2003). Over 50% of patients continue to report symptoms at follow-ups ranging from 1-8 years (Lankhorst, Bierma-Zeinstra, & van Middelkoop, 2012; M. S. Rathleff, Graven-Nielsen, et al, 2019; M. S. Rathleff, Holden, et al, 2019; M. S. Rathleff, Rathleff, Holden, Thorborg, & Olesen, 2018; M. S. Rathleff, Rathleff, Olesen, Rasmussen, & Roos, 2016; M. S. Rathleff, Roos, Olesen, Rasmussen, & Arendt-Nielsen, 2016). It is possible that the key to achieving long-term symptom relief has not yet been identified and could lie in better understanding the pain mechanisms in the condition.

Central sensitization describes an altered functional state of nociceptive neurons in the central nervous system such that they demonstrate increased responsiveness to an innocuous stimulus or subthreshold afferent input ("International Association for the Study of Pain Terminology," 2021). Woolf (2011) suggests that persistent pain becomes a reflection of the functional state of the central nervous system circuitry, rather than reflecting a noxious stimulus. Therefore, even if PFJ loading induced initial symptoms, persistent pain may not reflect PFJ

loading, and treatment aimed at the loading instead of the pain may not lead to long-term symptom relief. A deeper examination of central sensitization in PFP is warranted.

Hallmark signs of central sensitization include pain with an innocuous stimulus such as touch (allodynia), widespread hypersensitivity to pain, increasing receptive fields, enhanced pain facilitation mechanisms and/or inefficient descending pain inhibition mechanisms (Staud, 2012; Woolf, 2011). These changes in somatosensation can be assessed clinically using quantitative sensory testing (QST). QST has been used to provide evidence of patient subgroups in other chronic musculoskeletal conditions such as low back pain and knee osteoarthritis (Dell'Isola, Allan, Smith, Marreiros, & Steultjens, 2016; Wright, Benson, Will, & Moss, 2017), predict treatment outcomes (Baert et al, 2016; Edwards et al, 2016; Kim, Yoon, Yoon, Yoo, & Ahn, 2015; Kurien, Arendt-Nielsen, Petersen, Graven-Nielsen, & Scammell, 2018), and guide treatment selection (Chimenti, Frey-Law, & Sluka, 2018; Lluch Girbes, Nijs, Torres-Cueco, & Lopez Cubas, 2013; Woolf, 2011). In PFP, evidence supports increasing pain area with prolonged symptom durations to include spreading of pain up and down the leg (Boudreau, Kamavuako, & Rathleff, 2017; Boudreau et al, 2018; M. S. Rathleff, Petersen, Arendt-Nielsen, Thorborg, & Graven-Nielsen, 2016), and at remote sites including the hip, back, and neck (Holden et al, 2018). Secondary hyperalgesia is also common in individuals with PFP (De Oliveira Silva, Rathleff, Petersen, Azevedo, & Barton, 2019; Holden et al, 2018; Noehren et al, 2016; Pazzinatto et al, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff, Roos, Olesen, Rasmussen, & Arendt-Nielsen, 2013; van der Heijden, Rijndertse, Bierma-Zeinstra, & van Middelkoop, 2018; van der Heijden, Vollebregt, Bierma-Zeinstra, & van Middelkoop, 2015), and that this finding is more common in females (van der Heijden et al, 2018). However, evidence is limited and conflicting for enhanced pain

facilitation and impaired pain inhibition (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017). With so few studies in this area, a consensus has not yet been reached regarding their occurrence in females with PFP (De Oliveira Silva, Rathleff, et al, 2019).

While QST can help identify somatosensory changes in the central nervous system indirectly, structural and functional changes of the central nervous system can also be observed directly using techniques such as transcranial magnetic stimulation and functional magnetic resonance imaging (fMRI). Structural and functional changes of pain and motor networks have been observed in PFP patients with symptom durations longer than 4 months (Te, Baptista, Chipchase, & Schabrun, 2017). The authors observed a more anterior and larger spatial representation of the quadriceps muscles compared to healthy individuals using transcranial magnetic stimulation (Te et al, 2017). Additionally, fewer discrete motor-evoked potentials of lower amplitude for the quadriceps muscles were observed, indicating the potential for altered neuromuscular control that is centrally driven [as opposed to peripherally driven at the muscle level (Te et al, 2017)]. More recently, fMRI investigation of the functional connectivity of sensorimotor networks (i.e. sensory areas included in the pain network and the motor network) has been assessed (Diekfuss et al, 2021). Specifically, hypoconnectivity was observed between the pain and sensorimotor control centers indicating less cohesive communication between the regions (Diekfuss et al, 2021). Additionally, hyperconnectivity was observed between the somatosensory and motor cortices, which, in addition to the aforementioned lack of discrete cortical peaks, suggests that sensorimotor processing may be disrupted by pain (Diekfuss et al, 2021; Te et al, 2017). Increased communication between the posterior cingulate cortex and the somatosensory cortex may also suggest potential alterations in sensory processing, giving further credence to the impact of central sensitization in the condition (Diekfuss et al, 2021). Authors

using both direct and indirect measures of central nervous system function have concluded that pain-sensation (Jensen, Hystad, Kvale, & Baerheim, 2007; Jensen, Kvale, & Baerheim, 2008; Noehren et al, 2016) and pain-motor tradeoffs (Diekfuss et al, 2021; Te et al, 2017), in which pain is selectively processed, disrupting sensation and motor function. Central sensitization is occurring in (at least a subset of) patients with PFP, but the impact of central sensitization on neuromuscular control and biomechanics during functional movements are unknown. A better understanding of these relationships would provide evidence about the pain aspect of PFP that, in conjunction with the pathomechanical model could inform more effective treatments.

The aforementioned changes in sensorimotor communication may lead to altered sensorimotor function such as longer sensory processing time (i.e. time to respond to a stimulus), delayed time to develop muscle force after the arrival of action potentials (i.e. electromechanical delay), inhibited Hoffmann reflexes, or delayed time to achieve peak activation. In individuals PFP, inhibition of the vastus medialis Hoffmann reflex (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Pazzinatto, de Oliveira Silva, Pappas, Magalhaes, & de Azevedo, 2017) has been observed in females with the condition compared to pain-free females. Additionally, in both male and female participants, longer electromechanical delay of the vastus medialis has been observed relative to the vastus lateralis and to pain-free controls during a maximal voluntary isometric contraction (MVIC) task (Chen, Chien, Wu, Liau, & Jan, 2012). These changes have been described as potential mechanisms driving the development of PFP, but it is possible they are the result of centrally mediated changes in sensorimotor control.

Changes in neuromuscular control have been well-documented in the quadriceps muscles of individuals with PFP, however, none of these findings have been universally observed (Aminaka, Pietrosimone, Armstrong, Meszaros, & Gribble, 2011; C. J. Barton, Lack, Malliaras,

& Morrissey, 2013; Brindle, Mattacola, & McCrory, 2003; Cavazzuti, Merlo, Orlandi, & Campanini, 2010; Cowan, Bennell, Hodges, Crossley, & McConnell, 2001; Cowan, Hodges, Bennell, & Crossley, 2002; Karst & Willett, 1995; T. H. Nakagawa, E. T. Moriya, C. D. Maciel, & F. V. Serrao, 2012b; Pal et al, 2012; Pal et al, 2011; Salomoni, Tucker, Hug, McPhee, & Hodges, 2016; Toumi et al, 2013; Van Tiggelen, Cowan, Coorevits, Duvigneaud, & Witvrouw, 2009; Willson, Kernozek, Arndt, Reznichek, & Scott Straker, 2011). Reduced peak amplitudes of thigh muscles have not been consistently observed, but altered activation onset and duration of the vastus medialis during functional tasks such as stair negotiation, single-leg squatting, and running have been well-documented (Aminaka et al, 2011; Brindle et al, 2003; Cavazzuti et al, 2010; Cowan et al, 2001; Cowan et al, 2002; Toumi et al, 2013; Van Tiggelen et al, 2009; Willson et al, 2011). The role central sensitization plays in these changes has not yet been explored. If sensorimotor processing is affected by central sensitization, stimulus response delays may occur, which could alter the time it takes to achieve peak muscle activation. Altered muscle function, could be an observable result of a centrally-driven change, which could alter quadriceps muscle function and knee kinematics.

1.1. Purpose Statement

The purpose of this study is to determine whether differences exist in quadriceps muscle function and knee kinematics in females with patellofemoral pain (PFP) grouped by central sensitization status.

1.2. Operational Definitions

- Central sensitization status (used a grouping variable) will be defined as those who experience at least one or more of the following signs of central sensitization: reduced remote pressure pain thresholds (PPTs), impaired conditioned pain modulation (CPM), enhanced temporal summation (TSP).
- Chronic pain and persistent pain will be used interchangeably, and are defined as pain lasting longer than 6 months.
- Quantitative sensory testing: the group of somatosensory tests including (in this study) local and remote PPTs, CPM, and TSP.
- TSP-response: the difference between the first and second set of VAS scores during TSP assessment (VAS II= VAS 8, 9, and 10; VAS I= VAS 2, 3, and 4; TSP-response= VAS II-VAS I).
- CPM-response: the difference in PPTs during application of the conditioning stimulus from baseline (no conditioning stimulus applied).
- Local PPTs: PPTs at the knee
- Remote PPTs: PPTs at a site remote to the knee
- Muscle function: the variables assessed using EMG and include stimulus response time and peak activation response time.
- Stimulus response time (SRT): the time, in milliseconds (ms) from the delivery of an auditory stimulus until the onset of EMG activity.
- Peak activation response time (PRT): the time from the delivery of an auditory stimulus until the peak activation is achieved. For the static task, peak activation

during the MVIC will be used for analysis. Peak activation during the stance phase of the second stair will be used for analysis during the functional task.

- Static task: Quadriceps MVIC
- Functional task: Stair descent

1.3. Specific Aims

Aim 1. To determine whether females with PFP exhibit signs of central sensitization relative to age-matched pain-free females.

Hypothesis 1. Females with PFP will exhibit signs of sensitization compared to pain-free females.

Aim 2. To determine whether differences exist in quadriceps muscle function during a static task in females with PFP grouped by central sensitization status and compared to a pain-free control group.

Hypothesis 2a. VM and VL activation onset timing will differ between groups (centrally sensitized, non-centrally sensitized PFP, and control).

Hypothesis 2b. VM and VL peak activation timing will differ between groups (centrally sensitized, non-centrally sensitized PFP, and control).

Hypothesis 2c. In the centrally-sensitized PFP group, VM and VL activation onset timing will differ.

Hypothesis 2d. In the centrally-sensitized PFP group, VM and VL peak activation timing will differ.

Aim 3. To determine whether differences exist in quadriceps muscle function and/or knee kinematics during a functional task in females with PFP grouped by central sensitization status.

Hypothesis 3a. VM and VL activation onset timing will differ between groups (centrally sensitized, non-centrally sensitized PFP, and control).

Hypothesis 3b. VM and VL peak activation timing will differ between groups (centrally sensitized, non-centrally sensitized PFP, and control).

Hypothesis 3c. In the centrally-sensitized PFP group, VM and VL activation onset timing will differ.

Hypothesis 3d. In the centrally-sensitized PFP group, VM and VL peak activation timing will differ.

Hypothesis 3e. Peak knee joint angles (flexion, abduction) will be different between groups (centrally sensitized PFP, non-centrally sensitized PFP, control).

1.4. Delimitations of the Project

I am choosing to include the quadriceps motor function (EMG) variables rather than including the entire lower extremity, despite the fact that we know muscle function throughout the lower extremity will affect movement strategy. I have chosen not to include hip or trunk variables, despite implications that hip and trunk kinematic or neuromuscular factors are important in controlling movement and development of PFP (Powers, Bolgla, Callaghan, Collins, & Sheehan, 2012; Powers et al, 2017). The selected variables are based on previous findings indicating that they are most likely to be affected by central sensitization and subsequently affected sensorimotor communication during the selected tasks.

For kinematic variables, segments are modeled as rigid, even though it is known that the body is not rigid. This modelling strategy is the most applicable and is commonly used in lower extremity biomechanics. While the type of task options are infinite, I selected the quadriceps MVIC as it is a common clinical assessment, and stair descent causes pain in 93% of individuals with PFP and is also considered to be a clinically diagnostic assessment (Collins, Vicenzino, van der Heijden, & van Middelkoop, 2016). Additionally, stair descent is a task that is often unavoidable, as stairs may be present in the home, work, or public buildings with no other options.

I am also choosing to only include females for this project, as PFP has an increased prevalence in females and there are clear movement and neuromuscular strategy differences between males and females with PFP.

1.5. Assumptions

I assume that participants will provide their actual responses on self-report and during quantitative sensory testing, and movement patterns, rather than a Hawthorne effect (when participants respond in a certain way because they are being observed). Additionally, when movement constraints are applied (timing with metronome, etc.) that natural movement strategies are not sacrificed.

1.6. Limitations of the Project

The limitations of this study include the cross-sectional design, which only allows for extrapolation and interpretation of data specific to this point in time and does not speak to condition progression over time. Additionally, there will not be a control group as most of the

self-report measures would be assumed to be no-pain and full function, and for the motor and movement variables, current evidence does not support a universal EMG response to the presence of pain (D. Turk, Melzack, R., 2011). Additionally, there are no cutpoints or dichotomous splits for quantitative sensory testing, so only the QST variables will be compared to a healthy population and will use comparative data from pilot testing. Another limitation is that the equipment used to assess movement may interfere with "natural" movement strategies. All attempts have been made to limit the number of constraints for the participant, but placement of markers, crossing arms over the chest, etc. could contribute to movement strategies used during each task, rather than the effect of pain. Another way I am trying to limit these effects is by having participants perform a baseline condition. Lastly, the movements chosen for Phase II align with the most painful movements for individuals with PFP and are commonly motions that are unavoidable in everyday life, so it is possible that a "pain-free" baseline condition will not exist. This explains why we are collecting VAS information at multiple stages of data collection.

Chapter II

Literature Review

2.1. Patellofemoral Pain

PFP is a chronic musculoskeletal condition in which patients report nonspecific retro- and/or peri-patellar pain with an insidious onset (Willy et al, 2019). PFP affects an estimated 25% of the population (range 3-85%), disproportionately affecting females (Boling et al, 2010; Smith, Moffatt, et al, 2018). Military personnel, runners, and athletes in jumping sports tend to be the most commonly afflicted with the condition (Smith, Moffatt, et al, 2018).

PFP has been described as a self-limiting condition due to the absence of tissue damage on imaging (Maffulli, 2000), however, numerous studies suggest that 50-94% of individuals with PFP continue to have pain (1-20) years after the onset of pain, often despite attempts to treat the condition. Nimon, Murray, Sandow, and Goodfellow (1998) followed a cohort for 14-20 years and found that only about one-quarter of the participants (22%) achieved complete pain relief, and estimated that only about 50% of PFP cases would resolve in a four year timespan, and that only an additional 23% of cases would resolve over the subsequent 12 years. Some authors (M. S. Rathleff, 2016; M. S. Rathleff, Vicenzino, et al, 2015) suggest that PFP often presents in adolescence and either recurs or persists in adulthood, though the mechanism for this recurrence is unclear.

Onset of PFP is typically insidious, leading researchers and clinicians to question the nature of the pain (Willy et al, 2019). PFP is commonly aggravated by activity, with incidence rates in runners reaching approximately 79% (Neal, Barton, Gallie, O'Halloran, & Morrissey, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017). Collins et al (2016) polled over 450 patients with PFP with the aim of identifying common factors leading to pain onset and found

that 94% of respondents experienced pain with squatting, 91% experienced pain with stair ambulation, 91% experienced pain with running, 54% experienced pain with prolonged sitting and 26% experienced pain with sitting following exercise. In fact, these four activities (running, squatting, stair negotiation, and sitting) are considered the best diagnostic tests for individuals with PFP (Willy et al, 2019) and are commonly used as inclusion criteria for research assessing individuals with PFP. In fact, pain with the single-leg squat is one of few diagnostic criteria for PFP [Specificity: 0.91 to 0.94; Sensitivity: 0.46 to 0.50; (Nunes, Barton, & Serrao, 2018; Willy et al, 2019)]. Pain with stair climbing (Specificity: 0.075 to 0.94; Sensitivity: 0.43 to 0.45) and pain with kneeling (Specificity: 0.84; Sensitivity: 0.50) have also been identified as clinical diagnostic tests (Nunes et al, 2018; Willy et al, 2019).

While a number of etiological hypotheses exist to explain the underlying cause of PFP, these theories commonly use a biomedical approach to solving the problem. Initial theories suggested that patellar maltracking or malposition may cause increased PFJ contact, which caused nociception to occur, however, more recent evidence suggested that the appearance of patellar maltracking or malposition may be due to femoral internal rotation during weightbearing activities (Powers et al, 2017). When the femur internally rotates, increased contact of the lateral patella on the lateral trochlea occurs, which may result in nociception (T. Q. Lee, Morris, & Csintalan, 2003). In addition, the amount of frontal plane knee motion continues to be a consideration as a risk factor and prognostic indicator for PFP (Collins et al, 2013; Lankhorst et al, 2016; Matthews et al, 2017). Greater femoral internal rotation and hip adduction angles contribute to the creation of an increased knee abduction (also known as "knee valgus") angle (Neumann, 2010b). While some studies demonstrate that individuals with PFP exhibit greater

knee abduction angles during running, walking, and jumping, other studies did not observe differences in movement strategies between those with PFP and healthy individuals.

Other suggestions to explain the nociceptive onset of PFP include fat pad impingement or contact, bone marrow lesions, and cartilage lesions (Besier et al, 2015; Ho, Hu, Colletti, & Powers, 2014a, 2014b; van der Heijden, de Kanter, et al, 2016). These theories have gained little traction considering the variability in study results examining these factors (van der Heijden, de Kanter, et al, 2016; van der Heijden, Oei, et al, 2016). Schiphof et al (2014) examined 1518 knees of women over the age of 45 and determined that 25% of the sample who experienced cartilage lesions or cysts, or bone marrow lesions were associated with history of PFP. Cross-sectional studies of PFP patients, however, showed no significant differences in MRI findings between individuals with PFP and healthy controls for presence of cartilage defects, bone marrow lesions, or Hoffa's pad signal intensity (cartilage: 23% for individuals with PFP, 21% for pain-free controls; bone marrow lesions: 53% PFP to 51% healthy; fat pad: 58% PFP to 51% heathy; (van der Heijden, de Kanter, et al, 2016; van der Heijden, Oei, et al, 2016).

Because pain in the PFP typically increases with physical activity, the concept that biomechanical differences may explain the pain in PFP have largely prevailed resulting in a pathomechanical model [Figure 1; (Powers et al, 2017)]. The pathomechanical model suggests that there are two routes to development of PFP. The first route suggests that impaired quadriceps function, impaired soft tissue restraints, excessive femoral IR, or abnormal PFJ anatomy lead to patellar malalignment or maltracking, which leads to reduced PFJ contact area, which causes increased PFJ loading, and ultimately, causes PFP (Powers et al, 2017). The other path is more complex. This route suggests that altered distal biomechanical factors (altered ground reaction forces, altered foot mechanics) or altered proximal factors (altered sagittal and

frontal plane trunk kinematics and/or altered frontal and transverse plane hi kinematics) lead to altered tibiofemoral kinematics and kinetics in all three planes of motion, and may cause muscular tightness or imbalance of the thigh muscles (Powers et al, 2017). These biomechanical tibiofemoral joint changes lead to increased PFJ reaction force, which lead to increased PFJ loading, and ultimately, to PFP (Powers et al, 2017).

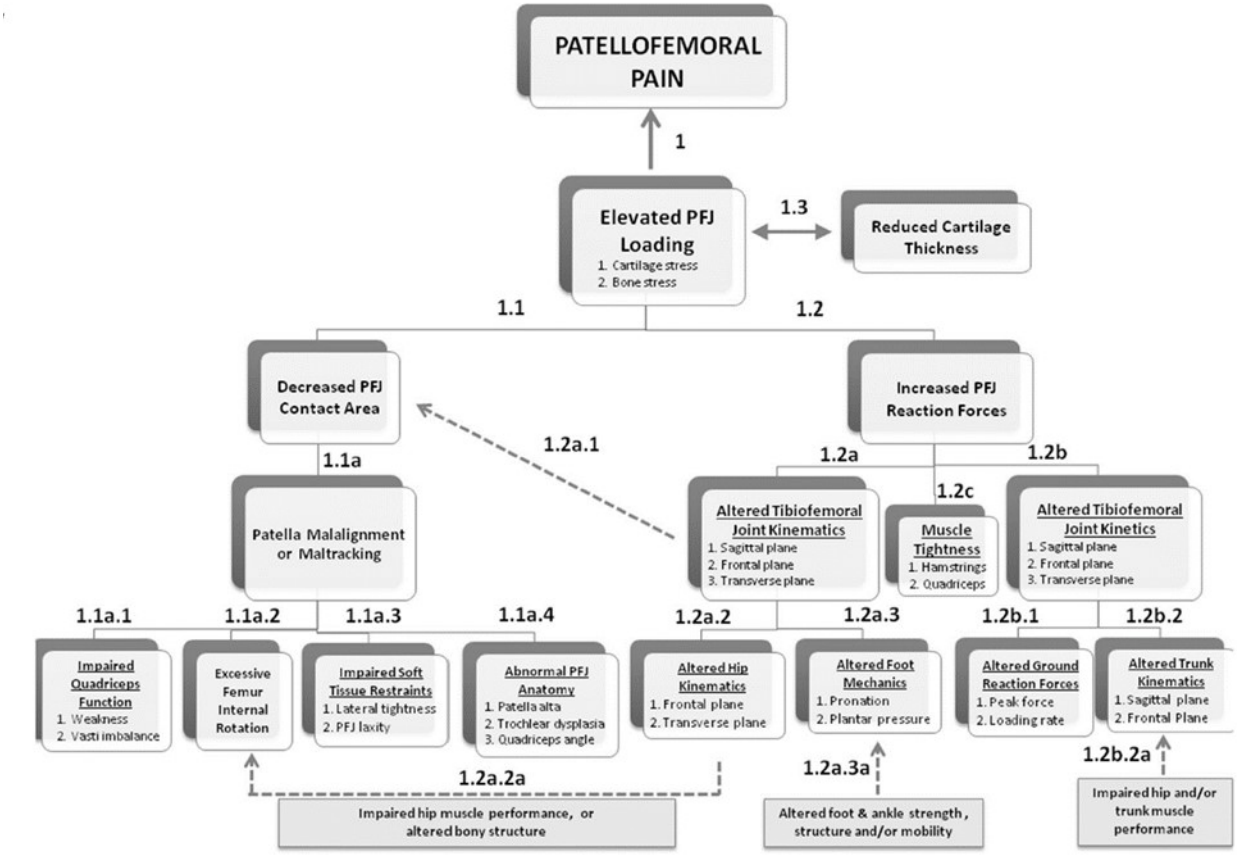


Figure 1: Pathomechanical Model of PFP (Reprinted with Permission; Powers et al, 2017)

While the pathomechanical model is attractive and has an abundance of research supporting each individual position, few of these findings are universally associated with individuals who have PFP, and there is little prospective evidence supporting any of the statements in the model (Powers et al, 2017). These discrepancies suggest that the pathomechanical model may better represent a snapshot of what an individual's biomechanics

may be when they are experiencing PFP, but may not represent risk factors or a linear path to development of the condition. Additionally, the pathomechanical model is a biomedical model which describes a nociceptive onset and suggests that there must be mechanical inducement of nociceptive activity. This is in contrast to biopsychosocial models of pain, which suggest that pain perception is the product of not only biological mechanisms, but also of psychological and sociocontextual factors (de Leeuw et al, 1994). The pathomechanical model neglects these variables in addition to neuroplastic changes that are known to occur with prolonged pain conditions (e.g. central sensitization). The authors of the pathomechanical model (Powers et al, 2017) state in their manuscript that leaving these characteristics out of the model was deliberate, as little evidence in those areas for individuals with PFP had been undertaken at the time, however, now, there is evidence to suggest that recognition of these factors will be integral to the etiology, experience, and treatment considerations for PFP.

Central sensitization refers to neuroplastic changes that occur with prolonged pain (Latremoliere & Woolf, 2009; Staud, 2012; Woolf, 2011). Neuroplastic changes can range from changes in neuronal activity at the spinal cord; to imbalances in pain excitation and facilitation pathways; to reorganization of the motor and somatosensory cortices (Latremoliere & Woolf, 2009; Staud, 2012; Woolf, 2011). In PFP, there is evidence of motor cortex reorganization, cortical inhibition (Te et al, 2017) and spinal inhibition (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Pazzinatto, de Oliveira Silva, Pappas, et al, 2017). It is plausible that these neuroplastic changes may drive changes in motor activity, and therefore, account for biomechanical differences observed within a PFP population.

2.2. Pain-Movement Theories

A number of pain-movement relationship theories exist, and nearly all take a biomedical approach. A biomedical approach assumes that pain is the result of tissue damage and will be correlated to damage and that pain relief will indicate healing (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). This approach does not explain pain in the absence of tissue damage, as seen with PFP (Gatchel et al, 2007; Woolf, 2011). High resolution magnetic resonance imaging fails to present evidence of cartilage defects, bone-stress reaction, bone marrow lesions, or Hoffa's pad abnormalities (van der Heijden, de Kanter, et al, 2016; van der Heijden, Oei, et al, 2016) compared to pain-free individuals. It also fails to explain why pain persists in some individuals and not others. While a number of studies have attempted to identify a mechanical nociceptive source in PFP, the biomedical approach has not kept up with neuroscientific findings which have since explained that a portion of persistent pain may actually be due to neuropathic or nociplastic changes in the central or peripheral nervous systems observed with pain sensitization (Gatchel et al, 2007; Latremoliere & Woolf, 2009; Woolf, 2011).

Pain and movement dysfunction are two byproducts of injury that appear to be related (Hodges, 2011). While pain is a normal protective response to injury, pain that outlasts tissue healing response can be problematic. Movement changes can also serve a protective purpose. For example, antalgic walking gait may serve to reduce pain-free range of motion to limit the risk of re-injuring a sprained ankle. However, changes in movement, however subtle or well-intentioned, alter load distribution to the affected body area and the surrounding body areas and can lead to secondary injury, changes in load distribution, and reduced movement variability which can all feed into pain sensation (Hodges & Smeets, 2015; Hodges & Tucker, 2011). Thus, in some cases, the initial protective response led to long term consequences of that response (Hodges & Smeets, 2015; Hodges & Tucker, 2011).

Once pain becomes "chronic" (defined here as pain lasting 6 months or longer,) it becomes more difficult for recovery to occur (T. J. Price, Ray P.R., 2019). Empirical evidence suggests that physical rehabilitation is only successful in about 50% of cases of chronic pain (Sluka, 2016). That statistic is consistent with PFP, where 40-50% of patients continue to experience pain 5 to 8 years after initial onset (Lankhorst et al, 2016). In these cases, pain is no longer serving a (biologically) protective response. Some authors (Hodges & Smeets, 2015; Hodges & Tucker, 2011; Merkle, 2019; Sluka, 2016) have suggested that altered movement in chronic musculoskeletal pain patients may be the result of operant conditioning (due to the learned response that the movement alteration reduced or avoided pain), or may be the result of changes in the motor system (denoted by changes in activation pattern, temporal or magnitude of activation factors) or nervous system (denoted by manifestations of central sensitization).

2.2.1. Suboptimal Tissue Loading Hypothesis

Most pathomechanical models follow the suboptimal tissue loading hypothesis, which proposed that tissue loads that are too high or not high enough (i.e. suboptimal) may induce excitatory nociception, leading to pain perception (Merkle, 2019; Sluka, 2016). This pain perception may occur without an initial onset of tissue damage, but is thought to also occur post-injury if mechanical changes are observed (i.e. limping or antalgic gait that may lead to suboptimal tissue loading, which increases excitatory nociception). This hypothesis postulates that continued use of an unfamiliar movement strategy, will cause mechanical excitation of nociceptors (Sluka, 2016). Additionally, non-nociceptive afferent information (e.g. position sense) will activate the pain network since patient is unaccustomed to the strategy (Sluka, 2016). While this theory is attractive to the clinician because it combines atypical postural and

movement observations with an expected pain response, there is little empirical evidence to support it.

In PFP, the suboptimal tissue loading hypothesis basically mirrors the pathomechanical model and there is limited evidence to support it. Noehren, Sanchez, Cunningham, and McKeon (2012) suggested that individuals with PFP may not change their movement strategy over the course of an endurance run, but may actually adopt a different strategy at the beginning of the run relative to healthy controls. This implies that individuals with PFP may be adopting a protective movement pattern to avoid or prolong the onset of pain during the run. Dierks, Manal, Hamill, and Davis (2008) identified increased hip abductor weakness at the end of the run that was not present at the beginning of a prolonged run, and following the run, the relationship between the weaker hips and increased hip adduction was more pronounced. It was unclear following this study whether this may have been a product of pain or fatigue. Bazett-Jones, Huddleston, Cobb, O'Connor, and Earl-Boehm (2017) also found that hip extension torque, hip extension and abduction internal joint moments after a repeated single-leg squat (SLS) protocol (which was intended to increase pain). In that study, a subsequent pain-relieving (transcutaneous electrical nervous stimulation) only restored the hip abduction joint moment. This implies that kinetics and muscle strength may not be affected by acute pain aggravation (Bazett-Jones et al, 2017). From these results, there does not appear to be strong support for the suboptimal tissue loading hypothesis from a macro- perspective, however, it is important to note that none of these studies actually examined loading at the PFJ.

Several authors (Glaviano & Saliba, 2018; Noehren et al, 2012; Noehren et al, 2016; Salsich, Graci, & Maxam, 2012) have also attempted to identify specific kinematic variables that are well-correlated to pain during movement, but caution should be employed before

extrapolating those results, as they are subject to the specific hypotheses of the author and may neglect additional kinematic, kinetic, or motor variables not examined in these studies. The peak knee abduction angle (or knee valgus angle) are associated with pain during single-leg squatting (Glaviano & Saliba, 2018; Noehren et al, 2012; Noehren et al, 2016; Salsich et al, 2012), however, these studies were cross-sectional and not indicative of changes in pain over time. Moreover, while some authors (Pairot de Fontenay, Esculier, Bouyer, & Roy, 2018) reported changes in kinematic factors with no reduction in symptoms, others (Ferber, Kendall, & Farr, 2011) have reported reduced pain with no changes in kinematic factors. Salsich et al (2012) are one of the only groups to correlate increases in knee valgus angle to increases in pain, however, participants were instructed to exaggerate the knee valgus angle and similar results with respect to *changes* in pain have not been replicated in within-subjects studies using their typical movement strategies (Bazett-Jones et al, 2017).

Lastly, elevated PFJ loading has only been observed in walking, and during a half-squat (45 degrees of knee flexion; (Farrokhi, Keyak, & Powers, 2011). During running, stair negotiation, squatting over 60 degrees of knee flexion, PFJ loading was no greater within individuals that it was for healthy persons (Brechter & Powers, 2002; Wirtz, Willson, Kernozek, & Hong, 2012). PFJ loading rate may be better related to PFP symptoms (Brechter & Powers, 2002). That finding has not been replicated at the PFJ, but Briani, Pazzinatto, Waiteman, de Oliveira Silva, and de Azevedo (2018) suggest that vertical ground reaction loading rate may be associated with greater pain in women with PFP.

One reason the suboptimal tissue loading hypothesis is problematic is because individual difference in movement strategy, excitatory nociceptive thresholds, and optimal tissue loading rates making it difficult to confirm (Hodges & Tucker, 2011). Additionally, pain perception

alone does not indicate that tissue loading is suboptimal or abnormal, or even that excitatory nociceptors have been activated (Melzack, 1999, 2001; Sluka, 2016). In fact, pain intensity is not reflective of the extent or amount of suboptimal loading (Sluka, 2016). These findings suggest that even if modified movement patterns may have initiated pain, it is likely not the reason the pain is maintained.

2.2.2. Conditioned Response Hypothesis

As previously mentioned, pain may cause an initial change in motor activity (excitation or inhibition) but it is unlikely to continue to alter motor activity beyond tissue healing (Hodges & Smeets, 2015; Hodges & Tucker, 2011; Merkle, 2019; Sluka, 2016). The conditioned response hypothesis takes into account the idea of classic operant conditioning to help explain continued motor dysfunction. Operant conditioning was made famous by Pavlov, who was able to condition dogs to salivate at the mere sound of a bell after several weeks of ringing the bell prior to feeding time (as cited in Sluka (2016). The dogs came to equate the sound of the bell with feeding time, and thus, anticipated food every time they heard the bell, which did not only cause a psychological expectation but manifested with the *physiological* response of salivation. In pain-movement theory, the individual experiencing pain with a certain movement may associate that movement with the expectation and experience of pain. This learned association may cause "pain memories" that lead the individual to adjust the movement in an effort to reduce the pain. In this case, the initial painful experiences provoked nociception, but the learned movement adaptation continued despite the absence of nociception.

Tucker, Larsson, Oknelid, and Hodges (2012) were able to demonstrate that similar motor unit recruitment strategies were used both in the experience of a painful condition and

during the mere expectation of pain based on an experimental design that used operant conditioning for the expectation condition. Adding to the intrigue is the fact that recruitment strategies used differed from a baseline condition where no pain was experienced or expected, and that the pain-expectation and pain-experience conditions demonstrated violation of the size principle (motor unit recruitment will occur from smallest to largest in the motor neuron pool (Tucker et al, 2012)]. No studies in PFP have demonstrated an operant conditioning effect for pain anticipation or whether participants qualitatively report anything like an operant conditioning or learned effect to avoid painful movements.

2.2.3. Interference/ Inaccuracy Hypothesis

The interference/ inaccuracy hypothesis takes a slightly different approach to the idea that pain does not always serve a protective response, but may still interfere with motor control (Hodges, 2011; Merkle, 2019; Sluka, 2016). This hypothesis suggests that nociceptive (or non-nociceptive) afferent input may inhibit motor neurons. A major critique on this model is that motor unit excitation and inhibition have both been demonstrated as responses to painful stimuli, which have been replicated in a number of pain experiments and within a number of pain conditions (as cited in Hodges and Smeets (2015). Altered afferent input can impair peripheral sensory function, which can create local chemical changes that alter muscle spindle sensitivity (Hodges & Smeets, 2015). There is some support for this hypothesis, and persistent or prolonged symptoms are also related to changes in motor or sensory cortex changes (Hodges & Smeets, 2015; Staud, 2012; Te et al, 2017; Woolf, 2011).

The part of the hypothesis often called into question is whether motor inhibition is due to "interference" with the efferent signal (as suggested) or whether this occurs as a normal

protective response to pain (Hodges & Smeets, 2015). It also suffers the same flaw as the suboptimal tissue loading hypothesis, that pain may initially cause motor inhibition, but it may not maintain it. Additionally, motor inhibition has not been associated with increases in pain perceptions, but has been identified in some studies [as cited in Hodges and Smeets (2015)].

2.2.4. Vicious Cycle Theory

Another theory that links pain and movement is the vicious cycle theory, also known as the pain-spasm-pain cycle. This theory suggests that pain will cause increased muscle activity (muscle spasm) which causes ischemic response and an accumulation of metabolites that increase pain and dysfunction, which increases spasm, which continues the cycle (Hodges & Smeets, 2015; Merkle, 2019; Sluka, 2016). The theory proposes that the metabolites present during muscle spasm stimulate excitatory nociceptive activity. The excitatory nociceptive activity facilitates motor neurons, increasing muscle spindle sensitivity and reflexive muscle stiffness (Hodges & Smeets, 2015; Merkle, 2019; Sluka, 2016).

Some research in the areas of myofascial trigger points, temporomandibular joint dysfunction, and low back pain support some aspects of the vicious cycle theory [as cited in (Hodges, 2011; Hodges & Smeets, 2015)]. Increased electromyography (EMG) of affected muscles during pain that can be reduced with muscle relaxing medication, suggesting that reduced muscle tension will lead to reduced pain (Hodges & Smeets, 2015). However, muscle relaxers also have a depressive effect on the nervous system and it is unclear whether pain reduction is the result of the effect on the motor or neurological systems. A common criticism of this theory lies in the variability of muscle activity experienced in a variety of musculoskeletal

pain conditions, including PFP, in which pain results in reduced muscle activity rather than increased activation.

2.2.5. Strength Inhibition Theory

A commonly accepted clinical finding is reduced muscle strength following pain. Although it not traditionally provided with a name, a recent review by (Merkle, 2019) dubbed this concept the "strength inhibition theory." In fact, strength assessments are often considered invalid if pain is present due to the idea of generalized inhibition (D. Turk, Melzack, R., 2011). This is problematic for clinicians, however, who need to grade strength following an injury or throughout the rehabilitation process. The strength inhibition theory directly contrasts the vicious cycle theory proposition that muscle excitation of the motor unit, however, there is some empirical support for this theory as well. Tucker and Hodges (2010) demonstrated that experimental knee pain resulted in reduced knee flexion and extension peak torque values, but once the pain subsided, torque values recovered to normal. Moreover, quadriceps (assumed to be a primary patellar stabilizer) weakness has only been identified in a subset of the PFP population (Powers et al, 2017).

Conversely, in support of the theory, reduced hip strength has been commonly observed in cross-sectional studies examining individuals with PFP (M. S. Rathleff, Rathleff, Crossley, & Barton, 2014; Van Cant, Pineux, Pitance, & Feipel, 2014), but is not commonly reduced prior to the onset of PFP (Finnoff et al, 2011; M. S. Rathleff et al, 2014; Thijs, Van Tiggelen, Willems, De Clercq, & Witvrouw, 2007). Additionally, Guney, Yuksel, Kaya, and Doral (2016) observed lower eccentric and concentric quadriceps and hamstring strength in individuals with PFP on the involved side compared to the uninvolved side. This suggests that the presence of pain (or the

PFP condition) reduced strength profiles, however, reduced strength outcome may not be as simple as the observation at the muscular level. Muscle-level activity is the net output of activity of the motor system, and may be reflective of inhibition at spinal or suprasinal levels, not just at the observed level (Hodges & Smeets, 2015). A point of interest for the latter study is that the average self-reported mean pain perceptions of the PFP sample during stair ascent, descent, sitting, and squatting ranged from 5.9-8.7, which is considerably higher than most studies.

Counter to this theory, Bazett-Jones et al (2017) only observed a reduction in hip extension strength following a pain-aggravating protocol that was not restored following pain relief. The authors (Bazett-Jones et al, 2017) also reported that hip or knee strength tests were not affected by pain-aggravation or pain-alleviation. Additionally, as previously stated, hip muscle weakness is not well- correlated with kinematic findings, and changes in pain perception is not well-correlated with muscle strength or kinematic variables, then there may be some mediating factor that has not yet been explored. I propose that central sensitization may be that mediator.

2.2.6. Pain Adaptation Theory

The pain adaptation theory combines the variation of muscular responses to pain during voluntary movement, suggesting that both facilitation and inhibition are potential responses depending on their relationship to the painful area (Hodges, Coppieters, MacDonald, & Cholewicki, 2013; Hodges & Tucker, 2011). The theory proposes that agonists (painful muscles and muscles producing painful movements) will be inhibited where antagonist muscles will be facilitated in response to pain (Hodges & Tucker, 2011). The suggestion is that nociception will converge onto interneurons in the dorsal horn of the spinal cord and in the brainstem, resulting in

reduced muscle force using a feed forward or anticipatory mechanism (as cited in Hodges and Smeets, (2015). The reduced peak EMG amplitude, velocity, and displacement of the painful body area will provide a protective response to prevent further pain or injury to the area (as cited in Hodges and Smeets, (2015).

In support of this theory, Tucker and Hodges (2009) observed uniform inhibition of the agonist muscles (quadriceps and flexor pollicis longus) did not occur under experimental pain conditions. Instead, a violation of the size principle occurred in which recruitment of active motor neurons did not follow a smaller-to-larger motor unit pattern. Instead, during non-painful conditions, some motor units in the quadriceps were activated that were not recruited during painful trials. Additionally, derecruitment of these motor units coincided with new recruitment of a different set of motor units during the painful trials which may have allowed for maintenance of whole-muscle activity (EMG) and force (Tucker et al, 2009).

To follow up this study, Tucker et al (2012) again demonstrated a violation of the size principle when new motor units were recruited within the quadriceps muscle when participants merely expected (laboratory-induced) pain to occur that were not activated during non-painful trials, and that these newly recruited motor units did not experience derecruitment once the threat of pain was eliminated, suggesting a lag in derecruitment timing (Tucker et al, 2012).

In another experimental pain condition, Hodges et al (2016) observed greater motor activation than was necessary during stair descent task involving steps of different heights during a pain-anticipation condition relative to a baseline condition when pain was not expected. This increased motor activity led to unnecessary joint loading. The authors (Hodges et al, 2016) suggested that increased stiffness (described in-text as reduced *joint range of motion*) of the lower extremity joints could be interpreted as a protective mechanism by using a motor strategy

reserved for situations with higher physical demands and joint loading. This could also be due to misperceptions about proprioception or of the position or size of the painful limb. The authors (Hodges et al, 2016) continue by arguing that neural inhibition to the agonist muscle may be observed during seated tasks but may not be possible during tasks when postural control is necessary, such as stair ambulation. They (Hodges et al, 2016) concluded with a call for research assessing temporal and spatial features of hip muscle activity during real or anticipated knee pain may provide further evidence to advance empirical evidence in this area.

Criticisms of pain adaptation theory include not accounting for facilitated agonist muscles, which have been observed in low back pain, knee osteoarthritis, and temporomandibular joint dysfunction research (Hodges, 2011; Hodges & Smeets, 2015). Moreover, this theory cannot explain the result of recent studies which found that new motor neurons were recruited within a muscle during pain despite maintenance of peak force (Tucker, Butler, Graven-Nielsen, Riek, & Hodges, 2009; Tucker & Hodges, 2009). Additionally, consider that for individuals with PFP, knee flexion is painful (Willy et al, 2019). According to pain adaptation theory, the hamstring (primary knee flexor) would be considered the agonist muscle and we should expect inhibition and the quadriceps would be considered the antagonist, which should be facilitated. The quadriceps are also agonists to patellar stabilization, so then it begs the question of whether the quadriceps should be considered the antagonist to the painful movement or the agonist because they stabilize the patella during the painful movement. Current theory that suggests that the quadriceps may be at least partially inhibited while other studies suggest no differences in quadriceps activation relative to healthy controls (Aminaka et al, 2011; Cavazzuti et al, 2010; Cowan et al, 2001; Cowan et al, 2002; Cowan et al, 2004; Karst & Willett,

1995). Thus, the pain adaptation theory is not adequate to capture the muscle activation patterns observed in PFP.

2.2.7. Protective Response Theory

Hodges and Tucker (2011) first explained this "new model" of pain adaptation, but the name "protective response" was first provided in a synthesis by (Merkle, 2019). This model (Figure 2) proposes that pain, injury, or the threat of pain and/or injury lead to redistribution of motor activity within or between muscles (Hodges & Smeets, 2015; Hodges & Tucker, 2011). Motor dysfunction or incoordination alter mechanical behavior including changes in load distribution, the direction of external forces, and reduced variability in muscle force and amplitude (Hodges & Smeets, 2015; Hodges & Tucker, 2011). Mechanical behavior modification leads to short-term protective responses such as increased joint stiffness (e.g. described as reduced joint range of motion) serving the purpose of protecting the injured body area, but over time these short-term changes lead to long-term consequences of modified distributions in load and load distribution including increased load on the affected or surrounding joints, reduced joint movement, and reduced movement variability (Hodges & Smeets, 2015; Hodges & Tucker, 2011). These long-term movement changes feed the painful sensation, leading to more changes in movement strategy, and potentially leading to central sensitization (Hodges & Smeets, 2015; Hodges & Tucker, 2011).

In 2015, the protective response theory was updated (Figure 2; (Hodges & Smeets, 2015)). While the "core" of the model suggesting that pain or the perceived threat of pain/injury lead to motor dysfunction, which lead to short-term biomechanical protective responses, was maintained. Also continued in this version was the idea that if the short-term protective

strategies were maintained longer than needed, long-term biomechanical consequences that may continue to feed into the pain or perceived threat, which leads to further motor alterations, and continues the cycle (Hodges & Smeets, 2015). The updated theory suggests that there are differences in discrete excessive loads and accumulated loads that, when combined, can lead to individual differences on the point at which load demand exceeds the individuals' ability to tolerate it (Hodges & Smeets, 2015). The authors (Hodges & Smeets, 2015) suggest that point at which load exceeds tolerance over time may lead to a sensitized nervous system and recognizes

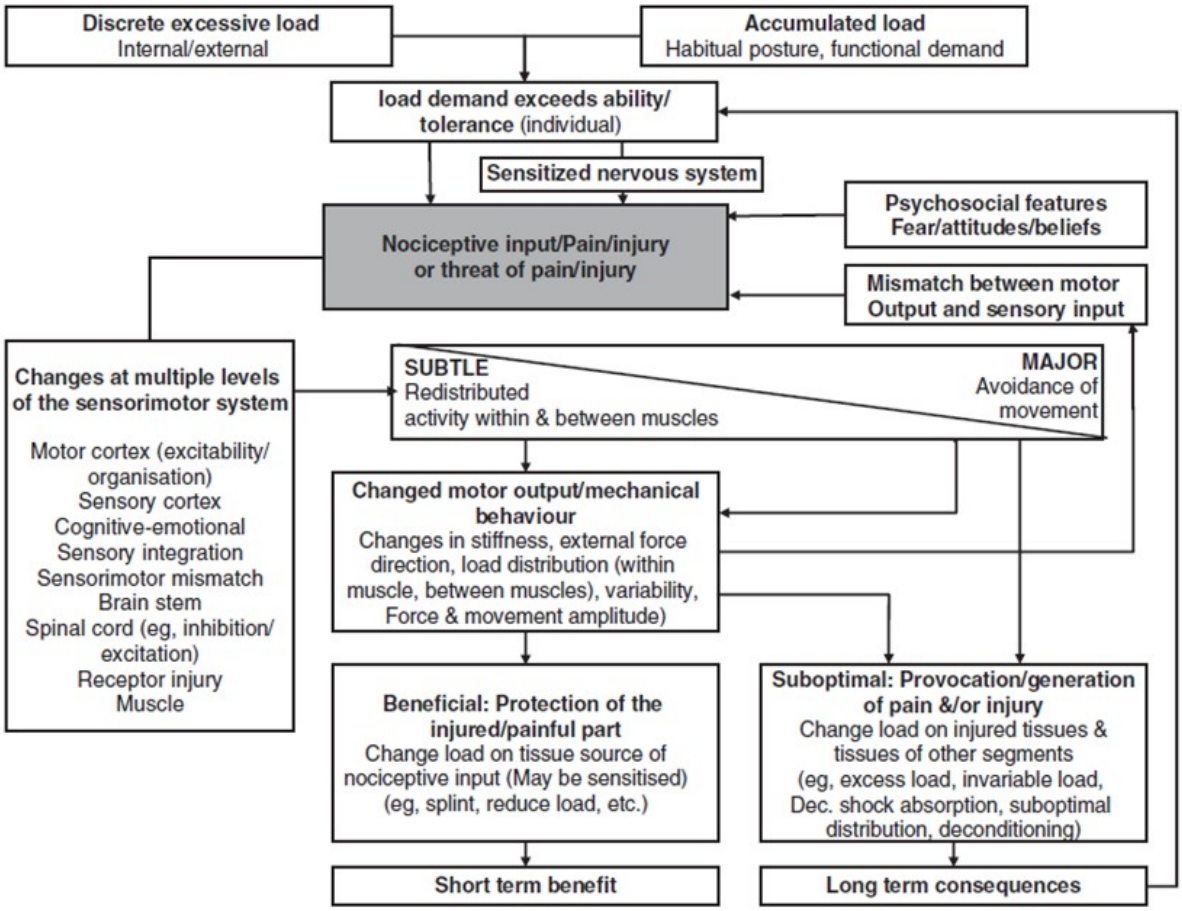


Figure 2: Protective Response Theory, originally titled "New Model" (Reprinted with Permission: Hodges & Smeets, 2015)

neuroplastic changes at multiple levels of the nervous system. Finally, the authors propose that nervous system sensitization, changes within the sensorimotor system, and psychosocial factors

feed the pain perception or perceived threat of pain and/or injury in addition to altering the aforementioned motor function (Hodges & Smeets, 2015). There is also a temporal factor in the new model which suggests that during the initial painful experience or injury, motor and/or biomechanical changes observed may be more subtle, but the longer pain persists, these outcomes become "major" and overall function may deteriorate (Hodges & Smeets, 2015).

2.2.8. Pain-Movement Summary

Prior to the protective response theory, pain-movement theories suggested that a universal muscular response to pain occurs. A unified neuromuscular response to pain may not have been observed due to changes over time that can influence the neuromuscular system such as sensitization of the central nervous system, sensorimotor system adaptations, and psychosocial factors. The protective response theory is the only current theory that considers all of these variables to help explain neuromuscular and biomechanical changes for patients with chronic pain. All of these variables have been previously identified as having an impact on neuromuscular control and movement. Additionally, the protective response theory does not assume that all pain is nociceptive, despite still taking a somewhat biomedical approach.

Each aspect of the updated protective response theory (known throughout the rest of the text as simply the protective response theory) will be presented along with the supporting or contradictory evidence from PFP research. A better understanding of the protective response in individuals with PFP will allow for a more robust understanding of the interaction of neuroplastic changes (i.e. central sensitization), psychosocial factors, motor, and biomechanical variables.

2.3. Protective Responses in Patellofemoral Pain

2.3.1. Pain

Pain is defined as the "aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury ("International Association for the Study of Pain Terminology," 2021)." First, it is imperative to understand that pain and injury are not synonymous. A biomedical model of pain suggests that pain sensation shares a perfectly linear relationship with tissue damage (Gatchel et al, 2007). This implies that a) pain cannot occur without tissue damage, and b) that pain will be reduced in concert with tissue healing. Under this model, any pain that could not be explained by tissue damage was deemed psychosomatic (Gatchel et al, 2007; Leeuw et al, 2007; Sluka, 2016). An updated review of neurophysiological aspects of pain suggests, however, that pain can be sensed without corresponding tissue damage (Latremoliere & Woolf, 2009; Woolf, 2011). In fact, there are a multitude of persistent pain conditions in which imaging findings are disproportionately related to pain (Culvenor et al, 2019; French et al, 2019) and conversely, there are plenty of pain-free individuals whose imaging comes back identifying tissue damage that goes unnoticed (Horga et al, 2019). In fact, Horga et al (2019) reviewed magnetic resonance imaging (MRI) results for 82 *asymptomatic* runners found that 36% had meniscal tears, 65% had cartilage damage, 42% has tendon injury, 42% had ligament lesions (almost all over the Anterior Cruciate Ligament). This supports the notion that pain and tissue damage are unrelated. Pain perception does not occur until the nociceptive signal reaches the cortical level and is interpreted as such, while nociception is simply the activity in a sensory pathway and thus, should be considered separate constructs (Sluka, 2016).

Loeser (2000) was the first to describe pain as biopsychosocial in nature. This model suggests that pain sensation, pain reporting, and pain coping can be affected by biological, psychological, and sociocultural factors (Loeser, 2000). Biological factors may include the type of tissue at the painful site (i.e. cartilage, bone, ligament), medications that may moderate or modulate pain whether intentional or not, comorbidities that may affect pain or other symptoms, the stage of healing (Loeser, 2000). Additions to this category over time have also included pathomechanical movement, motor dysfunction, sleep patterns, circulatory and respiration activity, autonomic nervous system activity, individual biochemistry, individual metabolism, nutritional factors, and immune system status (Brewer, Andersen, & Van Raalte, 2002). Psychological factors include pain behaviors, coping styles, self-efficacy, learned heplessness, cognitive distortion, and personality characteristics (Loeser, 2000). More recent additions to the model have included cognitive appraisal of pain or of the condition, affect, behavior, anxiety and/or depressive disorders, and stress (Brewer et al, 2002). Sociocultural factors include social support, spousal responses or parental responses (when applicable), and cultural practices influencing pain interpretation and reporting (Brewer et al, 2002). Updated models have also included environmental stressors, situational characteristics, sport or physical activity cultures, and the rehabilitation environment (Brewer et al, 2002; Loeser, 2000).

Pain sensation can occur regardless of whether or not activity has taken place in the nociceptor pathway (Woolf, 2011). The interpretation of pain is created based on a lifetime of sociocultural and personal experiences with pain, threat of pain or injury, and injury (D. Turk, Melzack, R., 2011; Woolf, 2011). Moreover, the experience of pain affects cognition, psychological, social, and physical aspects of one's life (D. Turk, Melzack, R., 2011). There are three main types of biological pain: nociceptive, neuropathic, and nociplastic (Chimenti et al,

2018; "International Association for the Study of Pain Terminology," 2021). These pain "types" are descriptive of the cause of pain (or perceived threat), and are not diagnostic (Woolf, 2011).

Nociception describes pain arising from nociceptive excitation, and is typically the result of actual or threatened tissue damage ("International Association for the Study of Pain Terminology," 2021). Nociception follows a typical afferent-efferent loop from the peripheral body region experiencing the noxious stimulus or threat, to the dorsal horn of the spinal cord and up to supraspinal regions for interpretation and integration (Moayedi & Davis, 2013). Pain perception does not occur until the signal reaches the somatosensory cortex. Once pain perception occurs, a variety of systems begin to send descending response signals [e.g. motor behavioral, emotional responses; (Moayedi & Davis, 2013; D. D. Price, 2000)]. Nociceptive pain occurs during acute pain and most nociceptive pain follows a trajectory in which pain severity is worse initially following tissue damage and lessens as tissue healing occurs (Chimenti et al, 2018). Some nociceptive pain can become chronic, which is a process that is not yet well-understood (T. J. Price, Ray P.R., 2019) and is thought to be related to sensitization of the nervous system, as discussed later in this section.

Current models of PFP treat pain perception as purely nociceptive which is possible, but the insidious nature of pain onset, it has been difficult to determine what factors induce the initial (excitatory) nociceptive signal and why they persist. Additionally, PFP is typically diffuse pain that expands over time (Boudreau et al, 2017; Boudreau et al, 2018), not acute and well-localized. PFP also outlasts a typical healing timeframe, failing to decrease as "healing" of the affected tissue (which has yet to be identified) occurs.

Neuropathic pain is pain arising from lesion or disease of the somatosensory nervous system, and can occur in the peripheral or central nervous system (Chimenti et al, 2018;

"International Association for the Study of Pain Terminology," 2021). Neuropathic pain ranges from an acute trauma to the nerve such as a compression, tension, or severing injury; to persistent irritation such as tunnel syndromes; to a disease underlying the lesion as may occur with diabetes mellitus, stroke, or genetic abnormality (Chimenti et al, 2018; "International Association for the Study of Pain Terminology," 2021). Neuropathic pain typically has a known origin and can be diagnosed using imaging, clinical presentation, or patient history (Smart, Blake, Staines, & Doody, 2011). Neuropathic pain does not always respond to the same treatment mechanisms that are effective for nociceptive pain (Chimenti et al, 2018). The prognosis of neuropathic pain varies depending on the severity of the lesion, the prognosis of the condition, and biopsychosocial mechanisms (Chimenti et al, 2018).

Previous researchers (Jensen et al, 2007; Jensen et al, 2008; M. S. Rathleff, Petersen, et al, 2016) have hypothesized that PFP was neuropathic in origin, and there is some support for that statement, however, it is unclear from these manuscripts which nerve pathway or portion of the nervous system has a lesion. M. S. Rathleff, Petersen, et al (2016) reported PainDetect scores (a questionnaire assessing the likelihood that the pain experienced is neuropathic) of 7.5 out of a possible 38 points (range 4.5-11), which falls in the negative or unlikely that pain is of neuropathic origin. Additionally, no lesion in the peripheral or central nervous systems have been identified on imaging so this seems like a difficult fit.

Nociplastic pain is pain that is not induced by actual or potential tissue damage, is not the result of a nervous system lesion, and occurs due to altered nociceptive processing ("International Association for the Study of Pain Terminology," 2021). In some cases, patients may have a combination of nociceptive and nociplastic pain, as nociplastic pain can, in some, but not all, instances, be the result of persistent nociceptive signals that lead to neuroplastic changes

of the peripheral or central nervous systems (Chimenti et al, 2018). Some hypothesized examples of this combination are persistent musculoskeletal pain conditions that transition from acute (nociceptive pain) to persistent pain. In other nociplastic conditions, there was never an initial noxious (mechanical) stimulus (i.e. fibromyalgia). This altered processing may be the result of central or peripheral nervous system sensitization, which will be discussed later.

Our study proposes PFP as a nociplastic condition. Nociplastic pain has been proposed for several chronic MSK conditions (Staud, 2012). Neuroplastic changes can include changes at the central nervous system (CNS), including reorganization and adaptation at the cortex, brainstem, and spinal cord levels (Pelletier, Higgins, & Bourbonnais, 2015a; Te et al, 2017; Woolf, 2011). Neuroplastic changes can also occur in the peripheral nervous system (Jensen, Hystad, Kvale, & Baerheim, 2007; Jensen, Kvale, & Baerheim, 2008; Rathleff, Roos, Olesen, Rasmussen, & Arendt-Nielsen, 2013) including adaptations to nociceptors, or changes in excitatory neurotransmitter amount or thresholds (Sluka, 2016). In fact, motor cortex reorganization can occur within as few as three months(Pelletier et al, 2015a; D. D. Price, 2000; Te et al, 2017), in addition to altered sensorimotor and nociceptive processing, and altered sensorimotor function (Akseki, Akkaya, Erduran, & Pinar, 2008; Jensen et al, 2008; Noehren et al, 2016) (Holden et al, 2018; Pazzinatto et al, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2013). To properly understand these adaptations, an understanding of current pain theories and neural pain pathways of the CNS must be explored.

2.3.1.1. Pain sensation. Pain is a multifaceted, interpersonal experience. Pain is a sensory modality traditionally believed to be a response to a noxious stimulus but a number of cognitive and psychosocial factors. Insidious pain and pain that outlasts a known stimulus or injury is not

well understood. In order to better understand dysfunctional pain modulation, an exploration of the pain pathways is warranted.

2.3.1.2. Pain pathways. The spinothalamic tract or the anterolateral tract is thought to transmit acute nociceptive events where tissue damage or the threat of tissue damage is present. Once nociceptive information is received at the dorsal horn of the spinal cord, the axon of the secondary neuron crossed the midline of the spinal cord and project to the thalamus. From the thalamus, the signal is then projected to the somatosensory cortex. The spinothalamic tract is thought to control the location and intensity of the stimulus (Blumenfeld, 2009).

The second set of ascending pathways control the receptive fields present with inflammation. The divergent ascending pathways describes a more variable network that aligns with the pain neuromatrix theory. Signals traveling on this pathway would reach the dorsal horn of the spinal cord, then continue to travel to the ventral posterolateral nucleus of the thalamus (Lundy-Ekman, 2012). After integration at the thalamus, the signal then "diverges" onto different paths (spinoreticular, spinomesencephalic, and spinolimbic) for integration (Lundy-Ekman, 2012). Information sent via the spinoreticular tract will terminate at the medulla-pons reticular formation and conveys emotional and arousal aspects of pain (Blumenfeld, 2009). The spinomesencephalic tract sends signals to the periaqueductal gray and the superior colliculi, where it conveys withdrawal responses and orients one to the pain (Blumenfeld, 2009). The periaqueductal gray area is also involved in descending pain inhibition networks, so this may be a point at which information is transmitted through those pathways (Sluka, 2016). Information transmitted through the spinolimbic tract continues to the limbic system. The limbic system is a complex network including the thalamus, hippocampus, amygdala, hypothalamus, and basal

ganglia, which conveys information regarding motivation, emotion, learning, and memory (Blumenfeld, 2009; Lundy-Ekman, 2012).

2.3.1.2.1. Neuromatrix theory. Neuromatrix theory was conceived out of research with phantom limb pain (Melzack, 1990). Melzack proposes that each pain experience has a unique "neuro-signature" created from neural impulses from the body-self matrix (also called the pain matrix) of the brain (Melzack, 2001). Each part of the pain matrix represents integration of the signal leading to the construction of the pain experience. In chronic pain, times of psychological stress, and pain with no associated tissue damage, the neuromatrix activates a series of behavioral, perceptual, and processes to restore homeostasis (Melzack, 2001). The neuromatrix can be influenced by other sensory inputs, but the neuromatrix is the mechanism generating the neural pattern that produces pain (Melzack, 2001). This is the first theory to propose that pain does not begin with nociception.

The neuromatrix theory is also unique in its proposition that pain experiences leave an imprint or memory in our neural networks that can be reactivated in the future under similar circumstances (Melzack, 2001). The neuromatrix itself is proposed to be made up of 3 main cyclical modules—cognitive, sensory, and affective (Melzack, 2001). All of these modules have overlapping roles and changes to one module would therefore, affect the other two modules (Melzack, 2001). Cognitive-evaluative processes include fixed traits such as cultural learning, past experiences and personality variables, as well as phasic input including attention, expectation, anxiety, and depression (Melzack, 2001; D. Turk, Melzack, R., 2011). Sensory-discriminative includes sensory, affective and cognitive processes and includes fluctuating cutaneous sensory input, visceral input, visual and vestibular information, other sensory input (Melzack, 2001; D. Turk, Melzack, R., 2011). Motivational-affective components include

cognitive and sensory processes such as hormone, neurotransmitter, and immune functioning, and the role of chemical mediators, inflammatory biomarkers, endogenous opiates, and inputs from the limbic system (Melzack, 2001; D. Turk, Melzack, R., 2011).

Cognitive and sensory processes can create pain perceptions which arise from the cognitive-evaluative, sensory-discriminative, and motivational-affective dimensions discussed previously. Responses from motor to verbal, can be affected by these interactions (Melzack, 2001), including the withdrawal reflex (withdrawing a limb from a noxious stimulus by flexing the limb), voluntary motor programs such as physically escaping the pain (running away) or attempting to move in such a way to protect the body area or avoid pain [i.e. antalgic gait patterns; Melzack, (2001)]. Finally, stress-regulation processes include cortisol and noradrenaline levels, cytokine levels, immune system response, and endorphin levels. In particular, Melzack (2001) proposes that increased cortisol levels may help explain chronic pain, auto-immune disease, and the sex-differences in chronic pain conditions.

The neural network also includes a series of areas in the brain associated with pain perception. The somatosensory cortex is involved in both the anticipation of pain and assigning descriptors (e.g. pain intensity, type, quality) to the sensation (Blumenfeld, 2009; Borkum, 2010b; Pelletier, Higgins, & Bourbonnais, 2015b; D. D. Price, 2000). The prefrontal cortex (dorsolateral region) is key in pain control due to its role in endorphin release. Interestingly, patients with higher pain catastrophizing scores tend to have reduced activity to this area of the brain (Borkum, 2010b; Pelletier et al, 2015b; D. D. Price, 2000).

The insula is involved in the emotional response to pain and activation of this area is seen on fMRI with the anticipation of pain (Pelletier et al, 2015b). The insula also controls changes that occur with musculoskeletal pain include perception of swelling, shape, size, and position

(Borkum, 2010b; D. D. Price, 2000; Schweinhardt & Bushnell, 2010). The cerebellum is more activated with pain catastrophization but little empirical evidence supports rationale for this finding (Borkum, 2010b). The brainstem amplifies pain and activates a reactive endorphin release to reduce pain (Blumenfeld, 2009).

The anterior cingulate cortex seems to be of particular importance in chronic pain (Borkum, 2010b). The anterior cingulate cortex controls the sensory and cognitive aspects of pain, often assigning a value or meaning to the pain experience. (Blumenfeld, 2009; Borkum, 2010b; Dube & Mercier, 2011; Schweinhardt & Bushnell, 2010). This area is important to interpreting pain perception and intensity (Schweinhardt & Bushnell, 2010). It is very active during pain anticipation and in persons with chronic pain conditions, suggesting it may play a role in central sensitization (Torta, Legrain, Mouraux, & Valentini, 2017; Woolf, 2011). When patients are fearful of pain, this area experiences increased activation and bloodflow (Borkum, 2010b). The posterior cingulate cortex also appears to be integral to chronic pain states, and is active in attentive processes to pain or the threat of pain (Borkum, 2010b; Schweinhardt & Bushnell, 2010; Torta et al, 2017). The amygdala controls perceived pain duration and is active during pain anticipation (Lundy-Ekman, 2012; Pelletier et al, 2015b; D. D. Price, 2000).

The posterior parietal cortex appears to be the site of integration for sensory and nociceptive inputs to convey information about the affective dimension of pain relative to environmental context (Leroux, Belanger, & Boucher, 1995; Schweinhardt & Bushnell, 2010). In animals, injury to the secondary somatosensory cortex or insula can lead to an absence of escape responses and in humans, injury to these same areas lead to a loss of the withdrawal reflex and neglect of the damaged body area (D. D. Price, 2000). After receiving information from the posterior parietal cortex, the anterior cingulate cortex then assists with integration of attentional

and evaluative functions that may help prioritize responses to pain (Borkum, 2010b; D. D. Price, 2000).

Once attentional, motivational, and evaluative processes have been integrated, the premotor area is able to formulate a response plan (Lundy-Ekman, 2012) which the primary motor cortex coordinates, adjusts, and implements (D. D. Price, 2000). If the chronic pain signals originate in the brain, it is possible that motor programming is influenced by chronic pain differently than nociceptive afferent-efferent communication loops. Reorganization of the primary motor cortex has been observed in patients with chronic pain conditions including low back pain, knee osteoarthritis, and PFP (Hodges & Smeets, 2015; Pelletier et al, 2015a; Te et al, 2017).

2.3.1.3. Pain Sensation and Modulation Theory Summary. In summary, the neuromatrix theory proposes that pain experiences leave a neurosignature that can later serve as a trigger for a pain signal generated by the brain (Melzack, 2001). The arising cognitive, affective, and sensory processes have the ability to inform motor planning and implementation. While the neuromatrix theory provided groundbreaking strides in better understanding chronic pain and lesser understood pain conditions, there are still questions to be answered. For example, if the pain is created within the brain, by what mechanism and how or why is it sustained? If each pain experience bears its "signature" within the neuromatrix, how is it that "triggers" for chronic pain cannot consistently be identified at the patient-specific or condition-specific levels? This theory is a step in the right direction, and considers a number of factors left out of previous model, however, it would be nice to be able to support this theory with imaging or biomarkers in support of it, or to advance beyond it.

2.3.2. Pain Dimensions

2.3.2.1. Pain Intensity. No matter the type of pain experienced, pain perception is typically characterized by four dimensions: intensity, quality, location, and affect. Pain intensity is defined as how much a person hurts and is the most frequently measured patient-oriented outcome of the pain experience, likely because of the linear relationship between pain intensity, treatment delivery, and discharge from therapy settings (Pelletier et al, 2015a). That is to say that clinicians typically use more aggressive treatment delivery for patients who report higher pain intensity, and tend to get better discharge outcomes (Pelletier et al, 2015a). Pain intensity is often measured with visual analog scales (VAS) or numeric pain ratings (D. Turk, Melzack, R., 2011) during research and clinical settings.

Research on pain intensity in PFP are variable in the method of collection, but two commonly reported outcomes are the VAS for worst pain and the VAS for usual pain or current pain (Crossley, Bennell, Cowan, & Green, 2004). Thus far, perceived pain intensity scales have largely been used to characterize the sample or to demonstrate a pre-to- post- test change following an intervention (Crossley, Bennell, et al, 2004; D. Turk, Melzack, R., 2011).

Numeric pain ratings are typically presented to the participant or patient with a 0-10 scale where 0 indicates no pain, 10 indicates the worst pain imaginable, and depending on the author, occasional, inconsistent descriptors provided for the midpoint of the scale (D. Turk, Melzack, R., 2011).

The value of numeric pain ratings is that they are extremely common clinically, so individuals who have seen a clinician about their pain will likely be more familiar with this categorical system. The problem with the numeric pain rating system is that there is some research that suggests that no matter what you consider "worst pain imaginable," the participants'

imagination is often only as creative as the worst injury they have experienced, and so there is a large individual difference into what "value" each number on the scale represents (D. Turk, Melzack, R., 2011). For example, a study conducted on emergency room visitors indicated that they believed a higher pain rating would grant them quicker admission and better healthcare, so they admitted to inflating the number provided due to an objective unrelated to the pain itself (D. Turk, Melzack, R., 2011).

The 11-point numeric pain rating scale (range in scored from 0 to 10) demonstrated excellent discrimination between individuals with PFP who experienced worsening scores compared with those who did not [area under the curve= 0.84; (Piva, Gil, Moore, & Fitzgerald, 2009)]. The minimal clinically important difference score is -1.2 points (receiver operating curve) for a decrease in pain score, making it a fairly sensitive measure of changes in pain (Piva et al, 2009).

The VAS is performed by presenting the participant or patient with a 10- or 100- cm line with the far left of the line described as "no pain" and the far right end of the line described as "worst pain imaginable" (D. Turk, Melzack, R., 2011). The participant marks the line with an "x" at the point where they feel their pain would be and a measurement is taken from the left hashmark to the "x" (D. Turk, Melzack, R., 2011). The VAS is useful in characterizing pain as a variable that allows for a more individualized response. The VAS also makes the prompt flexible, allowing researchers to ask different pain questions with responses captured on the VAS. For example, PFP researchers typically gather VAS for the current pain intensity, the average pain intensity over the past 7 days, "usual" pain, "worst" pain, or for activity-specific pain (D. Turk, Melzack, R., 2011). The Eng and Pierrynowski Questionnaire (EPQ) was developed by Crossley, Bennell, et al (2004) by collecting VAS for 6 typically aggravating

activities for individuals with PFP (walking, running, squatting, sitting, ascending stairs, and descending stairs). The VAS, numeric pain ratings, and EPQ are all viable options for collecting and reporting self-reported pain information.

2.3.2.1. Pain Quality. Pain quality is the sensory aspect of pain, or what sensations the patient feels during the pain experience. Examples include burning, sharp, shooting, or throbbing pain (Melzack, 1987; D. Turk, Melzack, R., 2011). This dimension of pain is helpful during clinical diagnostic phases, but is not commonly tracked over time because it is not expected to vary as a result of treatment modalities, but instead it is expected to diminish in intensity, consistency, or duration (D. Turk, Melzack, R., 2011). Pain quality can also be useful in discriminating between pain types [nociceptive, neuropathic, nociplastic; (Smart et al, 2011)]. One of the most common measures for this dimension is the McGill Pain Questionnaire (Melzack, 1987; D. Turk, Melzack, R., 2011). Thus far, no studies have assessed pain quality in individuals with PFP.

2.3.2.2. Pain Location. Pain location is also a useful aspect of pain during the diagnosis and refers to the perceived area where the sensations are felt (Belanger, 2010). In acute instances, pain is often felt at the site of tissue damage (when present) but referred pain and pain associated with central sensitization that is without mechanical or threatened tissue damage (Belanger, 2010). Recently, innovations in technology have allowed researchers to utilize pain mapping techniques to determine typical pain patterns for patients to better understand typical pain location characteristics. Interestingly, whether the pain experienced in PFP is localized to the peri- or retro- patellar area appears to depend on the sample being assessed (Boudreau et al, 2017; Boudreau et al, 2018; M. S. Rathleff et al, 2017; M. S. Rathleff et al, 2013).

Retrospective evidence suggests that when pain duration continues beyond 5 years, the pain pattern continues to complete an O-shape around the patella (Boudreau et al, 2017; Boudreau et al, 2018). Patients with bilateral PFP tend to have highly symmetric mirror-image pain patterns (Boudreau et al, 2017; Boudreau et al, 2018), suggesting the potential for nociplastic pain. Future research should consider assessing body maps rather than knee maps alone, which may better represent receptive field sizes and widespread pain.

2.3.3. Sensitized Nervous System

Sensitization (to pain) describes structural and/or functional changes to the nervous system resulting in amplification of nociceptive signals (Woolf, 2011)**.** Peripheral sensitization is a normal process that may occur following a nociceptive event, and typically serves a protective purpose (Woolf, 2011). Reduced thresholds for excitatory neurotransmitter release and nociceptor firing allow the patient to sense pain prior to the point they normally would, protecting them from continuing to experience a stimulus that would cause further tissue damage. Clinical signs of peripheral sensitization include pain with non-noxious stimulus (allodynia), pain hypersensitivity (hyperalgesia) at the painful site, and a widening painful area beyond the affected or threatened structures [increased receptive fields; (Staud, 2012)]. Individuals with PFP exhibit several of these signs.

Allodynia is thought to be the result of activation of "silent" nociceptors (Schaible & Schmidt, 1988). "Silent" nociceptors are the nociceptors in the skin, joints, muscle, and viscera that are typically dormant in response to mechanical stimuli but are activated with the presence of inflammatory or chemical mediators (Schaible & Schmidt, 1988). Another potential explanation of allodynia is the idea of the "touchgate." The touchgate was first described by

Apkarian, Stea, and Bolanowski (1994) as the inhibition of tactile signals in the presence of pain, allowing the nervous system to prioritize pain.

Thus far, Jensen et al (2008) is the only author thus far to assess allodynia in patients with PFP. In that study, 22% of patients experienced pain when a soft brush was applied to the knee. Jensen et al (2008) also reported that 22% of the sample experienced pain with application of a vibrating tool to the skin in the affected area.

Receptive fields are the areas responsive during stimulation of a specific sensory neuron (Sluka, 2016). Increased receptive fields occurs due to the presence of inflammatory markers and chemical mediators (Sluka, 2016). These clinical signs can alter cognitive attentional processes to redirect the individual to the pain and allow protection and healing to occur (Torta et al, 2017). It is important to note that this only explains sensitization from a biomedical viewpoint, and that biopsychosocial processes that can affect this process will be discussed later.

Hyperalgesia is thought to occur due to a reduction in nociceptive firing threshold or an increase in firing rate (Staud, 2012; Woolf, 2011). Hyperalgesia may also be the result of increased excitatory neurotransmitter release or release at subthreshold levels (Staud, 2012; Woolf, 2011). Hyperalgesia can be observed throughout the body (widespread) or only around the site of pain or injury (local). Local hyperalgesia is thought to occur due to changes at the peripheral nervous system, where remote hyperalgesia is thought to occur due to central mechanisms (Staud, 2012; Woolf, 2011).

Hyperalgesia is commonly measured using an algometer to measure pressure pain thresholds. Pressure pain thresholds (PPTs) that are lower than a pain-free condition or group are indicative of sensitization either at the affected site (patella/knee), on the contralateral but unaffected side (opposite knee), distal to the site (lower than the spinal level of the affected area),

or remote to the painful area (upper extremity). Lower local PPTs are indicative of primary hyperalgesia (Staud, 2012; Woolf, 2011). Lower contralateral and distal PPTs indicate secondary hyperalgesia with at least spinal-level involvement of the central nervous system (Staud, 2012; Woolf, 2011). Lower remote PPTs indicate widespread central nervous system sensitization (Staud, 2012; Woolf, 2011).

A number of strong studies support reduced local and remote PPTs in individuals with PFP relative to healthy controls (De Oliveira Silva, Rathleff, et al, 2019; Holden et al, 2018; Noehren et al, 2016; Pazzinatto et al, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2013; M. S. Rathleff, Roos, et al, 2016) indicating potential central sensitization. These findings have been replicated in adolescent females (M. S. Rathleff et al, 2013), young female adults [ages 18-40 years; (Holden et al, 2018; Noehren et al, 2016; Pazzinatto et al, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff, Petersen, et al, 2016), but have not yet been assessed in women over the age of 40 years. Two studies (M. S. Rathleff et al, 2017; van der Heijden et al, 2015) were unable to replicate between group (PFP vs. pain-free) differences, and both studies included males and females (analyzed as a single group). A recent meta-analysis with subgroup analysis suggested (Sigmund, 2020) that mixed-sex studies (including males and females) were more likely to have non-significant differences and were heterogeneous, suggesting that the samples included in these three studies were unable to be grouped due to some factor. I believe that sex may be that difference, but this has not been confirmed by any studies, and no studies have assessed males only.

Central sensitization challenges the concept that pain sensation must involve peripherally activated nociceptive response to a stimulus (Latremoliere & Woolf, 2009; Woolf, 2011) and

describes pain that is driven from the altered structure and/or function of the pathways in the CNS (Fillingim, Loeser, Baron, & Edwards, 2016; Staud, 2012). Many conditions formerly described as psychosomatic in nature can be explained by central sensitization (Woolf, 2011). Central sensitization is thought to drive nociplastic pain (Chimenti et al, 2018) and is characterized by allodynia, widespread hyperalgesia, increased receptive fields, enhanced temporal summation, spontaneous pain, and impaired descending pain inhibition (Woolf, 2011). Another way to explain central sensitization is enhanced pain facilitation mechanisms with attenuated pain inhibition pathways (Staud, 2012). This altered functional state may help explain the lack of long-term pain reduction following treatment and provide rationale for failure of traditional exercise therapy for individuals with PFP.

Allodynia resulting from central changes is hypothesized to be the result of increased excitability of wide dynamic range neurons or increased responsiveness and prolonged response following noxious stimulus (Staud, 2012). Increased wide dynamic range responsiveness to innocuous stimuli may explain this phenomenon from a central nervous system perspective. In healthy animals, low threshold neurons respond to innocuous stimuli, high threshold respond to noxious stimuli, and wide-dynamic range neurons respond under both innocuous and noxious conditions (Sluka, 2016). Sluka, O'Donnell, Danielson, and Rasmussen (2013) a study in which rats were introduced to 3 stimuli: an innocuous (brush) stimulus, a pressure stimulus, and a noxious (pinch) stimulus. The authors (Sluka et al, 2013) demonstrated that at 3 hours post-inflammation inducement, the high threshold neurons were only active in the noxious stimulus and the low threshold neurons were only active during the innocuous stimulus, however, the wide dynamic range neurons were highly active in all three conditions. This demonstrated that

wide dynamic range neurons may be active following a painful condition regardless of the stimulus experienced and helps explain allodynia.

Widespread hyperalgesia is increased pain sensitivity throughout the body. In this case, it is not just the peripheral nerve that has become sensitized, but a host of issues arising from transmission of the hypersensitive signal sent to the spinal cord and supraspinal areas (Latremoliere & Woolf, 2009). One commonly accepted theory is that a loss of pain inhibition mechanisms allows the system to remain sensitized (Latremoliere & Woolf, 2009). As fewer (or ineffective) pain inhibition signals are sent, the pain signal persists. In addition, if excitatory neurotransmitters are being released either in larger amounts or at subthreshold levels, then the imbalance shifts toward pain enhancement (Latremoliere & Woolf, 2009). In persistent musculoskeletal pain conditions of the lower back or lower extremity, it is common to observe hyperalgesia at the upper extremity, demonstrating this phenomenon (De Oliveira Silva, Rathleff, et al, 2019).

As with peripheral sensitization, increased receptive fields can be present when central sensitization occurs, however, the receptive field size is much broader and more consistent than with peripheral sensitization (Schaible & Schmidt, 1988). This indicates that the central neurons are receiving information from a larger region than normal, and increases the tender area. Some nociplastic pain conditions such as fibromyalgia, it is not uncommon for patients to report pain over large portions of the body (Sluka, 2016). In neuropathic conditions, it is common for patients to report pain in an area loosely correlated to the affected nerve or nerve root path (Sluka, 2016).

TSP describes a phenomenon in which a patient has an enhanced response to a noxious stimulus that it either repeated or constant (Woolf, 2011). In healthy, pain-free individuals, TSP

is a normal reaction, but in patients exhibiting signs of central sensitization, earlier response (i.e. lower number of repetitions or shorter time duration) results in increased pain intensity (Woolf, 2011). TSP is hypothesized to be caused by increased excitability of nociceptive neurons in the central nervous system (Fillingim et al, 2016; Staud, 2012). When C-fibers receive constant or repetitive stimulation, the number of action potentials released in the dorsal horn progressively increases (Fillingim et al, 2016; Staud, 2012). Enhanced TSP relative to pain-free individuals is predictive of risk for persistent pain (despite treatment or surgery), post-surgical persistent pain intensity, and negative coping responses [i.e. pain catastrophizing; (Woolf, 2011)]. TSP represents a state in which the pain facilitation mechanisms are enhanced, and can only be restored with effective descending pain inhibition.

Thus far, TSP for individuals with PFP has only been evaluated only two studies (Holden et al, 2018; M. S. Rathleff et al, 2017) with equivocal results. The researchers both used cuff algometry to assess TSP. Results of one study found that young females (under age 30) who were currently experiencing demonstrated higher VAS measures than those who has self-reported recovery from PFP, and healthy, pain-free controls (Holden et al, 2018). While the difference between the current-PFP group and the recovered-PFP group was not statistically significant, both PFP groups demonstrated enhanced TSP relative to the control group. Results of the second study (M. S. Rathleff et al, 2017) suggested that no statistical difference exists (with a small standardized mean difference) between pain-free, age- and sex-matched controls and adults with PFP on TSP measures. The authors did include males and females, for which there may be a difference in central sensitization, however, both studies were conducted on participants with median symptom durations of 2 (M. S. Rathleff et al, 2017) and 8 years (Holden et al, 2018).

CPM describes the "pain inhibits pain" phenomenon and describes the efficiency and integrity of the descending pain inhibition network (Fillingim et al, 2016; Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016). CPM uses a test stimulus that will be tested under a baseline condition and repeated with an additional noxious stimulus (Kennedy et al, 2016). CPM response is defined as the change in the test stimulus threshold from the second condition to the baseline condition (Kennedy et al, 2016). In healthy, pain-free humans, the observed CPM response is that the addition of the second noxious stimulus increases the pain intensity of the test stimulus, meaning the individual is able to withstand greater amounts of the stimulus prior to reaching threshold (Fillingim et al, 2016). In healthy, pain-free people, variability in CPM response is expected (Kennedy et al, 2016). In people with persistent pain conditions, variability should still be expected, but the overall CPM response for the sample is typically lower than pain-free individuals—meaning they were unable to withstand as much of the stimulus before achieving threshold—indicating either ineffective or inefficient pain inhibition (Staud, 2012). CPM response is a predictor of treatment response, as well as predict those at risk for future chronic pain. Some authors have argued that CPM can be used as a biomarker for chronic pain (Kennedy et al, 2016). CPM can also be described in terms of "responders" so those who still have an inhibition response and "non-responders" who demonstrate no change or reduced pain threshold with the addition of the second stimulus (Sluka, 2016).

CPM has been assessed in individuals with PFP in three studies (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017). In one study, the authors reported non-significant differences between PFP and healthy groups (M. S. Rathleff et al, 2017). This study included males and females and used a cold pressor test (i.e. PPTs repeated pre- and during- ice water immersion) to assess CPM (M. S. Rathleff et al, 2017). In another study,

differences between PFP, recovered PFP, and pain-free individuals were assessed (Holden et al, 2018). Authors reported significant differences between the current- and recovered-PFP groups, but not between either of the PFP groups and the pain-free group (Holden et al, 2018). In the third study, significant differences were observed between PFP and pain-free females. CPM was assessed using a cuff algometer in the latter two studies. The difference in data collection method may be one reason for the difference in results. Cuff algometry is a unit that provides circumferential pressure to a limb, where PPTs are a more localized pressure application (Kennedy et al, 2016). Additionally, the temperature, water circulation, and cultural considerations must be considered when the cold pressor test is used. Temperatures between 6-8 degrees Celsius, with some circulation typically yield the most reliable results (Kennedy et al, 2016). A review of reliability of CPM methodology stated that a minimum of a 20 minute washout period is required following the cold pressor test (Kennedy et al, 2016).

Spontaneous nociceptor activation is also a hallmark sign of central sensitization and occurs with unprovoked nociceptor activity (Latremoliere & Woolf, 2009). Increased (and spontaneous) activation of wide dynamic range neurons may help explain this phenomenon as well (Sluka, 2016; Sluka et al, 2013). If the wide dynamic range neurons fire have increased response to innocuous stimulus, they may continue to fire when no stimulus is presented. Spontaneous nociceptor activation has been observed in animals but is difficult to assess in humans.

Somatosensory tests such as QST indirectly assess the efficiency and functional state of the peripheral and central nervous systems. Transcranial magnetic stimulation (TMS) is a more direct method of assessing motor function by stimulating the motor cortex to assess the organization and cortical outputs (i.e. motor evoked potentials). In patients with PFP, the

quadriceps were mapped to reveal reduced and overlapping area with a more anterior representation compared to pain-free controls. In addition, reduced number of cortical peaks were observed in patients with PFP. The lack of discrete cortical peaks is hypothesized to be related to reduced intramuscular coordination, which is consistent with the results of EMG studies, which suggest differences in vastus medialis and lateralis neuromuscular control. This altered control may contribute to changes in alignment or movement of the patella on the trochlear groove. All participants in the TMS study had symptom durations of 4 months or longer (range: 4-84 months, median: 18 months) and relatively low pain intensity reports at the time of the study (mean 2.45 out of 10 on a numeric pain scale from 0-10, median: 2, range: 0-6) and average pain over the previous six months [mean: 4.9, median: 5, range: 3-7; (Te et al, 2017)].

Observation of changes in bloodflow can be observed using fMRI in the brain which can be used to infer connectivity and therefore, connectivity between different neural networks. A recent study examined fMRI in individuals with PFP and the broad changes in the central nervous system changes for the PFP group compared to pain-free age- and sex-matched participants. Reduced pain (thalamus, anterior cingulate cortex) and pain (anterior cingulate cortex, insula)-sensorimotor control (cerebellum) connectivity was observed, indicating inefficient communication in those regions (Diekfuss et al, 2021). Additionally, increased connectivity was observed between the somatosensory and motor cortices. Increased communication can stem from needed continuous input from the pain-disrupted somatosensory cortex in order for appropriate motor execution to occur, indicating a potential tradeoff between both pain and sensory function and between sensory information and motor output (Diekfuss et al, 2021).

2.3.3.1. Pain Summary. While traditional views of pain are biomedical, the current state of the evidence suggests that pain is biopsychosocial. There is sufficient evidence to suggest that chronic pain does not follow a traditional afferent-efferent path, but may originate at the cortical levels, and that nociceptors may spontaneously be activated in nociplastic pain (Latremoliere & Woolf, 2009; Woolf, 2011). If PFP research embraces these ideas, strides could be made in movement analysis beyond the search for a common nociceptive onset. Signs of central sensitization may actually help explain some of the biomechanical and motor discrepancies we observe in the literature but the first step is to embrace a paradigm shift in the way we conceptualize pain as a variable.

2.3.4. Psychosocial Factors

Nociception, pain perception and the threat of pain are different constructs. The threat of pain is a cognitive appraisal in which the individual expects or anticipates that injury (i.e. tissue damage) will occur (Hodges & Smeets, 2015). An example is slicing the finger on a piece of paper. The individual may anticipate that a papercut has occurred and prepare for pain or blood to appear but if the paper did not move through the outer layers of the epidermis, neither pain nor injury may be present, and the individual may go on with his or her day. The threat of injury is typically linked to the threat of pain, as most individuals assume these are synonymous. They are not.

The threat of pain is the cognitive appraisal of a situation in which one expects or anticipates that pain will be the result of the activity or situation (Hodges & Tucker, 2011). A key example for PFP might be the avoidance of stairs or squatting because one anticipates that it may be painful. Avoidance of specific movements or of physical activity has been described a

number of ways in the literature from the more serious pain catastrophizing, kinesiophobia, and fear-avoidance. Pain catastrophizing is characterized by an irrationally negative future outlook, exaggerated and negative cognitive appraisals of pain, and exaggeration of the threat value or seriousness of pain sensations (Chaves & Barber, 1974; Quartana, Campbell, & Edwards, 2009). The threat of pain or injury may be mediated by one's perception of their ability to cope with that pain, a phenomenon known as pain self-efficacy (C. L. Miles, Pincus, Carnes, Taylor, & Underwood, 2011). These constructs are further reviewed below, but at the core of each of these ideas is that it may not be the actual pain perception but the threat that pain or threat of injury presents that induces these negative coping styles.

2.3.4.1. Pain Catastrophizing. Pain catastrophization was first introduced by Ellis (1962; Quartana et al, 2009) as an exaggerated and negative coping style used by people diagnosed with depression and anxiety. Later, it was suggested (Spanos, Radtke-Bodorik, Ferguson, & Jones, 1979) that catastrophizing may be an extreme response to worry over pain or hyper-attention to pain. Hallmarks of pain catastrophizing include an irrational outlook of the future (Ellis, 1962); exaggerated, negative pain appraisals (Quartana et al, 2009);and magnified threat or severity of pain sensations (Chaves & Brown, 1987). Pain catastrophizing is a risk factor for increased pain intensity and greater disability compared to non-pain catastrophizers (Borkum, 2010a; Picavet, Vlaeyen, & Schouten, 2002) and has been linked to abnormal quantitative sensory testing (Borkum, 2010a; George, Wittmer, Fillingim, & Robinson, 2007; Granot, Granovsky, Sprecher, Nir, & Yarnitsky, 2006) and affects movement and brain activity, making it a potentially important coping response.

Pain catastrophizing is positively associated with perceived pain intensity, depression, anxiety, and reduced social support (Quartana et al, 2009). It is negatively associated with

physical activity and self-reported function (Borkum, 2010b). Individuals with chronic pain conditions who score higher on the pain catastrophizing scale (PCS) tend to exhibit increased pain behaviors and experience poor treatment, rehabilitation, and surgical outcomes (Dave et al, 2017; Domenech, Sanchis-Alfonso, & Espejo, 2014; Taub, Sturgeon, Johnson, Mackey, & Darnall, 2017).

Catastrophizing has also been linked to enhanced pain facilitation [e.g. TSP (Borkum, 2010a; Granot et al, 2006)] and hyperalgesia (George et al, 2007). Additionally, catastrophization increases activation in the anterior cingulate cortex, medial frontal cortex, secondary somatosensory cortex, and cerebellum (Gracely et al, 2004). The suggestion was that tendencies to catastrophize increase attention to pain, which increases perceived pain intensity, and the individual prepares a motor plan that allows escape or avoidance of additional pain (Borkum, 2010b; Gracely et al, 2004). While this sounds intriguing, activity in a few key areas is lacking. While the cerebellum does play a role in coordinating and planning movement, several other areas would be expected to be activated as well with motor planning such as the primary somatosensory cortex or the premotor areas.

Criticisms of the pain catastrophizing include the lack of standardized interview techniques in initial studies (Quartana et al, 2009), leaving the entire construct up for debate. While survey instruments have been developed to measure the degree of pain catastrophizing as a coping behavior, if the construct itself is not sound, then it would be difficult to call the measures valid, let alone reliable.

Pain catastrophizing and coping behaviors in individuals with PFP have only been examined in four studies (Domenech et al, 2014; Domenech, Sanchis-Alfonso, Lopez, & Espejo, 2013; Maclachlan, Matthews, Hodges, Collins, & Vicenzino, 2018; C. R. Rathleff, W. N. Baird,

et al, 2013). In all three studies, PCS scores were higher in individuals with PFP than in healthy control groups, which included adolescents and adults of both sexes. PFP participants who reported higher levels of catastrophizing also tended to have higher perceived pain intensity ratings, and reduced self-reported functional levels (Maclachlan, Collins, Matthews, Hodges, & Vicenzino, 2017; Thomee, Thomee, & Karlsson, 2002). Moreover, patients who experienced symptom improvement over 6 months reported lower levels of catastrophizing than at baseline (Domenech et al, 2014; Maclachlan et al, 2017).

Another factor that may be important in examination of catastrophizing coping is that it appears to be associated with quantitative sensory testing (Glass et al, 2014; Sluka et al, 2012; Taub et al, 2017). Individuals who have signs of central sensitization tend to report higher levels of pain catastrophizing (Taub et al, 2017; Woolf, 2011). It has been suggested that there may be a physiological link between negative coping responses to pain and neuroplastic changes of the central nervous system but an exact biomarker has not yet been identified (Sluka et al, 2012). If this physiological link exists, it could be an important factor in understanding both conditions and to examine sex differences within individuals with chronic pain, as females tend to experience higher rates of chronic pain conditions, report more negative coping responses, and exhibit different movement patterns than males (Sluka et al, 2012). Until then, it appears as though pain catastrophizing is an important factor to better understand the pain experience of individuals with PFP.

2.3.4.1. Fear-Anxiety-Avoidance. Fear-avoidance is a cognitive-behavioral model first described by Vlaeyen and Linton (2000) that basically states that if one anticipates pain with a certain activity or movement, they will avoid that activity or movement. The original authors (Vlaeyen & Linton, 2000) followed up with updated perspectives on their model after critical

review, stating that an anxiety-anticipation model was perhaps more appropriate (Leeuw et al, 2007; Vlaeyen & Linton, 2006). Anxiety was added as a factor between fear and avoidance in the updated model, as the former model did not account for the fact that the three main components of fear—interpretation of a stimulus as a threat, increased sympathetic arousal, and defensive behavior (Leeuw et al, 2007)—were not necessarily observed in chronic pain patients.

Anxiety is similar to fear, but is a less intense future-focused emotional state in which the source of the threat is not clearly defined (Leeuw et al, 2007). While people experiencing true fear of an actual threat may engage in defensive behavior, anxiety tends to produce more protective and preventative behaviors (Leeuw et al, 2007). Additionally, one component of anxiety is hypervigilance, which encompasses behaviors such as scanning the environment for potential threats and causes the individual to selectively attend to that threat (as cited in Leeuw et al, 2007). Second, anticipation of pain was added to the model, since one cannot avoid pain if one is already actively experiencing pain (Leeuw et al, 2007). In the updated version of the model, if one experiences fear of pain, the resulting behavior would be related to escaping that pain, whereas, if one was anxious about an upcoming pain experience, they would attempt to avoid the painful experience (Leeuw et al, 2007). This model can directly inform our understanding of how anticipation of pain may affect movement.

Much like the catastrophizing response, PFP patients who exhibit high levels of fearful anticipation of pain or pain-related fear tend to exhibit lower levels of self-reported function and higher levels of pain (Maclachlan et al, 2017; Thomee et al, 2002). Both coping response types, however, imply that patients who score higher on catastrophization or fear-avoidance may be attending to their pain to a higher degree than those who score lower on the same scales. While the fear-anxiety-avoidance model and its construct of anticipation of pain seems to lend itself to

a more direct relationship with movement, attention to pain should also be considered since it may account for both coping responses (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012). Maclachlan et al (2017) conducted a cross-sectional study analyzing years of survey data and found that 26% of the adolescents in the cohort with PFP reported high fear-avoidant behaviors but other studies have examined a similar construct called kinesiophobia.

2.3.4.3. Kinesiophobia. Kinesiophobia was developed to help explain movement avoidance in the presence of pain, however, this theory suggests that the patient experiences a fear of completing the movement (Lundberg, Grimby-Ekman, Verbunt, & Simmonds, 2011). Kinesiophobia has recently been criticized for improper use of the terms fear and phobia (Lundberg et al, 2011). Fear is a negative emotional response to a (real or perceived) threat (Lundberg et al, 2011). A phobia, however, is an extreme, irrational fear or avoidance that can interfere with daily life (Lundberg et al, 2011). While participants may experience a perceived threat due to anticipated onset of unwanted pain, it is unlikely that this fear will become a phobia (Lundberg et al, 2011). Additionally, the fear is likely not of the movement itself, but is of the fear associated with the movement, ergo the name of the term is incongruous with the construct it is trying to capture (Lundberg et al, 2011). In a scathing review, Lundberg et al (2011) concluded "for most questionnaires [about pain-related fear], there was no underlying conceptual model to support the questionnaire's construct" and that construct validity had not been assessed or was actually unsupported for the most common assessments. This is particularly disconcerting, as there is clearly some form of state-anxiety or hope to avoid movement if patients are responding to the questions posed on these inventories, however, more qualitative research is needed in this area prior to continued use of these questionnaires.

Kinesiophobia is typically measured using the Tampa Scale of Kinesiophobia, which is a 17-item inventory that assesses items on a 4-point Likert (Maclachlan et al, 2018). Higher scores indicate greater fear of movement with a proposed cut-off score of 37 separating those with high-fear from those considered low-fear (Maclachlan et al, 2018).

In a cross-sectional study examining the psychological factors for individuals with PFP, both kinesiophobia and depression were associated with higher levels of disability (Knee Osteoarthritis Outcome Survey-Patellofemoral Subscale scores) while a weak relationship was observed between kinesiophobia and anxiety (Maclachlan et al, 2018). While Smith, Moffatt, et al (2018) did not identify themes of kinesiophobia or fear-avoidance in his qualitative analysis on the lived experience of PFP, he was able to identify that participants believe that treating clinicians do not believe they should take part in physical activity, so it is plausible that a Hawthorne effect could also help explain questionnaire responses if they believe the researchers hold the same opinions on physical activity.

Research has recently begun to examine relationships between psychological factors and movement. de Oliveira Silva, Barton, et al (2019) reported that higher kinesiophobia scores were associated with slower stair descent and reduced knee flexion angles, despite the fact that strength was not significantly correlated with these movement alterations. Additionally, Glaviano and Saliba (2018) suggested that (while holding other variables constant), knee abduction angles explained 37.5% of the variance in Fear-Avoidance Behavior Questionnaire scores. The implication is that knee abduction angle may be the movement that participants are attempting to avoid, however, there is no qualitative evidence to support this statement.

While fear-avoidance and kinesiophobia do not have strong construct validity, further qualitative research should be undertaken to determine the constructs that do explain concepts of avoiding certain behaviors or movements in the face of pain.

2.3.4.4. Depression and Anxiety. Pain perception is influenced by a number of cognitive and emotional variables, as demonstrated by the previous section on the neuromatrix theory (Crofford, 2015). Crofford (2015) reported that, on average, 30-60% of patients with chronic musculoskeletal pain also have a depressive disorder, and that self-reported hypersensitivity to pain is a common complaint in this population. In fact, changes in pain perceptions was identified as a strong predictor of depression severity and vice-versa in a large longitudinal study assessing these factors in patients with chronic back, hip, and knee pain (Bair, Wu, Damush, Sutherland, & Kroenke, 2008; Crofford, 2015). In fact, 20% of the sample of 500 participants (in that same longitudinal study) self-reported pain and depression, 23% reported that they experience pain, anxiety, and depression, and 3% reported pain and anxiety. In that study, the combination of pain with depression and/or anxiety reported poorer health-related quality of life and higher levels of disability than those who did not have an accompanying psychological comorbity (Bair et al, 2008).

While few studies have examined links between depression, anxiety, and PFP, Machlachlan et al (Maclachlan et al, 2017; Maclachlan et al, 2018) reported on common psychological factors among participants with PFP in both a systematic review and follow-up cross-sectional study. The authors (Maclachlan et al, 2017) reported that nearly 9% of a Danish cohort of adolescents with PFP reported depressive symptoms, while Smith et al (2018) reported that 26% of a UK cohort experienced anxiety or depressive symptoms. This could indicate that cultural or age differences may exist in either diagnosis or reporting of psychological conditions.

Conversely, techniques of participant recruitment or screening may also play a role in these differing statistics.

Depression is a psychological condition, and for non-psychologists to conduct a research study where identifying whether participants were depressed would largely be unethical, depending on the practice guidelines set forth for the profession(s) represented on the research team, however, asking participants to self-report a current or past diagnosis, or to complete a depressive symptoms survey is a commonly acceptable method of data collection. Therefore, only self-report inventories identifying depressive and anxious symptoms will be examined in this review.

The Hospital Anxiety and Depression Scale is a 14-item questionnaire with two subscales, and was developed to identify depressive and anxious states, rather than clinical diagnosis (Bjelland, Dahl, Haug, & Neckelmann, 2002). Each item is rated on a 4-point scale and participants are asked to report their response for how they felt over the past seven days (Bjelland et al, 2002; Maclachlan et al, 2018). Scores range from 0 to 21, with higher scores being indicative of higher anxious and depressive states (Bjelland et al, 2002; Maclachlan et al, 2018). A recent review of over 700 studies that used the measure suggested that scores of 8 or higher may be indicative of anxiety or depression (Bjelland et al, 2002).

2.3.4.5. Pain Self-Efficacy. Pain self-efficacy describes the degree of certainty that an individual feels as if they can cope with or handle pain (C. L. Miles et al, 2011; D. C. Turk, Fillingim, Ohrbach, & Patel, 2016). To incorporate all aspects of pain self-efficacy, a measure would need to include all aspects hypothesized to be salient for individuals with persistent pain, including: ability to control the pain and negative emotions associated with the pain, maintain everyday life including work, communicate needs to healthcare providers, and apply advice

about their pain (C. L. Miles et al, 2011; D. C. Turk et al, 2016). It is also common for pain self-efficacy scales to include a comparative prompt to allow the participant to assess their coping and beliefs relative to another behavior (C. L. Miles et al, 2011).

Pain self-efficacy is thought to be related to the amount of perceived threat that pain poses to the individual and responses may be reflective of perceptions of: available resources, coping responses, ability to maintain normal functioning and activity, and pain tolerance (C. L. Miles et al, 2011). Pain self-efficacy has been used to help researchers better understand behaviors such as reducing or stopping physical or athletic activity, medical care-seeking behaviors, and seeking specific treatments like medications, surgical intervention, braces or orthotics (C. L. Miles et al, 2011)

In chronic low back pain, pain self-efficacy may be more important at mediating the pain-function relationship than negative coping responses such as kinesiophobia and pain catastrophizing (Kamper 2012). In PFP research, pain self-efficacy has only been observed in one study (Maclachlan et al, 2018). In a cross-sectional regression analysis, kinesiophobia, local PPTs, pain self-efficacy, and pain catastrophizing together explained 40% of the variance in self-reported knee function (Maclachlan et al, 2018). This suggests that pain self-efficacy may be an important variable, though not extensively examined among individuals with PFP.

2.3.2.6. Psychosocial Summary. It is well-accepted that psychosocial variables affect pain perceptions and the overall pain experience, but they may also play a role in movement avoidance, selection, or physical activity involvement. Additionally, psychosocial variables have neural components that are well-associated with signs of central sensitization. While there is a paucity of qualitative evidence supporting some constructs currently being assessed in PFP research, it is important to continue to develop these constructs and measures.

2.3.5. Adaptation of the Sensorimotor System

2.3.5.1. Motor System Adaptation and Changes in Excitability. Hodges and Tucker (2011) suggest that changes in muscle activity may not be explained by simply assessing changes in motor neuron excitability, but may be a sign of a larger adaptive process of the nervous system. Spinal cord, cortical, or other central nervous system changes may help explain observed motor activity (Hodges & Tucker, 2011) and these changes may be different at varying levels of the nervous system. Some studies suggest that pain suppresses cortical excitability, while other suggest that the cortical signaling is inhibited, and those responses are not always predictive of motor unit or muscular activity (Hodges & Tucker, 2011). These contradictory findings are puzzling, but could be explained by inhibition or excitation occurring in the spinal cord or at supraspinal yet subcortical levels.

In laboratory-induced low back pain, reduced deep abdominal muscle activity has been observed with EMG, however, increased motor-evoked potential amplitude were observed suggesting that the motor cortex was sending strong action potentials, but without a corresponding muscular reaction. This could be explained by inhibition at the spinal cord, but is difficult to observe and interpret in humans. The Hoffmann reflex and stretch reflex provide opportunities for observation, but several issues with interpretation (e.g. size of the reflex is dependent on mechanisms beyond excitability) limit the applicability and reliability of this method (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016). By contrast, in patients with low back pain, an increased threshold for motor-evoked potentials firing has been observed, which implies that it takes more stimulus for the motor cortex to send a signal to contract (Hodges & Smeets, 2015; Hodges & Tucker, 2011).

Some previous studies have reported depressed excitability of the motor-evoked potentials but increased motor neuron excitability at the spinal level, suggesting a paradox of effects between the cortical and spinal levels (Hodges & Smeets, 2015; Hodges & Tucker, 2011). Most studies examining motor-evoked potentials during pain demonstrate cortical inhibition, however, at the muscular and motor unit levels, inhibition is not always the observed response (Hodges & Smeets, 2015; Hodges & Tucker, 2011). This conflicts with pre-existing pain-movement theory, which suggested that a universal motor response would be observed when pain is introduced (Hodges & Smeets, 2015; D. Turk, Melzack, R., 2011).

Te et al (2017) observed motor cortex changes in individuals with PFP with as little as four months symptom duration (mean 29 ± 26 months; range 4-84 months; median: 18 months) compared to healthy, pain-free controls. The authors (Te et al, 2017) describe an anterior shift in the primary motor cortex organization of the quadriceps. Specifically, greater overlap between the quadriceps and adjacent muscles are represented, along with a reduced number of discrete cortical peaks (representing comparative motor-evoked potentials amplitude to surrounding muscles), suggesting reduced motor control and intramuscular coordination (Te et al, 2017). These findings are suggestive of cortical inhibition compared to pain-free individuals, and suggest that individuals with PFP may exhibit reduced coordination and motor variability during movement (Te et al, 2017).

Females with PFP have lower Hoffmann reflex amplitudes for the vastus medialis compared to healthy controls (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Pazzinatto, de Oliveira Silva, Pappas, et al, 2017). This lower VM Hoffmann reflex was associated with higher self-reported pain, lower self-reported function, and longer symptom duration (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Pazzinatto, de Oliveira

Silva, Pappas, et al, 2017). de Oliveira Silva et al (2016) concluded that although females with PFP exhibited reduced VM activation during MVICs compared to healthy controls, they demonstrated greater VM activation during stair descent. The clinical relevance of this finding is that females with PFP may appear to make improvements if they only assessment used to identify improvement is a maximal isometric contraction, but that at the neuromuscular level, the story is a little less clear. Overall, results from observations of the neuromotor system suggest that cortical spinal inhibition occur in women with PFP.

Muscular and motor unit analyses will be presented and synthesized later in this review. The key findings at the muscular level include intra-quadriceps (e.g. vastii muscle) differences in activation onset and duration between healthy individuals and individuals with PFP, differences in GMed activation onset and duration in individuals with PFP, and only limited, non-conclusive data examining GMax and hamstring neuromuscular patterns (Aminaka et al, 2011; C. J. Barton et al, 2013; Boling & Padua, 2013; Cowan et al, 2001; Cowan et al, 2002). Vastii and GMed onset and duration differences have been observed during SLS, stair descent, and postural control tasks (C. J. Barton et al, 2013). This suggests an inhibitory pattern at the muscular level.

At the motor unit level, R. Mellor and P. Hodges (2005) observed reduced VM to VL motor unit synchronization during isometric knee extension relative to healthy, pain-free individuals. Mellor and Hodges (2005) were the first to identify differences in motor unit synchronization in the presence of pain. Motor unit synchronization is believed to be a plastic phenomenon controlled by supraspinal and spinal processes (Hodges & Smeets, 2015). The findings indicate that, for individuals with PFP, the outcome of reduced synchronization may be reduced intramuscular coordination. While this may not be reflected in force variables, it may be rationale for reduced patellar control. Gallina, Salomoni, et al (2018) identified higher VL motor

unit firing rates in women with PFP, but higher VM firing rates in healthy, pain-free women. Martinez-Valdes et al (2019) did not find higher VL motor unit firing rate but they did report increases motor unit discharge rate variability. It may be important to note that the participants in the (Gallina, Salomoni, et al, 2018) study had symptom durations of (interquartile range) 12-60 months, but Martinez-Valdes et al (2019) did not report the mean or median symptom duration. These findings indicate at the motor unit level, firing rates are increased, despite cortical and spinal inhibition. They also are suggestive of intra-muscular differences which are supported by muscular-level timing and activation pattern differences (Hodges & Smeets, 2015).

In the protective response theory, Hodges and Smeets (2015) suggest that cortical changes reflect altered motor planning or enacting an altered motor strategy, while motor unit or muscular response may be reflective of the *net response* of the nervous system, as it may be mediated by spinal cord or other supraspinal processes, psychosocial influences or nervous system adaptations to pain. In PFP, we see an inhibition at cortical and spinal levels, no reduction in quadriceps of gluteal muscle peak amplitude, but altered timing and pattern has been demonstrated across a variety of tasks. Central sensitization may cause neuroplastic changes in the pain pathways, which may influence sensorimotor system adaptations or output (Woolf, 2011). Central sensitization may, therefore, explain some of the variance in motor responses to pain.

2.3.6. Autonomic Nervous System Function

Changes in the autonomic nervous system has been implicated in chronic musculoskeletal injuries. The theory relating autonomic nervous system function and chronic musculoskeletal injury hinges on the idea that chronic injury is due to malfunction of the normal

tissue healing processes, (again suggesting a biomedical view of pain) and aligns with the suboptimal tissue loading hypothesis to explain the pain-movement relationship (Gisselman, Baxter, Wright, Hegedus, & Tumilty, 2016). As tendon undergoes healing, neuron growth occurs into the tendon, and chemical mediators arrive to the affected site from sensory, autonomic, and pain-regulating systems, which can modulate pain and inflammatory processes (Ackermann et al, 2014; Gisselman et al, 2016). When loading exceeds the body's ability to repair the tissue, collagen damage can occur (Gisselman et al, 2016). This collagen damage can lead to an imbalance between pro- and anti- inflammatory chemical mediators, which signal the body to attempt to start the healing process (Gisselman et al, 2016). This causes additional stress during tissue repair, and autonomic functions may be adjusted (Ackermann et al, 2014; Gisselman et al, 2016).

The heart is innervated by both the sympathetic and parasympathetic nervous systems (Gisselman et al, 2016). Despite the role of other systems on heart rate, the autonomic nervous system is primarily responsible for the heart's rate, rhythm, conduction velocity, and strength of contraction during systole and amount of inhibition during diastole (Ackermann et al, 2014). Sympathetic and parasympathetic neurotransmitters (norepinephrine and acetylcholine, respectively) influence the time period between beats (Ackermann et al, 2014). These neurotransmitters have opposing functions (norepinephrine to excite and acetylcholine to inhibit) with respect to electrical activity of the cardiac nerve cells. Beat-to-beat adjustments, called heart rate variability, reflect the system dominating the balance during a period of time. Therefore, heart rate variability is considered a measure of autonomic nervous system functioning (Gisselman et al, 2016). Reduced heart rate variability is associated with chronic stressors such as chronic pain conditions (Staud, 2008). Monitoring heart rate variability offers a profile

specific for each individual that may be monitored (Gisselman et al, 2016). Biofeedback techniques can be taught in order to improve self-regulation of these functions to allow a return to homeostasis during this time of increased stress and tissue healing, making this a clinically relevant assessment (Gilliam et al, 2010).

While PFP does not have the same tendon-healing process as described above, the process of bone-stress injury is similar to that described. In a biomedical, pathomechanical model of PFP, bone-stress injury may be the closest healing process that can be applied assuming an attempt at healing is made. It is important to note that no studies have assessed the presence of inflammatory markers in PFP. Inflammation is not a common clinical presentation of PFP and typically helps rule out the condition (Willy et al, 2019), but that does not mean that biomarkers are not present in the bloodstream. Additionally, this model integrates evidence of altered sensorimotor and nervous system function, however, it uses a fairly outdated biomedical model of pain. There are a few interesting relationships, however, that may be able to be applied to PFP that are not directly related to the (currently unknown) etiology of the condition.

First, heart rate variability is well-correlated with signs of central sensitization [impaired CPM and hyperalgesia; (Appelhans & Luecken, 2008; Van Den Houte, Van Oudenhove, Bogaerts, Van Diest, & Van den Bergh, 2018)]. Pain is not only a chronic stressor, but also causes physiological arousal (Staud, 2008). In fibromyalgia patients, this arousal typically causes increased heart rate, but reduced heart rate variability (Staud, 2008). Importantly, heart rate variability also appears to be sensitive to symptom changes, providing clinical utility (Staud, 2008).

Additionally, heart rate variability is linked to pain catastrophizing coping responses and fear-avoidant behaviors (Appelhans & Luecken, 2008). This may be a chicken-egg argument, as

heart rate variability is also linked with depressive symptoms, which may mediate the relationship between chronic pain and these responses (Appelhans & Luecken, 2008). Depressive symptoms may be an indicator of reduced excitatory neurotransmitters and/or increased inhibitory neurotransmitters, and therefore, the parasympathetic nervous system (e.g. rest/digest) may already be functioning at a higher level in someone experiencing these symptoms. Additionally, Appelhans et al (2008) suggest that increased activity of the anterior cingulate cortex, which is active in the affective-motivational aspects of pain, may result in more negative affect which may increase pain sensitivity.

2.3.7. Somatosensory Mismatch

Tactile and vibration sensation are integrated at the "touchgate" in the dorsal horn of the spinal cord. While the gate control theory suggests that pain can be inhibited by touch, Apkarian, Stea, & Bolanowski (1994) first described the "touchgate" and demonstrated that tactile sensitivity can also be reduced in the presence of pain. This "hypoesthesia" (reduced tactile sensation) is the product of the nervous system prioritizing pain over touch information (Jensen et al, 2007; Latremoliere & Woolf, 2009). The authors (Apkarian et al, 1994) go on to suggest that the pain does not need to be perceived (i.e. reach cortical level), but that nociceptors merely need to be active to reduce tactile thresholds, requiring more tactile stimulus before touch sensation can be sensed. Hypoesthesia is centrally-mediated, is typically assessed using tactile or vibration thresholds (Jensen et al, 2007; Jensen et al, 2008) and may be an additional sign of nervous system adaptation (Jensen et al, 2008).

Only a few studies have assessed somatosensation (tactile or vibration) in individuals with PFP. Jensen et al (2007) identified reduced sensitivity with application of a soft brush on

the affected knee in 48% of the PFP sample. Jensen et al (2008) reported that 22% of the PFP patients in the sample experienced hypoesthesia and 22% of the sample experienced pain when a vibration tool was applied to the affected knee (allodynia). The sensory mismatch was not found in the contralateral knee of participants with unilateral PFP. Noehren et al (2016) also observed hypoesthesia using monofilaments to assess tactile thresholds, in addition to local and remote hyperalgesia. Both studies concluded that pain may be prioritized over touch.

While this finding may not seem like it relates to motor or movement abnormalities, consider the effect of reduced sensation on joint position sense or proprioception. When afferent information is altered and sent to the nervous system for integration, the response may be altered as well. Askeki, Akkaya, Erduran, & Pinar (2008) conducted a study to determine whether joint position sense was different for individuals with PFP compared to healthy individuals. The authors (Akseki et al, 2008) not only found reduced joint position sense at all tested angles (15, 30, 60 degrees of knee flexion), but also observed significantly reduced joint position sense for the unaffected knee. Because the study was cross-sectional, the authors were unable to determine whether this lack of proprioception was the cause of or result of PFP, but it provides additional evidence of altered somatosensation in individuals with PFP (Akseki et al, 2008).

2.3.8. Redistribution of Muscle Activity

Hodges and Tucker (2011) propose that inter- and/or intra-muscular responses to pain may not be universal and postulate that muscle activation as the net effect of the neuromotor system output, accounting for differences between central and peripheral efferent signaling. This aspect of the theory is based on data suggesting recruitment of new motor units in the presence of experimentally-induced pain. The recruitment of these new motor units may explain force and

peak surface EMG activation in the presence of pain (Tucker et al, 2009; Tucker & Hodges, 2009). The size principle states that motor units will be recruited from smallest to largest because smaller motor units would reach activation potential earlier than larger units. The authors demonstrated violation of the size principle in the presence of experimentally-induced pain (Tucker et al, 2009; Tucker & Hodges, 2009). The explanation is an imbalance of excitatory and inhibitory signals. Inhibitory signals may de-recruit smaller motor units, leaving larger motor units, which have higher activation thresholds, to become activated at a lower force (Tucker & Hodges, 2009; Tucker et al, 2012). When larger motor units are recruited earlier and decrecruited later than small motor units, intra-muscular variability will occur (Tucker & Hodges, 2009; Tucker et al, 2012). This variability may be enough to create subtle changes in load distribution or biomechanics in the short-term, but may not alter kinematics or entire-muscle behavior (Tucker et al, 2012). If these intra-muscular differences last long-term and create changes in the nervous system, then increased load, reduced movement variability and reduced movement of the affected body area (i.e. joint ROM) may occur (Hodges & Tucker, 2011).

In PFP, there is conflicting evidence to support differences in motor unit discharge firing rates (Gallina, Salomoni, et al, 2018; Martinez-Valdes et al, 2019) and one study that demonstrated reduced motor unit synchronization (R. Mellor & P. W. Hodges, 2005). In healthy, pain-free individuals, motor unit firing rate is indicative of efferent neural signaling to recruit the maximum number of motor units in order to generate more force (Conwit et al, 1999), however, little work has been done demonstrating what happens to motor unit firing rate in the presence of pain. Experimentally-induced pain may alter the recruitment strategy within the motor neuron pool, but experimentally-induced pain may also be purely nociceptive. Pain that occurs with central sensitization may have a different effect on motor unit recruitment or

discharge rates, as changes to multiple levels of the nervous system may influence the motor response.

Impaired quadriceps muscle function has been observed in a number of studies and includes peak activation differences, activation timing and pattern differences (Cowan et al, 2001; Cowan et al, 2002; Karst & Willett, 1995; Powers, Landel, & Perry, 1996; Powers et al, 2017). Altered quadriceps neuromuscular control may help identify risk factors of or compensatory movement patterns of individuals with PFP. Specifically, altered quadriceps motor activity can increase PFJ reaction forces and lateral contact (as cited in Powers et al, 2017). Delayed VM activation onset and shorter activation duration relative to VL have been observed in individuals with PFP during stair ascent, descent, a heel-raise, SLS (Cowan et al, 2001; Cowan et al, 2002; Thomee et al, 2002; Toumi et al, 2013). Meanwhile, there is little support for peak activation differences in vastii muscles between individuals with PFP and healthy individuals, suggesting that the amount of activation may not be as important as timing of activation with regards to biomechanical differences between groups (Cowan et al, 2001; Powers et al, 1996). While the VM and VL typically act as synergists at the tibiofemoral joint, sharing common knee extension action, it is possible that they oppose one another to provide optimal patellar stabilization during movement (as cited in Powers et al, 2017). Delayed or reduced VM activation relative to the VL may lead to malposition or maltracking of the patella as the VL fires unopposed.

Sex differences in quadriceps EMG have not yet been assessed for individuals with PFP, though one study did limit the study sample to males (Mirzaie et al, 2019). Results of that study suggest that males with PFP have differences in mean VM and VL activation during a single-leg squat and single-leg stance compared to healthy controls (Mirzaie et al, 2019). Additionally

males with PFP exhibited earlier activation of the VL compared to healthy controls during a single-leg squat, but no differences were observed for a single-leg stance task (Mirzaie et al, 2019). Overall, these suggest altered intra-quadriceps activity in individuals with PFP.

The pathomechanical model of PFP also suggests that proximal muscle function may influence femoral motion or position (Powers et al, 2017). Increased hip adduction and femoral internal rotation are fairly consistent findings that contribute to increased peak knee abduction angles (i.e. valgus position), increased lateral PFJ contact, and increased PFJ reaction force (Powers et al, 2017). Abdominal muscle and hip muscle firing patterns have been implicated in improper control of hip and femur positions.

Abdominal muscles firing patterns differ between individuals with PFP and heathy individuals during postural control tasks. Abdominal muscles are typically activated prior to distal extremity movement when an external perturbation is introduced (Hodges & Richardson, 1996), however, individuals with PFP activated abdominal muscles 100ms following activation of the soleus, and nearly 150ms after the GMed, allowing less postural control following the perturbation (Biabanimoghadam, Moteallah, & Cowan, 2016; Rojhani Shirazi, Biabiani Moghaddam, & Moteallah, 2014). Additionally, during an unexpected medially-directed postural perturbation task, PFP participants also demonstrated altered activation patterns for hip and muscles (Rojhani Shirazi et al, 2014). the deep abdominal muscles (i.e. transverse abdominals, internal obliques) of the PFP group activated earlier and for a longer duration than the healthy controls, followed by activation of erector spinae, while the GMed fired last (Rojhani Shirazi et al, 2014). This firing pattern was opposite of the findings for the healthy control group, in which the abdominal muscles fired first, followed by the gluteus medius, with the erector spinae contracting much later. The authors (Rojhani Shirazi et al, 2014) suggested that earlier activation

of the abdominal and erector spinae for the PFP group may indicate that the PFP group had more difficulty stabilizing following the perturbation, which resulted in the immediate need to stabilize the core and the inability of the GMed to control pelvic motion.

At the hip, only one group has observed differences in peak GMed or GMax activation between those with PFP and healthy individuals, however, there is substantial support for altered activation timing. A systematic review (C. J. Barton et al, 2013) concluded that the gluteus medius (GMed) is activated later and for a shorter duration (calculated as onset to offset time) during stair ascent, descent, and running (Aminaka et al, 2011; Brindle et al, 2003; Willson et al, 2011). No studies have assessed GMax onset timing or duration between PFP and healthy groups. Moreover, no studies have assessed muscle activation differences within a PFP group following pain aggravation.

Changes in muscular activation patterns are indicative of altered neuromuscular control (Hodges & Smeets, 2015). Changes in activation patterns have been observed in males with PFP, which could lead to altered biomechanics (Mirzaie et al, 2019). During a single-leg stance, healthy males stabilize the body with the GMed activation first, followed by the the VM then the VL, which may offer patellar stabilization and reduced lateral movement (Mirzaie et al, 2019). Conversely, following initial GMed stabilization, males with PFP activate the GMax, which may serve to limit femoral internal rotation or hip flexion, then activate the VL prior to the VM, which may increase lateral contact of the patella against the distal femur (Mirzaie et al, 2019). During a single-leg squat (SLS), heathy males activated the GMed followed by the GMax, then VM, and finally, the VL. Males with PFP, however, activated the VL first, which may increase lateral patellar contact, followed by the GMax, VMO, then GMed (Mirzaie et al, 2019). This suggests that during a SLS, males with PFP may experience lateral pull of the patella with little

medial stabilization. Additionally, the last activated muscle helps control dynamic femoral adduction which is commonly observed during unipedal movements (Mirzaie et al, 2019). Because males are less commonly afflicted with PFP, it would be interesting to determine whether similar activation pattern differences occur.

Considering the four most commonly painful tasks for the individual with PFP (running, stair negotiation, SLS, and sitting), running and stair ambulation have been the most frequently studied (C. J. Barton et al, 2013; Collins et al, 2016). More evidence is needed to better understand the motor patterns of individuals with PFP during SLS and sitting in order to fully appreciate why these specific tasks induce pain. Additionally, gender differences in neuromuscular control across tasks may help differentiate why females are more commonly diagnosed with PFP and typically have worse outcomes.

Motor timing (onset, duration, offset) and activation pattern (order of activation) appear to be integral neuromuscular variables and may offer a better understanding the etiological factors in PFP. Surface EMG research suggests that intra-quadriceps activation timing and intermuscular (core, GMed, and vasti muscles) differs from healthy populations, and that intermuscular timing and activation patterns differ between individuals with PFP and healthy controls. While the vicious cycle and strength inhibition theories suggest changes in overall muscle activity in response to pain, the protective response theory suggests that timing and pattern variables may be more important than peak activation or strength observations (Hodges & Smeets, 2015; Hodges & Tucker, 2011). There seems to be support for this concept in PFP, as peak amplitude does not differ between PFP and healthy groups, but timing and activation patterns do appear to demonstrate consistent differences between groups (C. J. Barton et al, 2013). A next step in this line of research would be to determine whether changes in activation

pattern may differ within a PFP group compared in non-painful and after pain-aggravating protocols, and whether changes can be observed between those presenting with signs of central sensitization and those without.

2.3.8.1. Changes in Mechanical Behavior. A core tenet of the protective response theory is that the aforementioned redistributed muscle activity alters biomechanics (Hodges & Smeets, 2015). These changes can be subtle or overt, depending on the redistribution patterns, the duration of symptoms, and the degree to which the motor and nervous systems have adapted to pain or threat of pain (Hodges & Smeets, 2015). An example of subtle biomechanical changes would be a minor shift in load distribution. For example, altering joint ROM, reducing joint velocity, or shifting center of pressure (and thereby, the ground reaction force vector) where there may not be a statistically significant difference, but there may be moderate to large effects (Hodges & Smeets, 2015). These changes may go unnoticed because the gross movement features are preserved, or they may be dismissed altogether as non-statistically significant differences but may be the beginning of long-term movement system consequences (Hodges & Smeets, 2015).

2.4. The Pathomechanical Model of PFP

The pathomechanical model of PFP (Figure 1) suggests that patellofemoral pain is caused by elevated PFJ loading, resulting from reduced PFJ contact area or increased patellofemoral reaction forces, which stem from a variety of proximal, distal, and local kinematic, kinetic, and EMG abnormalities (Powers et al, 2017). Though many of the findings in the model are not universally observed across all patients with PFP, there are three proposed paths leading to the development of patellofemoral pain. The first pathway hypothesizes that abnormal PFJ anatomy,

impaired soft tissue restraints (i.e. lateral retinacular tightness, patellofemoral hypermobility), excessive femoral internal rotation, and impaired quadriceps function lead to patellar malposition or maltracking (Powers et al, 2017). This malposition or dysfunctional movement of the patella over the trochlear groove reduces PFJ contact area, which increases PFJ loading, ultimately leading to PFP (Powers et al, 2017).

The second hypothetical path states that altered trunk kinematics, altered ground reaction forces cause abnormal tibiofemoral kinetics, which leads to increased PFJ reaction forces, elevated PFJ loading, causing PFP (Powers et al, 2017). The third proposed path suggests that altered distal or proximal factors may influence tibiofemoral kinematics or kinetics, or thigh muscle tightness which increases PFJ reaction forces, leading to increased PFJ loading, causing pain (Powers et al, 2017).

2.4.1. PFJ Biomechanics

Elevated PFJ loading is proposed to be the final common path to development of PFP (Powers et al, 2017). Elevated PFJ loading, and/or increased PFJ cartilage and bone-stress has been observed during walking and squatting (45 degrees of knee flexion), however, this finding is not consistently observed across all tasks. In fact, during running, stair negotiation, or squatting with greater knee flexion (60 degrees) PFJ loading is no greater than it is for healthy persons (Powers et al, 2017). Additionally, a study assessing healthy participants suggested that males actually exhibit higher peak PFJ stress compared to females (Almonroeder & Benson, 2017). Considering that females are more likely to develop PFP, this finding demonstrates the complexity of suggesting that elevated loading is the final common path to PFP development. Some authors have suggested that it is not elevated loading, but rather the loading rate that

increases pain. This finding is supported by Schaffler, Radin, and Burr (1989) who concluded that loading rate may be more predictive of symptom behavior than peak loading. Regardless, the mechanism by which this increased loading or loading rate causes the pain in PFP is still debated.

From a biomedical standpoint, for loading to cause pain via nociception, the question remains what structures are impacted and/or why nociceptors are activated in these individuals compared to healthy individuals. Loading does not cause tissue damage, made evident by the lack of MRI findings in individuals with PFP (van der Heijden, de Kanter, et al, 2016; van der Heijden, Oei, et al, 2016). The suboptimal tissue loading hypothesis could offer a potential explanation. This hypothesis was created to provide an explanation for post-injurious movement pattern changes (i.e. antalgic gait), and suggests that non-optimal tissue loading may excite nociceptors, leading to pain. Once a patient finds and continues to use an alternate movement strategy, the nociceptor may fire at a lower pain threshold (as cited in Hodges, 2011). While this theory makes logical sense, individual difference in finding pain-alleviating positions or movements makes it difficult to prove and it does not explain the insidious onset of pain initially for the individual with PFP. Additionally, "dysfunctional" movement patterns such as dynamic knee valgus or increased femoral internal rotation can be present in individuals with no lower extremity injury or pain history, so the generalizability of the hypothesis may be limited.

Another theoretical explanation is that repetitive loading of the PFJ may increase interosseous water content, which could elevate interosseous pressure in the patella and mechanically stimulate nociceptors (Ho, Hu, et al, 2014b; Ho, Keyak, & Powers, 2014). This hypothesis also follows a biomedical perspective, that pain can only be induced via some mechanical "trigger" acting on a nociceptor and has not been extensively evaluated.

PFJ contact area describes the retropatellar surface area contacting the femoral condyles (Powers, 2000a, 2000b). Reduced PFJ contact area is thought to be the result of patellar maltracking or malposition, leading to hypermobility of the patella within the trochlear groove (Powers et al, 2017). Lateral patellar displacement in individuals with PFP has been consistently observed in a large number of studies (Powers et al, 2017), however, differences in PFJ contact area between healthy individuals and controls may be dependent on the type of movement assessed [e.g. static or dynamic, weightbearing or non-weightbearing; (Powers et al, 2017)]. Some authors have also hypothesized that increased knee (tibiofemoral joint) flexion will lead to increased contact area is hypothesized to occur, especially on the medial and lateral patellar facets (Powers, Chen, Scher, & Lee, 2006; Salsich & Perman, 2013). However, some authors have not observed differences in contact area at varying degrees of knee flexion, causing researchers to ponder whether this finding is specific to the anatomical alignment of each individual (Powers, 2003). Theoretically, joint stress dispersed over a smaller contact area would lead to increased PFJ reaction forces and is theorized to induce nociception (though the latter has not been confirmed).

PFJ reaction force describes the resultant compression force acting on the joint and is calculated as the PFJ stress divided by the contact area (Powers, 2000b). In order to be properly calculated, a model with kinematic, kinetic, and muscle force or tension data needs to be used. Powers an colleagues (Powers, Ho, Chen, Souza, & Farrokhi, 2014; Teng & Powers, 2014) proposed a model using participant-specific kinematics (knee flexion angle) and kinetics (knee extensor moment) and quadriceps EMG, combined with data from existing literature (PFJ contact area, quadriceps lever arm, etc.) is commonly used to calculate this force. In older studies, a constant describing the relationship between the quadriceps force and patellofemoral

reaction force was used, but in more recent studies (as cited in Atkins et al, 2018), this relationship was calculated to be participant-specific. Higher knee abduction angles are theorized to reduce patellofemoral contact area. High joint reaction forces over a small contact area would yield greater PFJ stress (Powers, 2000b). Of course, as with other biomechanical findings, the results have been varied.

Individuals with PFP exhibit lower peak PFJ reaction force than healthy individuals during stair negotiation, running, and walking (Powers et al, 2017). The authors of these findings have suggested that lower reaction forces may be the result of compensatory movement patterns, however, no empirical evidence exists to support this claim (Brechter & Powers, 2002; Heino Brechter, Powers, Terk, Ward, & Lee, 2003). For females with PFP, peak PFJ reaction force was identified as the best predictor of the rate of change in pain during repetitive single-leg landings (Atkins et al, 2018). This indicates that females who land with greater peak joint reaction force experience greater increase in pain across the number of landing trials.

For elevating PFJ loading to be considered the final common element leading to PFP development, I suggest that more evidence is needed before a consensus can be supported. Reduced PFJ contact area and increased PFJ reaction forces are not consistently observed, and reduced contact area may be a misleading misnomer, considering increased lateral PFJ contact may actually be increased, not reduced. Whether or not this is a nociceptive factor is has not yet been determined, so this model may need to evolve in order to include a more biopsychosocial perspective and including known changes to the sensorimotor and nervous systems, which the authors cite as factors that may be included in future conceptualizations of this model.

2.4.2. Altered Tibiofemoral Biomechanics

The distal femur articulates with the tibial plateau, making up the tibiofemoral joint. The patella then articulates with the trochear groove, which lies between the medial and lateral femoral condyles, making the PFJ. Thus, any malposition or movement of the femur or tibiofemoral articulation affects the PFJ. For individuals with PFP, altered kinematics and kinetics have been observed at the tibiofemoral joint in all three planes of motion (Powers et al, 2017). Though each faulty movement pattern is not observed universally, each identifies a potential risk factors or pathomechanical causes of PFP.

2.4.2.1. Sagittal Plane Knee Biomechanics. At the knee, the most striking consistency across studies are altered knee sagittal plane kinematic and kinetic factors. Reduced knee flexion has been observed during heelstrike and the loading response phase of walking (Nadeau, Gravel, Arsenault, & Bourbonnais, 1996; Powers, Heino, Rao, & Perry, 1999; Powers et al, 1996), stair ascent and descent, squatting, and running in studies where timing variables are not standardized (Crossley, Cowan, Bennell, & McConnell, 2004). Reduced knee flexion velocity during stair descent has also been observed in one study (Grenholm, Stensdotter, & Hager-Ross, 2009). Reduced knee extension moments have also been reported by some authors during running, walking, and stair negotiation, but others have not demonstrated the differences between individuals with PFP and healthy groups (Powers, 2017). Besier, Fredericson, Gold, Beaupre, and Delp (2009) suggested that greater co-contraction of the hamstring and quadriceps muscles reduced total knee joint moments due to reduced knee range of motion. Authors typically explain this as a pain-reducing or pain-avoiding strategy, however, no study has asked individuals whether this strategy reduces pain or if it was selected in order to avoid pain.

Theory suggests that reducing knee flexion would reduce patellofemoral loading and thereby reduce pain (Powers et al, 2017), however, as identified previously, lesser knee flexion

angles typically produced greater loading at the patellofemoral joint. This disparity may be due to the fact that increased contact between the patellar facets with the femoral condyles occurs in knee flexion over 135 degrees (T. Q. Lee et al, 2003). Increased contact area may actually allow forces to be dispersed, thereby reducing stress and therefore, reaction forces at the joint. Another counterpoint is that statistical regression modeling has identified a "stiffer" (i.e. lower knee flexion angle) landing strategy as a risk factor for PFP development (Besier et al, 2009). A "stiffer" landing strategy allows for the force to be distributed over a smaller area of contact, thereby increasing (patellofemoral) joint reaction forces and stress at the joint. Therefore, theoretically, reduced knee flexion and increased knee extension moments would increase patellofemoral reaction force, thereby elevating joint loading and leading to PFP over a repetitive impacts.

2.4.2.2. Frontal Plane Knee Biomechanics. Frontal plane knee kinematics have long been proposed to be the underlying pathomechanics for knee injury, including PFP (Powers et al, 2017). Specifically, increased knee abduction angles have been purported to increase lateral PFJ reaction forces and reduce patellofemoral contact area. It is also one of the sole biomechanical components well-correlated with changes in pain (Glaviano, Huntsman, Dembeck, Hart, & Saliba, 2016; Glaviano & Saliba, 2018; Graci & Salsich, 2015; Salsich et al, 2012). Recently, two-dimensional (2D) video methods have been validated against three-dimensional (3D) motion capture techniques to better allow clinical assessment of dynamic frontal plane movement (i.e. knee valgus). While 3D has the ability to separately identify each plane of motion within a complex movement, the disadvantage of this technology is that it is costly and is not widely clinically available. Additionally, when clinicians observe a complex multiplanar movement, they are unable to separate components of the motion visually, so 2D analysis may provide a

more realistic clinical view. In 2D videos, typically "knee valgus" angles are assessed, which is a combination of increased femoral internal rotation, hip adduction, and tibial abduction motions. Therefore, because the rotational component is an integral piece to understanding valgus motion at the knee, 2D movement analysis may yield slightly different findings than 3D motion capture. The frontal plane projection angle and the dynamic valgus index have been validated relative to 3D motion capture to identify frontal plane changes and are suggested for clinical interpretation of frontal plane kinematics (Willy et al, 2019).

The frontal plane projection angle is the angle created between the anterior superior iliac spine to the midpoint between the malleoli of the ankle, using the midpoint of the femoral condyles as the axis (Willson & Davis, 2008b). The frontal plane projection angle during a SLS and running are highly correlated, however, one study (Rees, Younis, & MacRae, 2019) concluded this angle is higher during the SLS than running and that researchers should not assume they are interchangeable. In another study, frontal plane projection angles during a SLS were two times higher in females with PFP (mean=16.8 degrees) compared to healthy females [mean=8.4 degrees; (Herrington, 2014)].

The dynamic valgus index was created out of criticism of the frontal plane projection angle stating that pelvic frontal plane motion may alter the amount of "hip adduction" that is observed (Scholtes & Salsich, 2017). If an individual drops the contralateral pelvis during a stepping or landing task, then effectively, the femur exhibits greater adduction relative to the pelvis, whereas the frontal plane projection angle uses the angle of hip adduction relative to a global, vertical line and may result in lower hip adduction values, (and therefore, lower valgus angles) than a measure that accounts for the amount of pelvic drop (Scholtes & Salsich, 2017).

When assessing studies that used 3D motion capture as a methodology, increased knee abduction angle has been identified across most tasks including squatting, stepping, single-leg landing, and walking gait, but has not been observed consistently during running and stair ambulation tasks (C. J. Barton, Levinger, Menz, & Webster, 2009; Glaviano et al, 2016; Glaviano & Saliba, 2018; T. H. Nakagawa, E. T. Moriya, C. D. Maciel, & A. F. Serrao, 2012a; Neal et al, 2016; Rees et al, 2019; Thijs et al, 2007; Willson & Davis, 2008b). Regardless of the method used to assess frontal plane motion at the knee, peak knee abduction appears to be an important clinical finding, as it is commonly associated with pain intensity during movement (Glaviano & Saliba, 2016; Salsich et al, 2012).

Increased tibiofemoral joint moments in the frontal plane have also been observed during running, vertical jump, and stair ambulation (Aminaka et al, 2011; Myer, Ford, Di Stasi, et al, 2010; Stefanyshyn, Stergiou, Lun, Meeuwisse, & Worobets, 2006). In fact, prospective evidence indicates that higher external knee abduction moments have been classified as a risk factor for PFP (Myer, Ford, Di Stasi, et al, 2010). However, Aminaka et al (2011) observed higher external knee adduction moments in women with PFP during stair descent which opposes the majority of PFP kinetics literature. The authors propose that differences may be due to a pain-avoidance or pain-reducing compensation, however, another possibility is that the timing of stair descent was not standardized and the step dimensions were slightly smaller (17.0cm rise, 25.0cm run) than the current United States building codes [17.78 cm rise, 27.94 run; ("United States General Site and Building Codes," 2018)]. Specifically, the building code minimum for the stair run is 25.4 cm, therefore, foot placement may have been altered based on a different stepping strategy that was necessary due to differences from "typical" stair negotiation ("United States General Site and Building Codes," 2018).

2.4.2.3. Transverse Plane Knee Biomechanics. In the transverse plane, rotation of the tibia-on-femur is important in open kinetic chain task, where femur-on-tibia motion may be more salient to assess during closed kinetic chain activities (Neumann, 2010b). Because most tasks that induce pain are closed kinetic chain, most empirical evidence assesses femoral internal rotation angles, which has been consistently demonstrated across a variety of tasks. Powers et al (2014) were the first to use dynamic MRI to identify that what we see clinically as lateral patellar maltracking may in fact be the result of an internally rotating femur moving relative to a stationary patella. This theory gained traction due to the fact that the patella cannot be manipulated to alter its position beyond using passive modalities such as taping or bracing, which have not effectively alleviated the condition. As the treatment paradigm shifted from affecting patellar position to affecting the degree of femoral internal rotation, active therapies such as gait retraining, neuromuscular education and control exercises, and muscular strengthening exercises began to dominate the literature (Neal et al, 2016).

Two caveats to this finding include that sex and task may mediate this finding, and that very few prospective studies have identified this as a causal or risk factor (C. J. Barton et al, 2009; Neal et al, 2016). First, females with PFP demonstrate increased external rotation at the knee during single-leg squats, jumping, and running but greater internal rotation during stair descent, so task and sex may play a role in anticipated findings (Graci & Salsich, 2015; Hollman, Galardi, Lin, Voth, & Whitmarsh, 2014; Sakaguchi, Shimizu, Yanai, Stefanyshyn, & Kawakami, 2015; Souza & Powers, 2009; Willson & Davis, 2009). And second, while there is an abundance of high- and medium- quality retrospective and cross-sectional evidence supporting hip internal rotation as a characteristic of individuals already diagnosed with PFP, there are no prospective studies demonstrating that those with higher femoral internal rotation will develop PFP (Neal et

al, 2019). Thus, it is possible that increased femoral internal rotation may be the result of the condition and not a causal factor.

Altered kinematic findings at the tibiofemoral joint may increase PFJ contact area, which may allow for reduced dispersion of these contact forces across the joint, concentrating them on the lateral side (Bryant et al, 2014; T. Q. Lee et al, 2003; Powers et al, 2017). In fact, cadaveric studies concluded that five degrees of knee valgus does not affect patellofemoral contact area, but increasing to ten degrees increases PFJ pressure by 45% but not contact area (Bryant et al, 2014). This suggests that increased valgus may affect PFP due to the increased PFJ reaction force, not due to increased joint contact (Bryant et al, 2014). This supports the pathomechanical model, which states that reduced contact, not increased contact, would induce PFP (Powers et al, 2017). Furthermore, if increased contact area were to induce excitatory nociception, then pain would occur, however, this assumption does not explain why these pathomechanical findings are not consistent across all individuals with PFP, or why healthy individuals may demonstrate similar movement strategies without the pain experience.

In the transverse plane, greater (internal) knee external rotation moments have been observed during the loading response phase of walking in a single study, but have otherwise not been observed (C. J. Barton et al, 2009; Paoloni et al, 2010). The authors (Paoloni et al, 2010) suggest that the delayed VM relative to VL activation may explain these values, suggesting that the tibia externally rotates on the femur with VL activation that is unbalanced with the delay in VM firing. While this is one plausible explanation, increased external rotation joint moments may also serve to counteract femoral internal rotation, which has been observed during loading response. Bazett-Jones et al (2017) did not observe any within-PFP group differences in

(internal) knee transverse plane moments between baseline, pain-aggravating, and pain-alleviating conditions.

Overall, while there is support for increased femoral internal rotation and knee abduction in individuals with PFP, they are not observed across all tasks. These kinematic features may not contribute to development of the condition but are present during the experience of PFP, therefore, they may not be a causal factor in nociception.

2.4.3. Altered Hip Biomechanics

The femur is the link between the hip and knee. As previously stated, femoral internal rotation has been observed among individuals with PFP but may be dependent on sex and task. Hip internal rotation is positively associated with knee abduction and tibial external rotation, supporting the hypothesis that internal rotation is a component of knee valgus (Sakaguchi et al, 2015).

2.4.3.1. Frontal Plane Hip Biomechanics. In the frontal plane, a trend toward increased hip adduction is commonly observed for PFP groups (C. J. Barton et al, 2009; Neal et al, 2016). Increased hip adduction angles have been observed during running and stepping tasks, but have not been observed consistently during walking or stair ascent (Aminaka et al, 2011; Boling et al, 2009; Di Staulo, Scholtes, & Salsich, 2019; Dierks et al, 2008; Graci & Salsich, 2015; Myer, Ford, Di Stasi, et al, 2010; Nakagawa, Maciel, & Serrao, 2015; Nakagawa et al, 2012a; Noehren et al, 2012; Paoloni et al, 2010; Sakaguchi et al, 2014; Salsich, Brechter, & Powers, 2001; Salsich & Perman, 2013; Willson, Binder-Macleod, & Davis, 2008; Willson & Davis, 2008a, 2009). Graci and Salsich (2015) demonstrated that hip adduction angle was reduced after movement retraining, suggesting that this may be a clinical variable of interest, however, Bazett-

Jones et al (2017) did not observe changes in peak hip adduction angles during running when following a pain-aggravating or a pain-relieving protocol. This disparity indicates that the change observed by Graci and Salsich (2015) may not be due to changes in pain, but in some other factor. Supporting this statement, the authors concluded that hip adduction was not significantly associated with decreased pain perception but lower femoral internal rotation was associated with reduced pain perceptions (Graci & Salsich, 2015). Another plausible explanation is that 88% of the sample for the Bazett-Jones et al (2017) study were experiencing bilateral pain, and two painful limbs could affect overall movement strategies employed.

2.4.3.2. Sagittal Plane Hip Biomechanics. Sagittal plane hip kinematics are not as commonly observed in the PFP literature as hip motion in the frontal and transverse planes. Increased hip flexion angles and corresponding increases in (internal) hip extension moments have been observed during running for individuals with PFP during running (Bazett-Jones et al, 2017; Neal et al, 2016). No differences in sagittal plane joint angles or moments of the hip have been observed during stair walking or stepping. Bazett-Jones et al (2017) actually observed reduced hip flexion angles during the stance phase of running, and did not observe differences between pain-aggravating and pain-alleviating conditions. Despite this finding, the authors did observe increased hip extension moments that was reduced with both pain-aggravation and pain-relieving protocols (Bazett-Jones et al, 2017). Hip motion is not just made up of the hip angle (typically defined as femur relative to trunk position) but would also be affected by trunk angle (defined as trunk position relative to the global coordinate system, or a global neutral), so it is possible that a hip extension moment could be affected by pain but could occur without corresponding hip flexion.

2.4.3.3. Transverse Plane Hip Biomechanics. Control and position of the hip is integral to control and positioning the knee during dynamic tasks. Transverse plane joint angles seem to be variables of interest and may play a role in the amount of knee abduction observed during knee flexion tasks. The role of hip adduction in development is less clear and has been inconsistently demonstrated between tasks. Sagittal plane hip angles have not been observed as frequently as angles in the frontal and transverse planes for the hip, but increased hip flexion may change the manner in which ground reaction force line of force through the kinetic chain, which could affect PFJ loading. Hip extension (internal) moments appear to be affected by pain modulation regardless of direction. While no real conclusions were drawn from this information, this may be due to a sample with bilateral PFP (Bazett-Jones et al, 2017).

2.4.4. Altered Trunk Kinematics

The trunk is controlled by the core muscles, including the abdominals, back extensor and rotator muscles, and the hip muscles. The trunk is a segmental link that is widely neglected in PFP research. One rationale for leaving the trunk out of most analyses may be the difficulty in assessment. In order to include the trunk in 3D motion analysis, one must model the trunk as a single rigid segment, when movement actually occurs at each intervertebral joint in all 3 planes of motion and these joint motion is often coupled into multiplanar movements. Additionally, when linking the trunk to the hip, the hip position may be defined relative to the location of the trunk, or relative to a global neutral plane (Andriacchi & Alexander, 2000; Grood & Suntay, 1983). The trunk is typically defined as the angle between the femur and a global neutral plane. In addition, when selecting joint variables, authors may select those adjacent to the knee (hip, ankle), rather than continue up the kinetic chain. This may be a point of contention, however, the

concept that proximal control is necessary to allow more efficient extremity movements is well-documented (Hodges, 2011; Hodges, Moseley, Gabrielsson, & Gandevia, 2003; Hodges & Richardson, 1996). In fact, the core muscles tend to fire prior to any muscle activity of the moving extremity (Hodges & Richardson, 1996) and in preparation for external forces (Biabanimoghadam et al, 2016). This may be important when considering abnormal kinematics or reaction to external forces. Therefore, though not adjacent to the knee, the trunk may be integral to motor control of the knee.

2.4.4.1. Sagittal Plane Trunk Biomechanics. The pathomechanical model suggests that PFJ stress (defined as PFJ force per unit area) would increase with increased PFJ reaction force or reduced PFJ contact area (Powers et al, 2017; Teng & Powers, 2014). Increased forward trunk lean would increase peak (internal) knee extensor moments, which would reduce PFJ stress (Teng & Powers, 2014). A greater (internal) knee extensor moment would reduce both PFJ stress and PFJ contact area. One factor that may affect the knee extensor moment is increased (sagittal plane) trunk flexion. (Teng & Powers, 2014) suggest that increased forward trunk lean (i.e. sagittal plane flexion) would reduce the knee extensor moment, leading to reduced PFJ reaction force, contact area, and stress. Increased forward trunk lean has been observed during walking, running, and single-leg hopping, and has been associated with reduced knee (tibiofemoral) extensor moments (Nakagawa et al, 2015; Nakagawa et al, 2012b; Teng & Powers, 2014). Teng and Powers (2014)supported not only that relationship, but they also observed relationships between PFJ kinetics and increased forward trunk lean during running. Increased forward trunk lean was associated with lower PFJ stress, which were primarily influenced by altered PFJ reaction force more than PFJ contact area (Teng & Powers, 2014).

This supports the relationship between the trunk and PFJ, using the knee extensor moment as a moderator for the relationship.

2.4.4.2. Frontal Plane Trunk Biomechanics. Researchers have also contended that frontal plane trunk movement may influence hip extension and abduction moments (Neumann, 2010a). "Pelvic drop" (i.e. away from the stance side) is thought to be related to weakness of the hip abductors or core muscles (Bolgla & Uhl, 2005). Individuals with pelvic drop can also lean the trunk to the ipsilateral side (toward the stance leg) to effectively pull the pelvis back to a neutral position which can help with leg clearance and smooth gait during walking or running (Neumann, 2010b). Both ipsilateral trunk lean and contralateral pelvic drop (i.e. away from the stance leg) would theoretically increase peak hip adduction and knee abduction angles (and typically the associated internal hip abduction and knee adduction moments) because both pelvic drop and lateral trunk lean toward the stance side would place the femur closer to the midline of the pelvis (Nakagawa et al, 2015; Nakagawa et al, 2012a; Teng & Powers, 2014). Now, it is important to note that not all 2D assessments of frontal plane hip and knee motion (e.g. the frontal plane projection angle) account for trunk and pelvic position, and therefore, trunk and pelvis position can confound study results (Scholtes & Salsich, 2017).

Nakagawa et al (2015) observed greater ipsilateral trunk lean in individuals with PFP compared to healthy controls during a single-leg squat. In addition, individuals with PFP demonstrated significantly reduced core strength during trunk extension, trunk flexion with rotation, and side bridge strength tests compared to the healthy group (Nakagawa et al, 2015). However, only the control group had significant correlations between trunk kinematics, strength, and hip and knee kinematics so the mechanism by which *frontal plane* trunk motion may influence the PFJ or be influenced by strength is still not well understood. Conversely, Salsich

and Perman (2007) observed contralateral trunk lean in individuals with PFP that was hypothesized to increase femoral internal rotation, and knee external rotation moments that could reduce PFJ contact area. It is also possible that individuals with PFP may self-select the strategy that works for them, and that the mechanism (reduced PFJ contact area, increased PFJ reaction force) may differ by individual.

Graci and Salsich (2015) identified greater ipsilateral trunk lean for women with PFP during a single-leg squat which were related to reduced femoral internal rotation and hip adduction. Some reasons for differences in the study may be the instruction provided to participants. (Graci & Salsich, 2015) instructed participants to "keep the knee over the toe" leaving participants to self-select trunk strategy, while Nakagawa et al (2015) instructed participants to cross their arms over the chest. Crossing the arms over the chest may have allowed participants feel less stable in a single-leg condition, since they were unable to use the arms to counter any balance errors, despite the fact that it was probably selected due to interference of the arms with tracking 3D markers. This may be one example of how the act of measuring biomechanics can interfere with a participant's natural movement patterns.

At this point, the role of frontal plane movement of the trunk is not well understood, and the effect appears to be moderated by the knee extensor moment. For clinicians, it appears that neuromuscular control and strength of the core may be important. For researchers trying to determine what variables to include in a biomechanical analysis, knee extensor moments may be more directly related to PFJ stress, reaction force, and contact area.

2.4.5. Ground Reaction Forces

Ground reaction forces describes the equal and opposite force applied during contact with the ground. Ground reaction forces can be measured in any plane but are most commonly assessed in kinetic studies as a quantification of either vertical or medial-lateral ground reaction forces. Increased vertical ground reaction forces increase lower extremity stress traveling up the kinetic chain. Higher loading rates (i.e. higher ground reaction forces applied over shorter time periods) have been linked to injury and cartilage degeneration (Briani et al, 2018).

While some authors have observed lower vertical ground reaction forces and lower loading rates during walking for individuals with PFP relative to healthy individuals (Powers et al, 1999), others have observed higher vertical ground reaction forces and loading rates during stair ascent and descent (Briani et al, 2018; de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & de Azevedo, 2015). Loading rates and ground reaction forces were also associated with higher pain perception and self-reported function (Briani et al, 2018; de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & de Azevedo, 2015; de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & Azevedo, 2015). No differences in vertical loading rate have been observed during running between individuals with PFP and healthy controls (Esculier, Roy, & Bouyer, 2015) and only one study (de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & de Azevedo, 2015) has analyzed relationships between these kinetic factors on the kinematics. No study has examined the relationship between neuromuscular control and loading rate or ground reaction forces, which seem to be variables of importance.

Reduced knee flexion angles during self-selected stair negotiation strategies may be one potential cause of higher loading rates and increased vertical ground reaction forces within the PFP population (de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & Azevedo, 2015). Reduced knee flexion has been hypothesized to be a pain-reducing compensatory pattern during

SLS and stair ambulation as a more extended knee position results in reduced PFJ reaction force. However, this compensation might not allow for load distribution. Reduced load distribution may directly affect the amount of compression of the tibiofemoral joint more than the PFJ, but if the femur is more internally rotated during compression, it could also lead to increased lateral contact of the PFJ (T. Q. Lee et al, 2003), though this has not been exclusively examined. Altered ground reaction forces change the line of force through the lower extremity and have the potential to affect joint moments, and reactive motor activity and joint angles.

2.5. Summary of the Literature Review

The pathomechanical model suggests that elevated PFJ loading leads to the development of PFP, and if that is true, that is the best estimate for a peripheral nociceptive source for the condition. However, even if PFJ loading is the initial source of nociception, pain persistence may be the result of a centrally driven response to loading (rather than a peripherally driven response). If this is true, it is possible that either a) nociceptors may fire spontaneously (Woolf, 2011) or at subthreshold levels, or b) that a centrally-mediated pain response is activated during subsequent movements inducing PFJ loading.

Regardless of the onset mechanism, altered afferent information in the areas of the brain classically associated with pain may impair communication with sensorimotor areas of the brain. Increased connectivity between the somatosensory and primary motor cortices may be indicative of increased communication in these areas and could lead to changes in motor planning and execution. Specifically, if sensorimotor processing is impaired, delays in muscle function may occur which may impact development of muscular activity and ultimately, movement patterns.

Delayed VM electromechanical delay (Chen et al, 2012), inhibited VM Hoffmann reflex (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Pazzinatto, de Oliveira Silva, Pappas, et al, 2017), and altered VM to VL onset times have been reported in individuals with PFP (Cavazzuti et al, 2010; Cowan et al, 2001; Cowan et al, 2002; Karst & Willett, 1995; Van Tiggelen et al, 2009). Delayed activation and/or delayed achievement of peak activation may help explain changes in tibiofemoral kinematics. It is possible that these alterations in muscle function may occur when the central nervous system is centrally sensitized to pain.

Like other chronic musculoskeletal conditions, PFP has most of the hallmarks of a central sensitization. Manifestations of central sensitization observed in individuals with PFP include widespread hyperalgesia (De Oliveira Silva, Rathleff, et al, 2019) and more widespread pain distributions and patterns (Boudreau et al, 2017; Boudreau et al, 2018). Altered CPM and TSP assessment, however, have demonstrated equivocal results thus far and additional studies are needed before a consensus can be obtained (Holden et al, 2018; M. S. Rathleff et al, 2017). These alterations of the nervous system are not limited to pain sensation. Somatosensory and sensorimotor adaptations have also been observed including reduced tactile thresholds (Jensen et al, 2007; Jensen et al, 2008; Noehren et al, 2016), worse proprioception (Akseki et al, 2008), motor cortex re-organization (Te et al, 2017), cortical and spinal inhibition of efferent signals (de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Pazzinatto, de Oliveira Silva, Pappas, et al, 2017; Te et al, 2017). These changes may impair muscle function and alter kinematics.

Future research should determine whether central sensitization occurs in females with PFP compared to pain-free controls, and determine what impact central sensitization has on muscle function and knee kinematics in this population. This information could affect

assessment of females with PFP and help guide treatment selection, in addition to impacting etiological models of PFP and pain-movement models.

Chapter III

Do Females with PFP Exhibit Signs of Central Sensitization?

3.1. Introduction

Patellofemoral pain a persistent musculoskeletal condition causing pain around or behind the kneecaps. Females experience greater risk (Myer, Ford, Barber Foss, et al, 2010; Tenforde et al, 2011), higher rates (Boling et al, 2010; Smith, Selfe, et al, 2018), and worse long-term outcomes (Sandow & Goodfellow, 1985) compared to males. PFP becomes recurrent in 70-90% of cases and approximately one-half of patients continue to experience symptoms at follow-ups ranging from one to eight years in case-controlled studies (Lankhorst et al, 2016; M. S. Rathleff, Graven-Nielsen, et al, 2019; M. S. Rathleff, Holden, et al, 2019; M. S. Rathleff, Rathleff, et al, 2016; M. S. Rathleff, Roos, et al, 2016). The pathomechanical model of PFP suggests that the etiology of the condition is due to a number of proximal, distal, and local biomechanical and muscular factors that lead to increased patellofemoral joint loading (Powers et al, 2017). The direction of the model implies that elevated patellofemoral joint loading as a nociceptive stimulus leading to pain, but while that may explain the initial onset of pain, it does little to explain why pain persists. Additionally, framing PFP as nociceptive fails to acknowledge the complexities of persistent pain states and the implications altered central processing has on treatment outcomes (Chimenti et al, 2018). Research on other persistent musculoskeletal pain conditions (i.e. low back pain, knee osteoarthritis) has included central sensitization as a potential mechanism explaining insidious onset and pain persistence (Arendt-Nielsen, Morlion, et al, 2018). Understanding whether central sensitization occurs in females with PFP may be paramount to updating and adapting etiological and treatment models of the condition.

Central sensitization describes an altered functional state of nociceptive neurons in the central nervous system such that they demonstrate increased responsiveness or subthreshold activation to non-noxious stimulus ("International Association for the Study of Pain Terminology," 2021). Central sensitization can reflect widespread pain hypersensitivity, inefficient descending pain inhibition networks, enhanced pain facilitation of ascending central pathways, or some combination of these (Arendt-Nielsen, Morlion, et al, 2018; Staud, 2012; Woolf, 2011). Woolf (2011) proposed that persistent pain is more likely to be driven by this altered central pain processing, as once nociceptive neurons begin to fire spontaneously or at subthreshold levels, the net product is increased pain without a clear stimulus. It is possible that if patellofemoral joint loading is initially a nociceptive stimulus, but as the central nervous system becomes more sensitized, the same loading magnitude need not be present for it to continue. This could occur because nociceptive neurons would be activated at lower loading thresholds. This could explain the high rates of recurrence, even after periods of rest or reduced loading. It could also explain rates of persistence if nociceptive neurons continue to activate spontaneously, even when activity has been stopped.

Quantitative sensory testing methods assess the functional efficiency and integrity of pain processing pathways (Arendt-Nielsen, Morlion, et al, 2018). Quantitative sensory testing can help identify patient subgroups in other chronic musculoskeletal pain conditions, predict treatment outcomes, and guide treatment selection (Arendt-Nielsen, Morlion, et al, 2018; Chimenti et al, 2018; Fillingim et al, 2016; Kennedy et al, 2016; Staud, 2012). Three common measures of quantitative sensory are pressure pain thresholds (PPTs), temporal summation of pain (TSP), and conditioned pain modulation (CPM). PPTs assess the moment a pressure sensation changes to a painful sensation. Lower PPTs can indicate hypersensitivity at the

affected site (i.e. local) or widespread (i.e. remote) and can be a sign of peripheral or central sensitization. TSP is the concept that applying a noxious stimulus at consistent, repeated intervals can induce pain perception over time. While this is a normally occurring phenomenon, individuals with signs of central sensitization exhibit quicker and higher pain intensity responses compared to pain-free individuals. CPM is performed by assessing a test stimulus before and during application of a second noxious conditioning stimulus in order to test the concept that pain inhibits pain (Kennedy et al, 2016). In efficient CPM responses, it takes more of the test stimulus before pain is sensed, so the threshold is higher. Lower CPM response indicates a lesser change from baseline to conditioning stimulus, indicating less efficient descending pain inhibition, a sign of central sensitization (Kennedy et al, 2016).

Recent systematic reviews suggest that at least a subgroup of individuals with PFP experience signs of central sensitization, however the strongest support for these statements was provided by evidence of lower pressure pain thresholds in PFP groups versus healthy groups (Bartholomew, Lack, & Neal, 2019; De Oliveira Silva, Rathleff, et al, 2019; Sigmund, Hoeger Bement, & Earl-Boehm, 2020). A number of studies have examined pressure pain thresholds in female-only cohorts with PFP compared to pain-free females, but few studies have examined temporal summation of pain and conditioned pain modulation (other manifestations of central sensitization) in samples of females with and without PFP (Bartholomew et al, 2019; De Oliveira Silva, Rathleff, et al, 2019; Sigmund et al, 2020). Gender differences have been well-documented in measures of temporal summation of pain and conditioned pain modulation, indicating a need to explore these results within samples of females with PFP as they relate to pain-free females (Popescu, LeResche, Truelove, & Drangsholt, 2010; Sarlani & Greenspan,

2002). A better understanding of the pain mechanisms for could help inform etiological and treatment models for females with PFP.

3.1.1. Purpose, Specific Aims, and Hypotheses

The purpose of this study was to identify whether females with PFP exhibit signs of central sensitization compared to pain-free females. We hypothesize that females with PFP will exhibit lower pressure pain thresholds, lower CPM response, and higher TSP response compared to a healthy control (CON) group of females. In order to characterize the sample, self-reported inventories regarding health and treatment status, physical activity levels, perceived knee function, pain and pain responses were collected.

3.2. Methods

3.2.1. Study Design and Protocol

This cross-sectional study took place in a laboratory setting in a large Midwestern university. Data were collected from the affected (or most painful) side for individuals with PFP. Once screened, participants took part in a single 45 minute session consisting of several clinical measures, quantitative sensory testing, followed by a series of self-reported inventories used to characterize the sample (Figure 3).

3.2.2. Participants

Thirty-three female participants volunteered for the study. Twenty females with PFP and thirteen pain-free controls (CON) participated (Table 3). Participants for both groups were recruited from college campuses and communities in the greater Milwaukee area using flyers and

social media posts. Participants were females between 18-40 years of age. Evidence supports differences between adolescent and adult experiences of PFP (M. S. Rathleff, Vicenzino, et al, 2015), and that the risk of patellofemoral and knee osteoarthritis increases after the age of 40 for females (Hinman, Lentzos, Vicenzino, & Crossley, 2014). Members of the PFP groups were included if they experienced non-traumatic onset of retro- or peri- patellar knee pain and met at least two of the following criteria: pain with squatting or kneeling, pain with stair ambulation, pain with prolonged sitting, or pain during or after physical activity or exercise (Cook, Mabry, Reiman, & Hegedus, 2012; Willy et al, 2019). Due to enrollment and data collection occurring between November 2020 and September 2021, all federal, state, local, and campus protocols related to COVID-19 were followed. Participants who were at high risk of contracting COVID-19 were, therefore, excluded from participation.

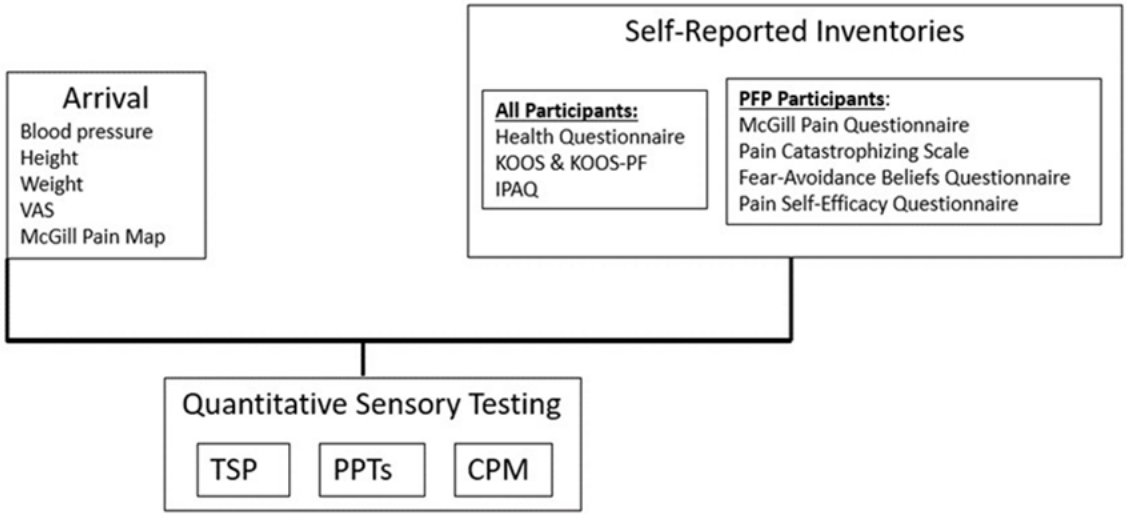


Figure 3: Protocol for Study (1). Once participants arrived at the lab, this is the order of the protocol, Abbreviations: VAS: Visual Analog Scale, TSP: Temporal summation of pain, PPTs: Pressure Pain Thresholds, CPM: Conditioned Pain Modulation; KOOS: Knee Injury and Osteoarthritis Outcome Score; KOOS-PF: KOOS-Patellofemoral Subscale; IPAQ: International Physical Activity Questionnaire

All interested individuals were screened in a telehealth-style videoconference prior to enrollment in the study. This meeting included a screening for inclusion and exclusion criteria, and if the individual passed the screening, they were offered the opportunity to have a telehealth

knee evaluation. The goal of the virtual evaluation was to exclude knee pain in healthy volunteers and to rule out other causes of knee pain in the PFP group. During the screening, individuals were excluded for the following: prior knee surgery or injury to the cartilage, meniscus, or ligaments of the knee; prior patellar subluxation or dislocation; prior lower extremity or back injury in the past 6 months; pain at the time of testing in the lower extremity, back, or hand that was not their knee pain; another chronic pain condition diagnosis (i.e. fibromyalgia); neurological conditions affecting movement or sensation; pregnancy; or a history of experienced adverse reactions to cold. These factors could have affected the biomechanical and/or quantitative sensory test results (Crossley, Callaghan, & van Linschoten, 2016; Maclachlan, Collins, Hodges, & Vicenzino, 2020; Ribeiro, Joao, & Sacco, 2013). Participants were also excluded during the screening for history of high blood pressure, due to the risk of vasovagal symptoms during CPM testing (Zhao et al, 2012).

During the virtual evaluation, the participant started by describing the onset, history, and duration of their knee pain. They were asked to point and show the researcher the location(s) of pain, and then were instructed through a series of self-palpations and double- and single- leg squatting. Reproduction of pain with squatting is considered the best clinical indicator of PFP when considered in conjunction with patient history and symptoms (Cook et al, 2012; Willy et al, 2019). This examination was conducted by a certified and licensed athletic trainer with 17 years of experience. Once eligibility was determined, enrolled participants agreed to a statement of informed consent that was approved by the university institutional review board.

3.2.3. Instrumentation and Procedures

3.2.3.1. Self-Reported Inventories. Self-reported inventories were used to characterize the sample. All participants completed a health questionnaire, and inventories for self-reported knee function, and physical activity levels. The PFP group also completed several inventories related to their pain. Current health status, knee injury and treatment history, history of depression and anxiety, and medication use were collected using a health questionnaire (Appendix E). Self-reported knee function was collected using the Knee Injury and Osteoarthritis Score (KOOS) and associated patellofemoral subscale (KOOS-PF). Physical activity levels were reported using the International Physical Activity Questionnaire (IPAQ). The PFP group also completed the following pain-related inventories: McGill Pain questionnaire and body pain map, the Pain Catastrophizing Scale, the Fear-Avoidance Beliefs Questionnaire for the Knee, and the Pain Self-Efficacy Questionnaire.

3.2.3.2. Quantitative Sensory Testing. All quantitative sensory tests were conducted by the same examiner on the affected side or the side with worse symptoms in the PFP group. Test limb side (i.e. right or left) were similarly distributed across the PFP and healthy groups (30% left leg, 70% right leg assessed in both the CON and PFP groups).

TSP was assessed using the monofilament method (300g nylon filament, Baseline, White Plains, NY, USA; Figure 4). Temporal summation was assessed by applying the monofilament perpendicular to the center of the tested patella until bending of the monofilament was observed (Figure 4). This application was repeated at one-second intervals for a series of 10 applications. Participants were provided a stack of paper Visual Analog Scales (VASs) and were asked to mark their current pain on a VAS form and flip to the next blank VAS between monofilament applications. The average of the second through fourth applications (VAS I) and the average of the eighth through tenth applications (VAS II) was used for analysis. TSP response was defined

as VAS II - VAS I, in alignment with other studies for this type of analysis (Holden et al, 2018). Enhanced TSP is defined as greater difference score, indicating enhanced pain facilitation.

PPTs were assessed using a computerized pressure algometer (Algomed, Meddoc, Israel) at a pressure delivery rate of 30kPa/s with a $1cm^2$ round rubber tipped applicator (Figure 5). PPTs were assessed at each of four locations: the center of the patella, 3 cm medial to the medial patellar border, 3 cm lateral to the lateral patellar border, and on the middle phalanx of the 3rd finger on the contralateral hand. Two repetitions of PPTs were recorded at each site and the average of each site was used for analysis, consistent with other study protocols (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017; M. S. Rathleff et al, 2013). Lower PPTs indicate increased pain sensitivity, indicating that pressure changed to pain sensation with less pressure application. Lower PPTs at the local (i.e. knee) sites relative to the opposite group indicates increased local pain sensitivity, a sign of peripheral sensitization. Lower

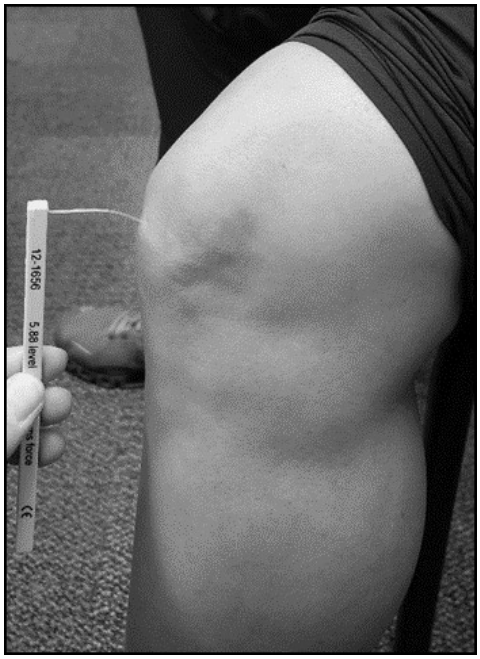


Figure 4: TSP using the Monofilament Method

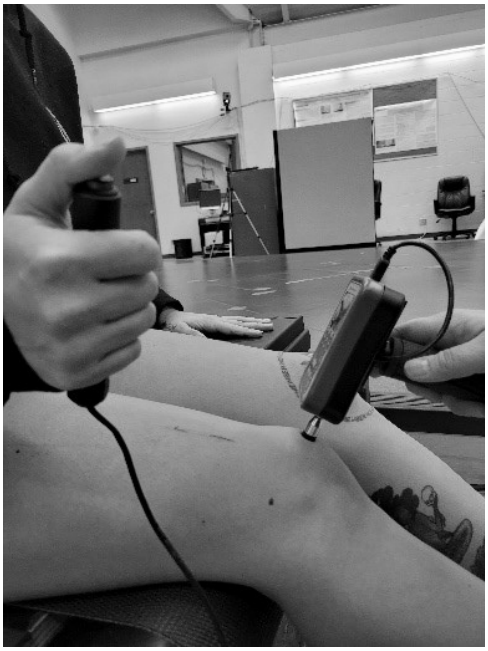


Figure 5: Knee PPTs. Measured by computerized pressure algometer. Lower PPTs indicate increased pain sensitivity.

remote PPTs (i.e. hand) indicate widespread pain sensitivity, a sign of central sensitization. Reliability of the PPT measurement was good to excellent for all test sites for the lead researcher (0.88-0.92).

CPM was assessed using the cold pressor test (Figure 6). The cold pressor test was performed by assessing PPTs at each site (in the aforementioned manner and locations), and were repeated while the contralateral foot and ankle were submerged in an ice water immersion. The ice immersion temperature was maintained at 7°C using a water circulation and temperature control device. The average for each site for each of the two time points (baseline and during ice immersion) was calculated. CPM response was defined as the percent difference from baseline to ice immersion and this was used for analysis. Impaired CPM describes lower PPTs in one group relative to the other. Pain inhibition mechanisms can also be inefficient, in which PPTs during ice immersion do not reach baseline values.

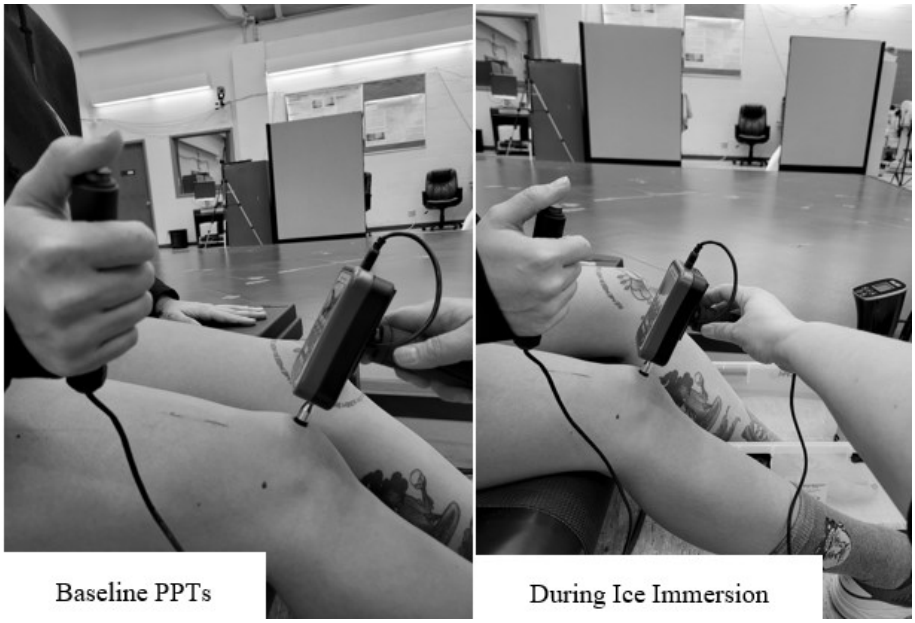


Figure 6: CPM using the Cold Pressor Test, which repeats PPTs in 2 conditions: baseline and during (7°C) ice immersion. If pain inhibits pain, PPTs should be higher during ice immersion. If CPM is impaired, PPTs will be lower in ice immersion or compared to the control group.

3.2.5. Analysis

Independent t-tests were planned for between-group comparisons. However, group samples were small and unequal, so the planned t-tests were no longer appropriate as they are highly sensitive to uneven sample sizes (Xu, Cui, & Gupta, 2009). Separate Welch's tests were conducted to compare between-group means for TSP, PPTs, and CPM. Alpha levels were Bonferroni-adjusted (α=0.0125) for multiple comparisons for PPT and CPM analysis, with group comparisons at each test site. Descriptive statistics were used to characterize the sample. Data normality were assessed using Kolmogorov-Smirnoff tests. Demographic and self-reported data were analyzed with independent t-tests to illustrate group characteristics. Effect sizes were calculated using Cohen's *d* for all comparisons and interpretations were based on ≤ 0.19 = trivial, 0.2-0.59 = small, 0.06- 0.1.19 = moderate, ≥1.2 = large (Hopkins & Batterham, 2016).

3.3. Results

Statistical analyses were conducted using SPSS 28.0 (IBM Corporation, Armonk, NY).

3.3.1. Participant Characteristics

Thirty-three females participated in the study (13 in the CON group, 20 in the patellofemoral pain group). There were no significant differences between groups for age, height, weight, or BMI. The PFP group reported greater perceived dysfunction (i.e. higher KOOS and KOOS-PF scores), but similar activity levels compared to the CON group. Descriptive group statistics for these and other self-reported inventories are reported in Table 1.

The PFP group had median symptom duration of 24 (IQR= 5, 120) months with 65% of the sample reporting worst pain in the right knee and 60% of participants reporting bilateral

symptoms. Fifty-five percent of the sample reported regularly taking some form of medication for their knee pain.

Table 1. Demographics & Self-Reported Data by Group (Mean ± SD) or Median (IQR) for Non-normal Distributions

Measure	PFP Group	CON Group	p-value
Age (y)	29.2 ± 7.0	28 ± 7.0	0.634
Height (cm)	166.7 ± 5.9	166.0 ± 9.5	0.778
Weight (kg)	66.7 ± 9.6	69.3 ± 7.5	0.415
Body Mass Index	24.0 ± 3.5	25.1 ± 2.6	0.674
Symptom Duration (mo)	15 (5, 120)	NA	NA
KOOS- Overall	71.1 ± 12.0	98.5 ± 2.0	<0.001[a]
KOOS- PF	64.9 ± 17.9	98.6 ± 2.9	<0.001[b]
IPAQ (Total MET-min)	7802.2 ± 6622.7	8591.5 ± 5970.4	0.731
Stress (100mm VAS)	37.4 ± 25.2	25.4 ± 21.8	0.158
Pain Catastrophizing Scale	9.6 ± 7.2	NA	NA
FABQ- Knee	22.7 ± 9.3	NA	NA
PSEQ	52.5 (50.2, 58.0)	NA	NA
McGill Pain Questionnaire (Summed Rank)	21.9 ± 10.7	NA	NA
McGill Body Pain Map (pixel area, cm^2)	10,666.0 (8586.75, 15,627.0)	NA	NA
VAS-current pain (mm)	16.6 ± 16.6	NA	NA

Abbreviations: IQR= Interquartile Range; PFP=Patellofemoral Pain; CON= control; KOOS=Knee Injury and Osteoarthritis Outcome Score; KOOS-PF= KOOS-Patellofemoral Subscale; IPAQ= International Physical Activity Questionnaire; VAS=Visual Analog Scale; NA= Not Assessed. a= PFP group reported significantly lower KOOS scores indicating greater perceived knee dysfunction compared to the CON group; b= PFP group reported significantly lower KOOS-PF scores, indicating greater perceived patellofemoral dysfunction compared to the CON group.

3.3.2. Quantitative Sensory Testing

TSP difference scores (VAS II- VAS I) were then compared by group using Welch's tests to determine whether TSP response was higher in the PFP group compared to the CON group. Females with PFP (M= 6.5, SD= 7.7) exhibited higher TSP responses compared to the CON group [M= 1.9, SD= 2.6; $t(1, 25.1) = 6.23$, p= 0.019; Figure 7]. Quantitative sensory testing group means are reported in Table 2.

Table 2. Quantitative Sensory Testing (Mean ± SD)

Test	PFP Group	CON Group	p-value	Effect sizes (*d*)
TSP (Difference in VAS)	6.5 ± 7.7	1.9 ± 2.6	0.019[a]	0.76
PPT- Lateral (kPa)	306.3 ± 123.8	359.9 ± 90.2	0.161	0.49
PPT-Center (kPa)	375.9 ± 134.5	378.3 ± 126.3	0.959	0.02
PPT- Medial (kPa)	285.5 ± 100.9	302.8 ± 302.7	0.678	0.09
PPT- Remote (kPa)	309.8 ± 123.7	345.4 ± 149.3	0.482	0.27
CPM- Lateral (% kPa difference)	-3.5 ± 22.2	-0.6 ± 21.9	0.714	0.14
CPM- Center (% kPa difference)	-6.2 ± 26.1	20.2 ± 26.7	0.010[b]	1.03
CPM- Medial (% kPa difference)	5.1 ± 36.7	8.0 ± 20.2	0.775	0.10
CPM- Remote (% kPa difference)	-10.7 ± 19.4	15.9 ± 27.8	0.007[b]	1.19

Abbreviations: PFP=Patellofemoral; CON= Control; TSP=Temporal Summation of Pain; PPT= Pressure Pain Threshold; CPM= Conditioned Pain Modulation. a= Significant at the 0.05 level; b= Significant at the 0.01 level. Effect size (Cohen's d) interpretations: Trivial effects d ≤ 0.019, small d= 0.2 to 0.059, moderate d=0.06 to 1.19, large d≥ 1.2.

CPM was assessed as the percent difference in PPTs between ice immersion and baseline trials and were compared by group using Welch's tests (Bonferroni-adjusted α=0.0125). Females with PFP exhibited lower CPM percent difference (e.g. CPM response) compared to the CONgroup at the hand (t(1,19.582)= 9.02, p= 0.007) and at the center of the patella (t(1, 25.34)= 7.86, p= 0.010) but no differences were observed at sites medial (t(1, 30.39)= 0.083, p= 0.775) or lateral (t(1,25.99)= 0.138, p=0.71) to the patella. Females with PFP exhibited impaired CPM responses at the remote site and the center of the patella compared to the CON group (Figure 8).

Group PPT differences were analyzed at each test site using Welch's tests, with a Bonferroni-adjusted α (0.05/4= 0.0125). No significant between-group differences in PPTs were observed at any of the four test sites: the lateral femoral condyle (t(1,30.5)= 2.06, p= 0.161) the enter of the patella (t(1, 26.95)= 0.003, p= 0.959), the medial femoral condyle (t(1, 22.05) = 0.177, p= 0.678), or the hand (t(1,22.29)= 0.512, p= 0.482; Figure 9).

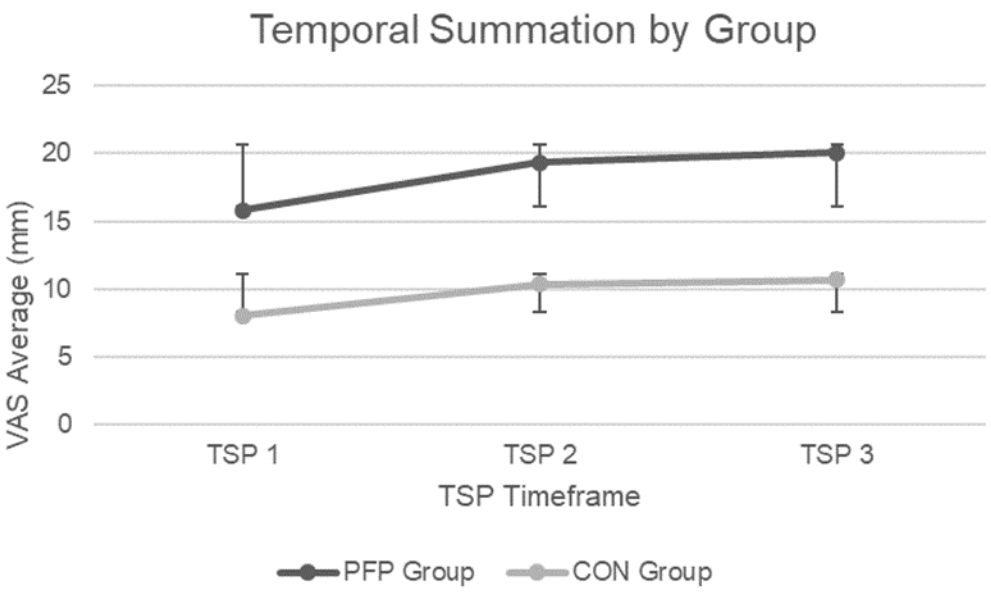


Figure 7: TSP by Group. TSP 1= mean of applications 2-4, TSP 2= mean of applications 5-7, TSP 3= mean of applications 8-10. In the statistical analysis, the difference score (= TSP 3- TSP 1) was compared between groups. PFP group TSP difference scores were higher than the CON group. This figure illustrates changes in pain intensity (visual analog scale) over time. Error bars represent standard deviations.

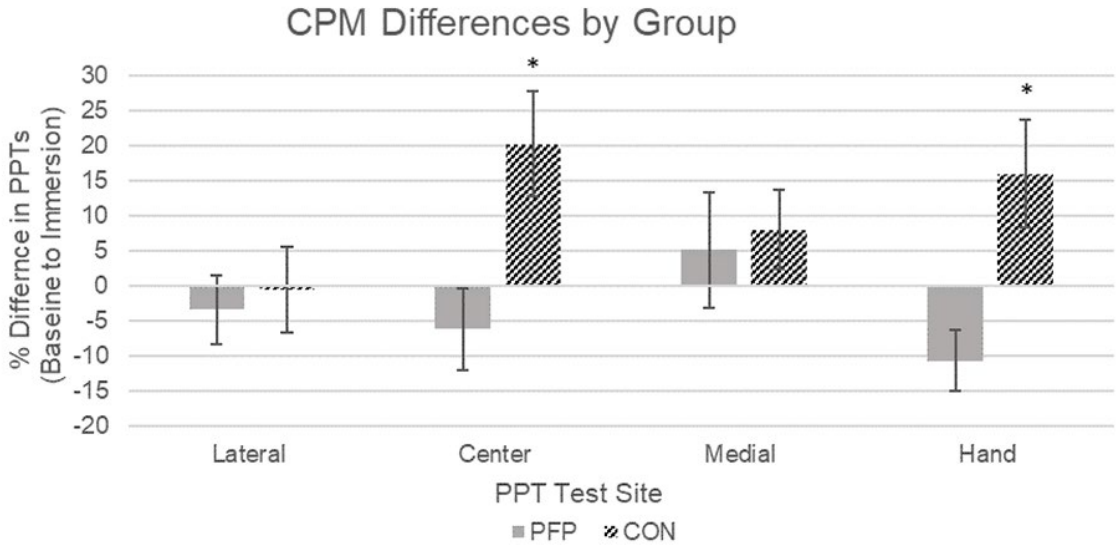


Figure 8: CPM Percent Differences by Group and Test Site. Bars indicate the percent difference between the ice immersion and baseline PPT values during the cold pressor test, with error bars representing the SEM. Lateral= 3 cm lateral to the patella, Center = Center of the patella, Medial= 3cm medial to the patella, Hand= 3rd Middle Phalanx (Remote site). Positive values indicate that the ice-immersion PPTs were higher than baseline (pain inhibits pain), while negative values represent ice immersion values that did not reach baseline (inefficient CPM response). *indicates significance at the 0.0125 level.

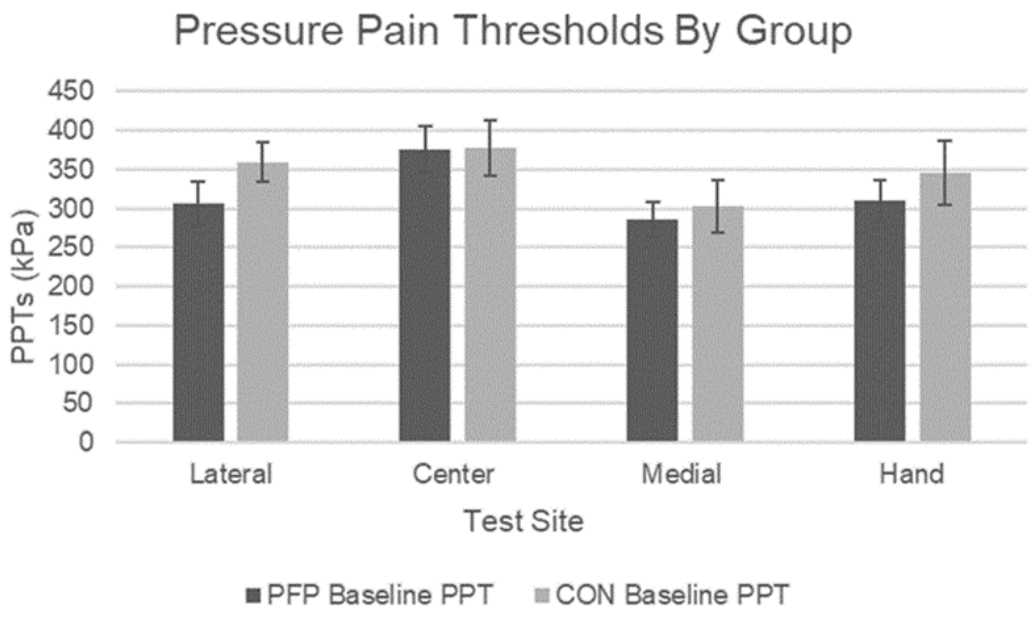


Figure 9: PPTs by Group and Test Site. PPT group means are displayed as bars (color indicates group), with error bars indicating the SEM. Lateral= 3 cm lateral to the patella, Center = Center of Patella, Medial = 3 cm Medial to the Patella, Hand = 3rd Middle Phalanx (Remote site). No significant differences were observed at the 0.0125 level.

3.4. Discussion

3.4.1. Key Findings

The purpose of this study was to determine whether females with PFP demonstrate differences in quantitative sensory testing compared to pain-free females. We observed differences in temporal summation and CPM responses, but no differences in PPTs at local or remote sites. These findings add to the mounting evidence that females with PFP demonstrate signs of central sensitization including enhanced pain facilitation mechanisms and inefficient descending pain inhibition that is both local and widespread. These manifestations can inform updated etiological models, clinical PFP assessment, and rehabilitation models for females with PFP.

Our key finding is enhanced TSP in the PFP group. TSP describes the enhanced pain facilitation experienced when repetitive stimuli are applied at consistent time intervals, resulting in summation of the noxious signals (Arendt-Nielsen, Morlion, et al, 2018). Only four studies have examined TSP in individuals with PFP (Holden, Rathleff, Thorborg, Holmich, & Graven-Nielsen, 2020; Holden et al, 2018; Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016). Only two of those studies assessed female-only samples (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016), while the remaining two analyzed males and females with PFP in a single group (Holden et al, 2020; Maclachlan et al, 2020). This is problematic since females have higher TSP responses than males, which could affect group means (Greenspan et al, 2007).

We observed significantly higher TSP in females with PFP compared to the CON group. These findings suggest amplification of pain occurs as excitatory nociceptive signals are integrated despite consistent stimulus intensity (Arendt-Nielsen, Morlion, et al, 2018). These results contradict other findings, which suggest that only a small subgroup of individuals with PFP present with this sign. One potential reason for this difference is that a range of TSP assessment methods have been used in PFP investigations. We used a monofilament method of TSP assessment, which has been used in research of other chronic musculoskeletal conditions as well as during clinical assessment of TSP, but had not yet been evaluated in patients with PFP (Cruz-Almeida et al, 2014; Osgood et al, 2015). An alternate approach, pinprick assessment methods, demonstrated significant group differences with small effect sizes (Maclachlan et al, 2020). However, the pinprick test yields only fair to moderate reliability (Maclachlan et al, 2020). A third approach, cuff algometry, has been used in patients with PFP, but has demonstrated equivocal results across studies (Holden et al, 2020; Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016). The monofilament method provided us with a reliable, cost-

effective method, using equipment accessible and familiar to clinicians (Cruz-Almeida et al, 2014; Osgood et al, 2015). Using the monofilament test facilitates clinical interpretation of our TSP findings to patient care.

Another potential reason our results may differ from previous investigations is the sex of the sample. Sex differences in TSP response have been well-documents in the population (Greenspan et al, 2007; Riley, Robinson, Wise, Myers, & Fillingim, 1998). Our study is only one of three female-only PFP investigations of TSP, so it is possible the current literature does not represent the female PFP population (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016). So far, significant group differences have only been observed in three studies (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020). Two of these samples included both males and females as one group while the other was a female-only sample. The PFP group means in this study were similar to those reported in female-only cohorts, which are slightly higher than those reported in studies including both sexes despite use of a less noxious stimulus (M. S. Rathleff, Petersen, et al, 2016). If males and females in the population respond differently to TSP assessment, including both sexes in the same sample may introduce heterogeneity into the data. Heterogeneity could lead to false acceptance or rejection of the null hypothesis.

In females with PFP who have enhanced TSP, nociceptive signals are transmitted more efficiently, thereby amplifying the pain sensation. In central sensitization, descending pain inhibition mechanisms that typically help control these excitatory signals are impaired. This impaired CPM leads to a net output of increased pain. We observed impaired CPM at the center of patella and remote site (hand) between groups, indicating impaired pain inhibition. During ice immersion, females with PFP reported lower PPTs that did not reach their baseline levels at three sites (center of the patella, lateral to the patella, and at the hand). However, the differences at the

lateral knee were not significant, as the CON group also reported PPTs that did not reach their baseline values at that site. Other researchers have reported mean percent difference from baseline to ice immersion between 6-49% for PFP groups (control group means were not reported), while our reported difference in means range was -11 to 2% for the PFP group, and -14 to 8% in the control group (Maclachlan et al, 2020; M. S. Rathleff et al, 2017). We did not observe significant differences at the medial site between groups, and both groups exhibited higher PPTs during ice than during baseline testing (i.e. pain did inhibit pain). Only one researcher has reported multiple CPM test sites, but there were no reported group differences at any site (M. S. Rathleff et al, 2017). Our findings indicate that the impaired descending pain inhibition (i.e. CPM response) observed in females with PFP is not enough to offset the facilitated TSP response.

CPM assesses the idea that pain inhibits pain (Arendt-Nielsen, Simonsen, et al, 2018; Kennedy et al, 2016). Impaired CPM has been observed in individuals with PFP, but only small standardized mean differences were observed during meta-analysis and there were not enough female-only studies to conduct subgroup analysis based on sex (Sigmund et al, 2020). Healthy females exhibit a lower CPM effect compared to males (Kennedy et al, 2016; Martel, Wasan, & Edwards, 2013; Valencia, Kindler, Fillingim, & George, 2013) but only two of five PFP studies have assessed female samples (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017). Impaired CPM response was observed in both female-only studies comparing PFP to control groups (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016). Impaired CPM response has been observed in one study that grouped adolescent males and females together (Holden et al, 2020). No study examining CPM

in male and female adults have observed differences between PFP and control groups (Maclachlan et al, 2020; M. S. Rathleff et al, 2017)

There are several CPM assessment methods, which could explain some of the differences in our findings relative to other studies. We chose to use the cold pressor test, as it is the most common CPM assessment method across conditions (Kennedy et al, 2016). However, only two of five studies examining CPM in individuals with PFP used the cold pressor test, and neither reported differences between PFP and healthy groups (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017). Males and females were both included in each of these study samples, which could have also impacted the results, as previously discussed (Maclachlan et al, 2020; M. S. Rathleff et al, 2017). Of the three studies assessing CPM using cuff algometry, two authors observed significant differences between PFP and control groups and one did not. Of these, one study included male and female adolescents, and two studies included young female adults, with significance only observed in one of the young female studies (Holden et al, 2020; Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016).

Both studies also used slightly warmer water temperatures (12° and 15°C, respectively) than ours (7°C). Ice immersion temperatures have been reported from 1°C to 12°C, and with similar results reported from 6-12° (Kennedy et al, 2016; Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016). Temperatures colder than 6° may be too extreme, and may not elicit a uniform response from a given sample, whereas temperatures over 12° may not elicit the desired painful conditioning response (Kennedy et al, 2016). Even though all published methods are valid, consistency is needed in CPM assessment in order to allow for better comparison across studies.

The cold pressor test was only used to assess CPM in participants with PFP in two other studies, and between-group differences were not observed in either study at any of the following sites: center of the patella, tibialis anterior muscle belly, or medial humeral epicondyle (Maclachlan et al, 2020; M. S. Rathleff et al, 2017). Similar CPM patterns (e.g. not all local sites are significantly impaired) have been observed in centrally sensitized patients with knee osteoarthritis (Arendt-Nielsen et al, 2010). Thus, the lack of significant differences at the medial and lateral sites does not detract from our central sensitization conclusion and provides a unique view into patterns of central sensitization in this patient population.

PPTs are the most widely published form of quantitative sensory testing (Arendt-Nielsen, Morlion, et al, 2018; Fillingim et al, 2016).Our results did not support the hypothesis that PPTs would be significantly lower in the PFP group. The age of our sample and lower CON group means may account for differences between our findings and previously published work. Authors have widely reported lower PPTs in PFP groups compared to pain-free groups (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020; Noehren et al, 2016; Pazzinatto et al, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017). Only one other published study did not observe lower PPTs in a PFP group, and interestingly, the mean age of our groups (29.2 PFP, 28.0 CON) and the mean age in that study sample (28.5 PFP, 27.1 CON) are similar and reflect older age means than most PFP studies (M. S. Rathleff et al, 2017). Three studies examining PPTs had mean ages over 25 years while group means for other studies ranges from adolescent (range of mean ages: 12-17 years) to young adult [range of mean ages: 19-23 years; (Maclachlan et al, 2020; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff et al, 2017)]. One of the other studies with mean age over 25 years examined all female runners (Pazzinatto, de Oliveira Silva, Pradela, et al, 2017),

and the other included both males and females in the sample (Maclachlan et al, 2020) which could have impacted results. In a recent meta-analysis, Bartholomew et al (2019) observed a moderate correlation between age and PPTs, concluding that younger individuals with PFP exhibited increased pain sensitivity. If this relationship holds true, then the older participants in our study [at the upper end of the range observed by Bartholomew et al (2019)] might experience less pain sensitivity. However, without studies examining age differences, this is only theoretical and should be considered within this context.

Significant PPT group differences were not observed at the sites medial and lateral to the patella. These test sites were unique to our investigation and were selected based on prior knee pain map studies that suggested females with PFP may exhibit greater pain intensity at either of those locations compared to the center of the patella (Boudreau et al, 2017; Boudreau et al, 2018; M. S. Rathleff, Petersen, et al, 2016). Self-reported McGill pain maps in our study demonstrated that our sample largely experienced pain over the entire anterior knee, with only 30% of the sample demonstrating a medial-only or lateral-only knee pain pattern.

The PFP group PPT means appear to be consistent with other PFP studies (range of means: 250-400kPa) but, the CON group means were lower than several studies [range of means: 350-620kPa; (Holden et al, 2018; Maclachlan et al, 2020; Noehren et al, 2016; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017)]. The same inclusion and exclusion criteria, (other than presence of PFP) were applied to both groups so extraneous pain conditions or co-morbidities should not have impacted our PPT results. Individuals with depression may exhibit lower pressure pain thresholds compared to non-depressed individuals, however, only one individual in the control group disclosed a current or previous diagnosis of depression.

High physical activity levels were reported for both PFP and control groups. High physical activity levels are typically associated with higher pressure pain thresholds, and higher CPM responses in healthy samples (e.g. lower pain sensitivity). Our study demonstrated lower PPTs (i.e. higher pain sensitivity) and lower CPM response compared to other study results despite these higher reported activity levels. Pazzinatto, de Oliveira Silva, Pradela, et al (2017) reported that females with PFP with higher running volumes demonstrated lower PPTs, indicating less pain sensitivity with higher activity levels. We did not examine running volume since we recruited from the broader population, but high physical activity levels were reported on the international physical activity questionnaire by 77% of the CON group and 70% of the PFP group with only 1 participant categorized as "inactive" per group (P. H. Lee, Macfarlane, Lam, & Stewart, 2011).

The international physical activity questionnaire asks participants to recall their moderate and vigorous physical activity during the past 7 days and self-report the number of hours and/or minutes of moderate and high intensity activity in a variety of situations (i.e. work, leisure, transportation, etc.). It is possible that overestimation of activity levels occurred due to the nature of recalling temporal aspects of past events, fear of judgment for reported values, or the observer effect (i.e. trying to demonstrate values you think the researcher wants) could have occurred. It is also possible that the ongoing pandemic affected physical activity levels due to changes in daily routines (i.e. reduced travel, working or studying from home), or the changes in the perception of active time.

Some authors have reported lower physical activity levels in PFP groups and our results did not support this (Glaviano, Baellow, & Saliba, 2017). Many factors could have led to this discrepancy, namely the timing of our study relative to the pandemic, as previously mentioned,

or the relatively low fear-avoidance beliefs, low pain catastrophizing, and high pain self-efficacy of our PFP group. If the participants in our sample did not feel that physical activity would affect their pain, or they were not as likely to attend to their pain, and felt confident about their ability to handle painful situations, physical activity may not be perceived as threatening.

While we assessed a number of contextual and psychosocial factors, we did not identify a lone contextual factor that affected our CON group PPT means. Pain is a biopsychosocial phenomenon. It is possible that any number of factors could affect the individual pain experience (i.e. nutrition, caffeine use, hormone levels, inflammatory markers, pain-related anxiety, social anxiety, etc.) that may not be identified in this study.

3.4.2. Potential Confounders

Confounders of the quantitative sensory testing that have not been previously discussed include psychological variables, pain intensity, and physical activity levels (Christensen, O'Sullivan, & Palsson, 2020; Flood, Waddington, Thompson, & Cathcart, 2017; George, Wittmer, Fillingim, & Robinson, 2006; George et al, 2007). Pain catastrophizing, depression, and anxiety are all associated with inefficient CPM responses and enhanced pain facilitation responses (Fillingim, 2000; Greenspan et al, 2007; Hennings et al, 2012; Riley et al, 1998). While many hypotheses exist discussing the potential nature of these relationships, they illustrate a chicken-egg problem (Fillingim, 2000). Chronic pain may lead to increased anxiety, depression, and pain rumination and catastrophizing, but the reverse could also be true (Crofford, 2015). Relationships between quantitative sensory testing and negative psychosocial attributes are widely supported (Campbell et al, 2015; Christensen et al, 2020; George et al, 2006; Maclachlan et al, 2020; Picavet et al, 2002) so we characterized potential pain responses (i.e.

pain catastrophizing, fear-avoidance, pain self-efficacy), history of depression and anxiety diagnosis, and current psychological medication use.

The PFP group demonstrated relatively low pain catastrophizing (mean 9.6 ± 7.2 out of a possible 52 points) and fear-avoidance beliefs (mean scores 22.7 ± 9.3 out of a possible 96 points) and high pain self-efficacy (median scores 52.5, IQR= 50.2, 58 out of a possible 60 points). It may be worth noting that despite our groups' high activity levels, the FABQ-knee physical activity subscale was 19.2 ± 7.6 and accounted for the majority of the FABQ-knee mean. Though our study design does not allow for causal inference, these findings indicate that a large portion of our sample believed that physical activity increased or caused their pain (per the FABQ-knee), but continued to engage in high volumes of physical activity. This behavior could be motivated by their high self-efficacy, indicating they have higher confidence in their ability to deal with painful situations. Collectively, these beliefs or behaviors could affect pain intensity reports or pain-reporting habits during quantitative sensory tests.

Forty and 45% percent of the PFP group self-reported depression and anxiety, respectively, compared to 7% and 15% in the CON group. Meanwhile, only 20% of the PFP group and 7% of the CON group reported taking medication for anxiety or depression. The high levels of depression and anxiety in the PFP group are concerning, and are higher than other PFP studies. Another reason for this potential difference is that we collected self-reported history or current depression and anxiety diagnoses, while other studies have used inventories to quantify depressive symptoms (Maclachlan et al, 2020; Thomee et al, 2002). These conditions have a high positive association with impaired CPM and enhanced TSP (Hennings et al, 2012; Valencia et al, 2013). Depression is also associated with pain catastrophizing, and the presence of depression or anxiety could alter quantitative sensory testing results or reporting of pain during

the tests (Valencia et al, 2013). Likewise, taking medication for the conditions could affect pain sensation, coping responses, and pain reporting.

Pain intensity is another factor that could play a role in our results. M. S. Rathleff et al (2017) observed an association between greater pain intensity and lower PPTs after grouping PFP participants by symptom duration. Post-hoc analysis of our data did not support this trend (Spearman's ρ=0.026, p= 0.912 for lateral; ρ= -0.222, p=0.348 for center; ρ= 0.016, p=0.947 for medial; ρ=0.105; p=0.659 for hand), however the PFP group baseline pain intensity mean was very low (16.6 ± 16.6mm) compared to other studies (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020; Pazzinatto et al, 2016; Pazzinatto, de Oliveira Silva, Pradela, et al, 2017; M. S. Rathleff et al, 2017). Our finding is supported in studies conducted on females with low back pain and shoulder pain, in which the authors concur that pain intensity ratings need not be high for dysfunctional CPM to be present (Martel et al, 2013; Valencia et al, 2013). One potential difference between our study and others is that we did not require a minimum pain intensity rating to take part in the study, while other authors have provided participation cutoffs of 3/10cm or higher. This minimum pain intensity inclusion requirement may be integral to observing a treatment effect that is greater than the minimal clinically important difference; however, our use of the information was to characterize the sample on the day of testing not eliciting pain reduction.

Although our PFP group exhibited lower pain intensity, they reported greater perceived knee dysfunction (i.e. KOOS and KOOS-PF scores), and higher physical activity than most studies (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2013). These findings indicate that although pain intensity at the time of testing was not high, participants perceived their knee pain interfered with their ability to

daily function. This finding is supported by M. S. Rathleff et al (2017), who did not observe significant relationships between pain intensity and KOOS scores in females with PFP. While statistical associations have not been assessed in other PFP studies, several authors report lower pain intensities with lower perceived dysfunction scores with means similar to our findings (Holden et al, 2020; Holden et al, 2018; Maclachlan et al, 2020).

Despite this perceived dysfunction, PFP participants continued to demonstrate high physical activity levels. It is possible that participants could have overestimated their physical activity levels on the IPAQ, or that the ongoing pandemic altered physical activity levels, so the 7-day recall instructed on the IPAQ could have overestimated activity levels across the sample. These results demonstrate the need to assess each of these variables during evaluation and treatment of PFP.

Athletes and individuals reporting high physical activity levels are also associated with more efficient CPM (Flood et al, 2017; Hennings et al, 2012). This effect is theorized to be the result of lower pain sensitivity in athletes (Flood et al, 2017). We did not observe between-group differences in physical activity levels and both groups reported similar distributions of high physical activity levels according to IPAQ categorization (Craig et al, 2003). Despite this, we still observed a difference in CPM response between PFP and CON groups. It may be relevant to note that the IPAQ may overestimate physical activity levels compared to objective assessments of physical activity and fitness monitoring (P. H. Lee et al, 2011). It may also be worth noting that the instruction for the IPAQ only asks participants about their physical activity levels for the past 7 days, which may or may not be related to their overall fitness or activity levels (Craig et al, 2003). Wide variability is also commonly reported with the IPAQ and was observed within our study sample. This increased variability means there is high interpersonal difference on the

measure. Clinically, it is important to assess individual physical activity levels as part of the PFP evaluation and treatment plan, and that individual results will require further discussion and consideration.

Pain is a multifactorial, personal experience and we decided to further explore how females with PFP describe their pain based on the McGill Pain Questionnaire. The uniqueness of the PFP experience is highlighted by our sample providing 189 total responses to 53 different descriptors. The wide variety of selected descriptors across multiple dimensions of pain add to the current literature. Specifically, the fact that every participant selected at least one descriptor from the evaluative list. This list indicates descriptors associated with negative cognitive appraisals of pain (e.g. tiring, cruel, punishing, exhausting, etc.) but other negative coping strategies such as pain catastrophizing and fear-avoidance were not reported. This may be due to the high pain self-efficacy of the sample. Maclachlan et al (2020) noted that 14% of participants reported low self-efficacy and our observations were similar, with only 15% of our sample in the lowest quartile of responses. Assessment of pain characteristics during initial evaluation can provide clinical clues that goes beyond simple description, but can provide insight into how patients appraise their pain.

3.4.3. Limitations and Future Research

This study has several limitations. As previously stated, several methods of quantitative sensory testing are able to assess the efficiency of the central and peripheral nervous systems. There is no current gold standard that is practical in both research and clinical situations, and females demonstrate higher variability than males in existing assessment methods (Kennedy et al, 2016). Second, within each quantitative sensory testing method, there are a variety of options

for analysis. We selected methods that yielded significant results in other PFP and knee osteoarthritis studies, but standardization is needed and has been called for by other authors (Kemp, Kennedy, Wu, Ridout, & Rice, 2019; Kennedy et al, 2016; Riley et al, 1998). Within these analyses and methods, there is still high interpersonal variability, so results are best interpreted for the individual patient with PFP. Interpreting group means improve our understanding of the pathoetiology of persistent PFP, however, making assumptions about each patient based on group means may not be appropriate. Last, the aim of the study was to identify whether signs of central sensitization occur in females with PFP. It is far more likely, given what is known in other chronic musculoskeletal pain conditions, that those with centrally sensitized PFP are a subgroup of the PFP patient population. Therefore, instead of assuming every patient who has PFP is centrally sensitized based solely on study results is not beneficial for every patient. Clinicians should assess signs of central sensitization and appropriate psychosocial factors for each patient in order to provide optimal patient-centered care.

Several treatment approaches exist to restore pain facilitation and inhibition mechanisms for individuals with musculoskeletal pain conditions (Chimenti et al, 2018; Hodges, 2011; Lluch Girbes et al, 2013). A PFP-specific approach does not yet exist. The current clinical practice guidelines for management of PFP only direct clinicians toward movement-based interventions such as strengthening and gait retraining (Willy et al, 2019). These approaches may not be effective for someone exhibiting signs of central sensitization, as effective pain inhibition and facilitation mechanisms need to be restored. If these mechanisms are not restored, pain persistence or recurrence is likely (Chimenti et al, 2018; M. S. Rathleff, Roos, et al, 2016). Researchers should continue to investigate the interaction of central sensitization and pathomechanics, treatment strategies, and psychosocial factors in patients with PFP. Once these

factors are better understood, treatment paradigms aligning with pain types should be explored and tested across sex and age groups with PFP.

3.5. Conclusions

The pathomechanical model of PFP proposes a number of lower extremity biomechanical factors leading to the development of retro- or peri- patellar pain. Based on this model, activation of nociceptors at the patellofemoral joint are theorized to result from elevated patellofemoral joint loading. Results from our work suggest that PFP may be more complex than loading-induced peripheral nociception. The presence of central sensitization indicates that pain may not be the result of a mechanical stimulus on a nociceptor at the affected site (i.e. patellofemoral joint). Instead, *central* nociceptive neurons are activated spontaneously or at subthreshold levels with an enhanced ability to facilitate nociceptive signaling and an inability to efficiently inhibit pain. This inefficiency of the pain network can lead to increased pain perception at the anterior knee, even if patellofemoral joint loading is reduced or eliminated. Therefore, central sensitization may perpetuate the high recurrence and persistence rates observed with the condition (Lankhorst et al, 2016; C. R. Rathleff, Olesen, Roos, Rasmussen, & Rathleff, 2013; M. S. Rathleff, Holden, et al, 2019; M. S. Rathleff, Roos, Olesen, & Rasmussen, 2015; M. S. Rathleff, Roos, et al, 2016).

Central sensitization status should be included as a factor in the development and persistence of PFP in etiological models. Clinical practice guidelines should be updated to include these findings now that multiple meta-analyses exist on the subject (Bartholomew et al, 2019; De Oliveira Silva, Rathleff, et al, 2019; Sigmund et al, 2020). Signs of central sensitization can be assessed clinically with quantitative sensory testing. Recognition of central sensitization is important in providing effective patient-centered care .

Chapter IV

In Females with PFP, Muscle Function During a Static Task is Not Altered Based on Central Sensitization Status

4.1. Introduction

Patellofemoral pain (PFP) is a chronic lower extremity condition characterized by persistent or intermittent retro- or peri-patellar pain (Willy et al, 2019). It is estimated that PFP affects approximately 25% of the population and that females are 2.2 times more likely to experience the condition than males (Boling et al, 2010; Smith, Selfe, et al, 2018; Willy et al, 2019). The pathomechanical model of PFP etiology synthesizes current PFP evidence, with the authors postulating that altered motor control and suboptimal lower extremity biomechanics elevate patellofemoral joint stress, and creating a nociceptive event (Powers et al, 2017). In the pathomechanical model, elevated patellofemoral joint loading is positioned as a nociceptive stimulus that ultimately leads to pain. This explanation does little to help us understand the high pain persistence and recurrence rates observed, especially in situations where rest or reduced loading has occurred (Lankhorst et al, 2016; C. R. Rathleff, J. L. Olesen, et al, 2013; M. S. Rathleff, Holden, et al, 2019; M. S. Rathleff, Roos, et al, 2016). In addition, it neglects the complexity of chronic musculoskeletal pain states and the potential neuromuscular and biomechanical outcomes of altered central pain processing (M. S. Rathleff, Roos, et al, 2016; Woolf, 2011).

The protective response theory provides a framework for relationships between neuromuscular control and pain (Hodges & Smeets, 2015). The authors (Hodges & Smeets, 2015) suggest that central sensitization affects sensorimotor function, which leads to alterations at multiple levels of the motor system. While these neuromuscular changes may serve an initial

protective or pain-relieving purpose, long-term consequences of adjusted movement pattern could occur. Motor cortex reorganization, reduced activation in sensorimotor cortices, and altered sensorimotor integration at the cortical level have all been observed in patients with PFP (Diekfuss et al, 2019; Te et al, 2017). Changes in sensorimotor function could lead to delayed quadriceps activation onset in response to a stimulus or the time to achieve peak activation (Quinlan et al, 2018). Delayed Vastus Medialis (VM) muscle activation response to a patellar tendon reflex compared to the Vastus Lateralis (VL), longer VM and VL electromechanical delay, and inhibited VM Hoffmann reflexes have all been observed in individuals with PFP (Chen et al, 2012; de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Witvrouw et al, 2003; Witvrouw, Sneyers, Lysens, Victor, & Bellemans, 1996).

Examining PFP using the protective response theory as a framework could provide additional insights into development and persistence of the condition. This framework would allow consideration of different types of pain and factors affecting pain as they relate to movement, rather than implicating pain as a simple product of specific movement patterns (Powers et al, 2017). The current pathomechanical model does not account for central sensitization of pain or psychosocial factors that could change pain perceptions. Central sensitization describes an altered state of the nervous system in which central nociceptive neurons are activated spontaneously or at subthreshold levels, and an imbalance between pain facilitation and inhibition occurs. This imbalance leads to increased pain sensation and is associated with several negative psychosocial features including depression and pain catastrophizing (Arendt-Nielsen, Morlion, et al, 2018; Woolf, 2011).

A number of investigations, including three recent systematic reviews and meta-analyses, have concluded that at least a subgroup of individuals with PFP experience manifestations of

central sensitization. These manifestations include local and remote pain hypersensitivity, inefficient central pain inhibition, and enhanced central pain facilitation (Bartholomew et al, 2019; De Oliveira Silva, Rathleff, et al, 2019; Maclachlan et al, 2020; Sigmund et al, 2020). When central sensitization is present, treatment options that only focus on movement and fail to address the altered central pain state may not achieve long-term success (Chimenti et al, 2018; M. S. Rathleff, Roos, et al, 2016). If central sensitization has the potential to affect neuromuscular function, muscle activation response to a stimulus may be prolonged. Examining this effect during a static task such as a maximal voluntary isometric contraction (MVIC) allows investigation of muscle activation response when the muscle is not additionally responsible for dynamic movement, postural or segmental stability, and weightbearing. Assessment of VM and VL muscle function would allow evaluation of a pathomechanical component of PFP in participants grouped according to central sensitization status. Central sensitization is only expected to occur in a subgroup of individuals with PFP. Therefore, grouping PFP participants by the set of quantitative sensory testing responses will allow us to determine whether each individual with PFP is categorized as centrally sensitized or not centrally sensitized. Due to the high variability for each quantitative sensory testing method, this novel method of grouping offers a clearer picture of how each female with PFP compares to the control group. Between-group comparisons will allow us to determine whether muscle function differences occur across groups who respond differently to pain.

4.1.1. Purpose, Specific Aims, and Hypotheses

The purpose of this study was to determine whether muscle function differs during a static task in females with PFP grouped by central sensitization status and compared to pain-free

females. The primary aim of this study was to determine whether time to VM and VL activation onset or peak activation differed by group [centrally sensitized (CS) PFP, non-centrally sensitized PFP (NS), and healthy controls (CON)] during a static task. A secondary aim of the study was to determine whether the CS group exhibited intramuscular differences (VM to VL) in neuromuscular activation timing. We hypothesized that the CS group would demonstrate delayed activation time to relative to other groups and that within the CS group, VM activation would be delayed compared to the VL.

4.2 Methods

4.2.1. Study Design and Protocol

This cross-sectional observational study was conducted in the neuromechanics laboratory of a large mid-western university. Participants arrived for a single session in the laboratory. Data were collected from the affected (or most painful) side for individuals with PFP. To characterize the sample, several clinical measures and self-reported inventories were completed (Figure 10).

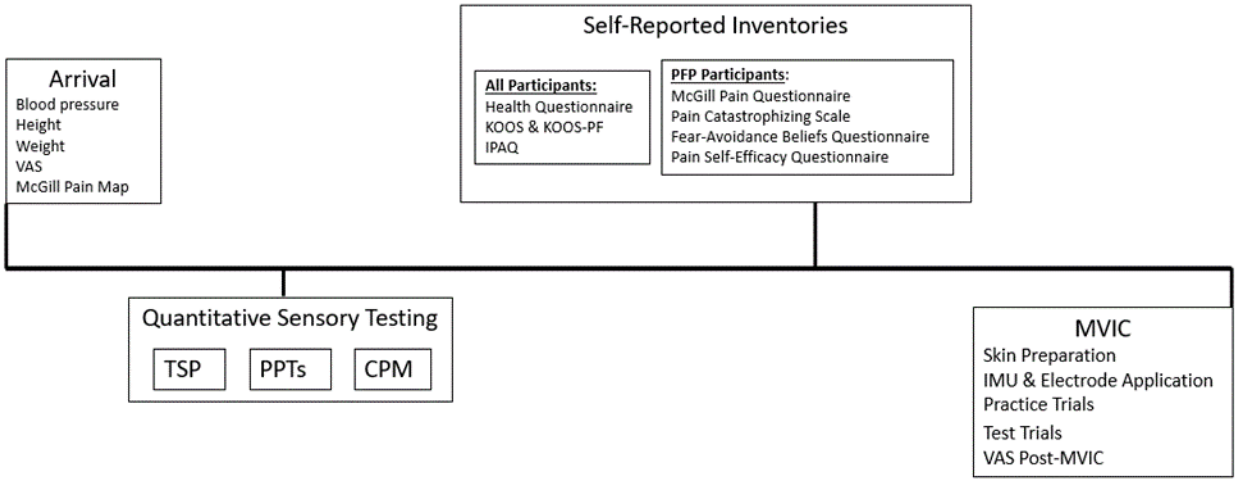


Figure 10: Study Protocol (2). After participants arrived at the lab, this is the order of the protocol. Abbreviations: VAS: Visual Analog Scale, TSP= Temporal Summation of Pain, PPTs: Pressure Pain Thresholds, CPM: Conditioned Pain Modulation, KOOS: Knee Injury & Osteoarthritis Outcome Score, KOOS-PF: KOOS-Patellofemoral Subscale, IPAQ: International Physical Activity Questionnaire, MVIC: Maximal Voluntary Isometric Contraction, EMG

Quantitative sensory testing was completed for all participants as a means of further grouping the PFP group by central sensitization status. Muscle activation response to an auditory cue was recorded using surface EMG during a quadriceps MVIC.

4.2.2. Participants

Female participants ages 18-40 years made up two groups, a PFP group and a healthy control (CON) group. Participants were included in the PFP group if they had non-traumatic onset of retro- and/or peri-patellar knee pain that increased with any 2 of the following: prolonged sitting, squatting or kneeling, ambulating stairs, or during or after exercise (Crossley et al, 2016; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017). Participants in either group were excluded from either group if they had any of the following: lower extremity or back injury in the previous 6 months, previous dislocations or subluxations, previous or known injury to the ligaments, cartilage, or meniscus to the knee, prior knee surgery to either knee, current pain in the back, lower extremity or hand (other than knee pain). Other exclusion criteria were hearing impairment, neurological conditions, other chronic pain conditions (i.e. low back pain, fibromyalgia, etc.), history of or current hypertension, implanted metal, adverse reaction to cold (i.e. cold urticaria, Reynaud's syndrome), and pregnancy (Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017; Zhao et al, 2012). Due to enrollment and data collection occurring between November 2020 and September 2021, all federal, state, local, and campus protocols related to COVID-19 were followed. Therefore, participants who were at high-risk of contracting COVID-19 were excluded from participation.

All participants were screened via teleconference by the lead researcher, and took part in a telehealth knee examination to rule out conditions and reasons for knee pain other than PFP. If

they passed the screening, they were scheduled for analysis. All participants provided informed consent to participate, approved by the university Institutional Review Board (protocols 20.050 and 20.327).

4.2.3. Instrumentation and Procedures

4.2.3.1. Self-Reported Inventories. All participants completed a health questionnaire, and inventories for self-reported knee function, and physical activity levels. The PFP group also completed several inventories related to their pain. Current health status, knee injury and treatment history, history of depression and anxiety, and medication use were collected using a health questionnaire (Appendix E). Self-reported knee function was collected using the Knee Injury and Osteoarthritis Score (KOOS) and associated patellofemoral subscale (KOOS-PF). Physical activity levels were reported using the International Physical Activity Questionnaire (IPAQ). The PFP group also completed the following pain-related inventories: McGill Pain questionnaire and body pain map, the Pain Catastrophizing Scale, the Fear-Avoidance Beliefs Questionnaire for the Knee (FABQ-Knee), and the Pain Self-Efficacy Questionnaire (PSEQ; Appendices E-G for more details on each inventory).

4.2.3.2. Quantitative Sensory Testing. All quantitative sensory tests were conducted by the same examiner on the affected side or the side with worse symptoms in the PFP group. Test limb side (i.e. right or left) were similarly distributed across the PFP and healthy groups (30% left leg, 70% right leg assessed in both the CON and PFP groups).

TSP was assessed using the monofilament method (300g nylon filament, Baseline, White Plains, NY, USA). Temporal summation was assessed by applying the monofilament perpendicular to the center of the test-side patella until bending of the monofilament was

observed (Figure 4). This application was repeated at one-second intervals for a series of 10 applications. Participants were provided a stack of paper Visual Analog Scales (VASs) and were asked to mark their current pain on a VAS form and flip to the next blank VAS between monofilament applications. The average of the second through fourth applications (VAS I) and the average of the eighth through tenth applications (VAS II) was used for analysis. TSP response was defined as VAS II - VAS I, in alignment with other studies for this type of analysis (Holden et al, 2018).

PPTs were assessed using a computerized pressure algometer (Algomed, Meddoc, Israel) at a pressure delivery rate of 30kPa/s with a $1cm^2$ round rubber tipped applicator (Figure 5). PPTs were assessed at each of four locations: the center of the patella, 3 cm medial to the medial patellar border, 3 cm lateral to the lateral patellar border, and on the middle phalanx of the 3^{rd} finger on the contralateral hand. Two repetitions of PPTs were recorded at each site and the average of each site was used for analysis, consistent with other study protocols (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017; M. S. Rathleff et al, 2013). Reliability of the PPT measurement was good to excellent for all test sites for the lead researcher (0.88-0.92).

CPM was assessed using the cold pressor test (Figure 6). The cold pressor test was performed by assessing PPTs at each site (in the aforementioned manner and locations), and were repeated while the contralateral foot and ankle were submerged in an ice water immersion. The ice water immersion temperature was maintained at 7°C using a water circulation and temperature control device. The average for each site for each of the two time points (baseline and during ice immersion) was calculated. CPM response was defined as the percent difference from baseline to ice immersion and this was used for analysis.

4.2.3.3. Electromyography. Surface electromyography (EMG) of the VM and VL were recorded using Noraxon MyoMotion 3.14 (Scottsdale, AZ, USA). Prior to data collection, the skin was prepared with coarse gauze and an alcohol wipe. Square 7/8" x 7/8" Ag/AgCl electrodes with 20mm interelectrode distance were placed on the VL and VM according to SENIAM guidelines (Figure 11). To place the VM and VL electrodes, the participant was positioned supine on a table with a bolster under the knee. The electrode was placed at 80% (to the distal end) of the line between the anterior superior iliac spine (ASIS) and medial joint line of the knee in the direction of the fibers. The VL electrode was placed at 2/3 the distance from the ASIS to the lateral angle of the patella ("Surface Electromyography for Non-Invasive Assessment of Muscles Project," 1999). Self-adhesive tape secured the electrodes and sensors in place to reduce the amount of movement artifact. Self-adhesive tape was used to secure electrodes and sensors and minimize their movement during testing.

Data were recorded at 1500KHz with analog-to-digital conversion. EMG amplitudes were rectified, providing the root mean squared value for a 50ms moving window. Additional smoothing of the signal was not conducted to ensure that onset time was properly identified.

EMG files were visually assessed for SRT and PRT to ensure accuracy and reduce the risk of false identification of onset (or lack of onset), consistent with prior research and current consensus (Besomi et al, 2020; Hodges & Bui, 1996).

4.2.3.4. Quadriceps MVIC. All participants performed a quadriceps MVIC as a response to an auditory cue (beep). Surface EMG assessed timing of muscle activation response to the cue during the MVIC. Participants were seated at the edge of a table with a rigid strap encircling the adjacent table leg and a handheld dynamometer on the anterior aspect of the anterior lower leg. Arms were crossed over the chest during calibration and all test trials. Participants were

instructed to listen for the auditory stimulus (beep) and kick as "fast and hard" as they could when it was delivered, holding the contraction for 3 seconds (Figure 12). Participants practiced the task twice, once at 50% maximal effort and once at 75% maximal effort. SRT was defined as the time from the audible cue until the onset of EMG activity for each muscle during stair descent. PRT was defined as the time from the audible cue until peak activation of stance phase for the second step during stair descent. Three test trials were recorded and the average SRT and PRT were used for analysis. The auditory cue was delivered at a random interval between 1-8 seconds after instruction to listen for the cue. Once the cue was delivered using the EMG system, a visual marker was automatically inserted into the EMG file denoting the time.

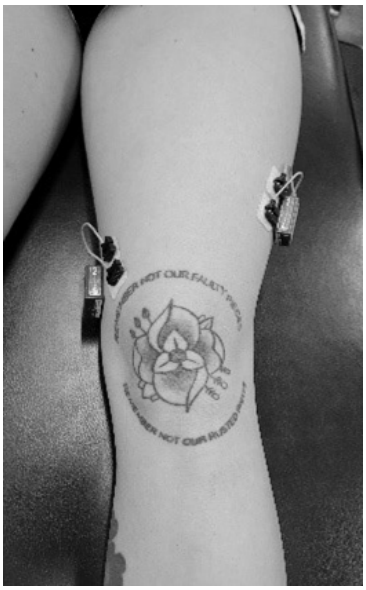
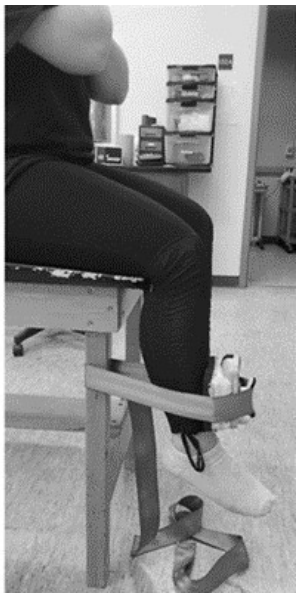


Figure 11: VL and VM Electrode Positions (SENIAM Guidelines, 1999)

Figure 12: MVIC Position



4.2.3.5. Central Sensitization Status Grouping. Following all data collection, PFP participants were further divided into two groups based on quantitative sensory test responses into a centrally sensitized (CS) group and a non-centrally sensitized (NS) group. The CS group had to exhibit at least 2 of the following: 1) TSP $\geq$ 1 cm higher than the CON group mean, 2)

remote PPTs that were at least 0.25 SD lower than the CON group mean, and/or 3) lower CPM response (percent change from baseline to ice immersion PPTs) than the CON group. Individuals with PFP who exhibited one or none of the above response were categorized in the NS group. Individuals in the CON group were not re-grouped.

4.2.4. Statistical Analysis

Participant characteristics were analyzed using descriptive statistics and between-group differences were assessed using Welch's tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. Repeated measures analyses of variance (RM-ANOVA) were conducted to examine differences in SRT and PRT across groups. The within-factor was muscle (VM, VL) and the between-factor was group (CS, NS, CON).

4.3 Results

Statistical analyses were conducted using SPSS 28.0 (IBM Corporation, Armonk, NY).

4.3.1. Participant Characteristics

Thirty-three females participated in the study. After grouping the PFP participants based on central sensitization status, a CS group (15 participants, 29.9 ± 7.4 years), NS group (5 participants, 27.2 ± 5.9 years), and CON group (13 participants, 28.0 ± 7.0 years) were included. The three groups did not differ based on age, height, weight, or BMI. Mean demographic and self-reported data can be found in Table 3. Additional supplemental demographic and self-reported data can be found in Appendices G-I.

The CS group reported higher pain at baseline, greater perceived dysfunction (KOOS, KOOS-PF), longer symptom duration, and more cases of bilateral pain than the NS group. The

CS group also reported greater pain catastrophizing, more fear-avoidant beliefs, and lower pain self-efficacy than the NS group and the CON group (Appendices G, H). Physical activity levels, McGill questionnaires or pain map area, and pain intensity following the MVIC did not differ between CS and NS groups (Table 3).

Table 3. Demographics & Self-Reported Data by Group (Mean ± SD) or Median (IQR) for non-normal distributions

Measure	CS Group	NS Group	CON Group	p-value
Age (y)	29.9 ± 7.4	27.2 ± 5.9	28.0 ± 7.0	0.688
Height (cm)	165.9 ± 5.5	169.2 ± 7.2	166.0 ± 9.6	0.671
Weight (kg)	64.5 ± 8.2	73.1 ± 11.6	69.3 ± 7.5	0.212
Body Mass Index	23.5 ± 3.5	25.5 ± 3.5	25.1 ± 2.6	0.532
Symptom Duration (mo)	24 (5, 120)	5 (5, 68)	NA	0.168
KOOS- Overall	67.2 ± 10.1	82.6 ± 10.4	98.5 ± 1.98	<0.001[a]
KOOS- PF	57.8 ± 14.5	84.9 ± 9.9	98.6 ± 2.7	<0.001[a]
IPAQ (Total MET-min)	7578.9 ± 6320.9	7373.7 ± 7282.3	8591.5 ± 5970.4	0.894
Pain Catastrophizing Scale	11.8 ± 7.8	5.0 ± 4.2	NA	0.025[b]
FABQ-Knee	26.1 ± 7.8	13.6 ± 8.8	NA	0.029[b]
PSEQ	50.5 ± 7.3	58.6 ± 5.0	NA	0.019[b]
McGill Pain Questionnaire (Summed Rank)	23.6 ± 11.9	18.4 ± 6.9	NA	0.242
McGill Body Pain Map (pixel area, cm^2)	3107.9 ± 7637.9	1708.5 ± 1795.7	NA	0.52
VAS- Baseline (mm)	20.4 ± 16.6	5.0 ± 11.2	NA	0.04[b]
VAS - Post-MVIC (mm)	27.0 ± 21.8	12.6 ± 24.4	NA	0.285
Unilateral/ Bilateral Symptoms (%)	20% / 80%	100% / 0%	NA	NA

Abbreviations: IQR= Interquartile Range; CS=Centrally Senstized; NS= Non-centrally Sensitized; CON= control; KOOS=Knee Injury and Osteoarthritis Outcome Score; KOOS-PF= KOOS-Patellofemoral Subscale; IPAQ= International Physical Activity Questionnaire; PSEQ= Pain Self-Efficacy Questionnaire;VAS=Visual Analog Scale; NA= Not Assessed. a= Significant differences between each group at the p<0.0001 value. b= Significant differences between CS and NS groups at the p=0.05 value.

4.3.2. Muscle Function

The data from this study met all assumptions for the repeated-measures ANOVA (independent observations, normality, sphericity). Kolmogorov-Smirnoff tests indicated normal and similar distributions for all variables.

4.3.2.1. SRT. No group-by-muscle interaction ($F(2,30)= 0.323$, $p= 0.727$) was observed, indicating similar stimulus response times across groups. A significant main effect for muscle was observed ($F(1,30)= 6.169$, $p=0.019$), indicating later VL stimulus response time regardless of group. No significant between-subjects effect of group ($F(2,30)= 1.09$, $p=0.349$) meaning group differences in stimulus response times did not occur based on group regardless of muscle. Means and standard deviations can be found in Table 4.

4.3.2.2. PRT. No group-by- muscle interaction ($F(2,30)= 0.868$, $p=0.430$), or main effects for muscle ($F(1,30)= 0.036$, $p=0.851$) or group ($F(2,30)= 2.94$, $p=0.068$) were observed. PRT did not differ between groups or within-groups by muscle.

Table 4. EMG Variables by Group During Quadriceps MVIC (Mean ± SD)

Variable	CS Group	NS Group	CON Group	Mean of All Participants
SRT - VL (s)	0.672 ± 0.06	0.649 ± 0.05	0.680 ± 0.06	0.672 ± 0.06[a]
SRT - VM (s)	0.656 ± 0.07	0.631 ± 0.03	0.656 ± 0.06	0.653 ± 0.06[a]
SRT Across Muscles	0.668 ± 0.014	0.629 ± 0.024	0.668 ± 0.015	0.658 ± 0.011
PRT - VL (s)	1.517 ± 0.56	1.455 ± 0.42	1.821 ± 0.48	1.626 ± 0.52
PRT- VM (s)	1.434 ± 0.44	1.291 ± 0.35	1.849 ± 0.62	1.576 ± 0.55
PRT Across Muscles	1.426 ± 0.117	1.517 ± 0.203	1.835 ± 0.126	1.593 ± 0.089

Abbreviations: EMG= Electromyography; CS= Centrally Sensitized; NS= Non-centrally Sensitized; CON= Control; SRT= Stimulus Response Time; PRT= Peak activation Response Time [a]= The VL was later than VM in all participants (p=0.031)

4.4. Discussion

4.4.1. Key Findings

Central sensitization can occur with activation of central nociceptive neurons, leading to increased pain facilitation and impaired pain inhibition within the central pain networks. These changes in the pain system can affect sensorimotor function, resulting in delayed muscle activation (Chen et al, 2012; de Oliveira Silva et al, 2017; de Oliveira Silva et al, 2016; Diekfuss

et al, 2021; Te et al, 2017). To our knowledge, this was the first study to determine whether muscle function differed during a static task comparing females with PFP grouped by central sensitization status and compared to pain-free females.

The primary finding was later VL activation onset compared to the VM in response to a stimulus across all groups. Time to peak activation response did not differ between-groups or within-muscle (VM-to-VL). Delayed VM activation in individuals with PFP is considered a pathomechanical factor leading to PFP development, but this finding is not universal. This study adds to ongoing debate regarding the presence and relevance of VM-to-VL muscle activation timing in individuals with PFP.

We selected a seated position within the optimal length-tension relationship to develop peak force, using a strap to allow the participant to produce maximal force against resistance while maintaining the knee position (Neumann, 2010b). This position allowed for assessment of muscle activation timing when EMG movement artifact, changes in movement strategy, or kinetic chain differences would be less likely to influence quadriceps muscle function (Besomi et al, 2020). A variety of MVIC test positions have been assessed in patients with PFP, ranging from full knee extension to varying degrees of knee flexion. Test positions closer to full extension being more likely to yield significant VM delays (Chen et al, 2012; Chester et al, 2008; de Oliveira Silva et al, 2017; Karst & Willett, 1995).

Weightbearing tasks are more likely to demonstrate delayed VM activation compared to the VL or to a control group (Chester et al, 2008). It is possible that during a static, seated MVIC, there is not enough demand on the quadriceps to create a situation where altered neuromuscular control occurs, leading to similar activation timing across groups. Earlier VM activation during weight-bearing may aid in patellar stabilization but this patellar stabilization

would not be warranted during a knee-flexed MVIC (Boling, Bolgla, Mattacola, Uhl, & Hosey, 2006; Powers et al, 2017). During weightbearing tasks, the quadriceps muscles are responsible for dynamic movement, postural control, and segmental control and have increased proprioceptive feedback (Chester et al, 2008). These additional task requirements may affect the timing of motor unit recruitment differently than during open-kinetic chain, static tasks.

High physical activity levels across groups could have also created a ceiling effect for activation response times. Even when activation response to a stimulus is longer, there is a physiological limit to the speed of the contraction due to timing of reflex latency and electromechanical delay. In individuals who are highly physically active, it is possible that they are closer to this ceiling compared to those with lower physical activity levels.

Limited empirical evidence has assessed relationships between central sensitization and motor function, despite the increasing recognition of central sensitization as a factor in chronic musculoskeletal pain development. Though we were unable to identify other PFP research examining central sensitization and muscle function, one study examined these relationships in patients with knee osteoarthritis. In that study, increased co-activation of the hamstring and quadriceps muscles was observed in the knee osteoarthritis group with the highest TSP response and lowest PPTs (Stefanik et al, 2020). This increased co-activation supports the intermuscular differences referred to in the protective response theory.

4.4.2. Potential Confounders

Psychosocial factors such as fear-avoidance beliefs and pain catastrophizing have been identified as potential confounders to pain, central sensitization, and neuromuscular outcomes. In our total PFP sample, we observed relatively low fear-avoidance beliefs and pain

catastrophizing, however, our CS group did exhibit significantly higher fear-avoidance and pain catastrophizing scores than the NS group. Of additional interest is that the fear-avoidance means were largely made up of scores in the physical activity subscale (CS mean = 21.6, NS mean= 11.2) but high physical activity levels were reported across all groups, as previously discussed. It is possible that the high pain self-efficacy, (e.g. confidence in the ability to handle painful situations), could have led the PFP groups to handle higher levels of physical activity, despite the belief that it may increase pain intensity. Also, the NS group reported higher pain self-efficacy compared to the CS group. When taken together, it indicates that the CS group exhibits a more negative outlook regarding their knee pain with beliefs that physical activity plays a role in increasing pain levels. It is possible that this the relatively high pain self-efficacy of both PFP groups allowed them to recruit more motor units despite any pain with the task.

Perceived knee function (e.g. KOOS and KOOS-PF) was significantly different between all groups while pain intensity reports were low compared to previous studies. Despite these comparisons to other study means, post hoc analysis demonstrated significant, strong associations between pain intensity ratings and KOOS scores (Spearman's rho = -0.671, p= 0.001). Interestingly, despite the low perceived knee function in the CS group, muscle function differences were not observed. Additionally, post-hoc analysis revealed no significant pain increase occurred between pre- to post-MVIC for either group (Appendix I), so pain during the task is unlikely to contribute to the task.

Psychological conditions or medications also have the potential to play a role in our results. The CS and NS groups reported similar trends in depression (40% in each group) which was higher than the CON group (23%). The CS group reported higher numbers of anxiety diagnoses (53%) compared to the NS (20%) and CON (7%) groups. Because PFP only affects

about 25% of the population, this higher rate of self-reported depression is concerning. Reports of depression and anxiety were also higher in our PFP groups compared to other studies, however, these studies used a depression symptoms scale to determine depression rather than self-reported methods,(Domenech et al, 2014; Domenech et al, 2013; Maclachlan et al, 2020). Depression is related to pain, perception of function, and quantitative sensory testing responses but could also reduce the time it takes to respond to a stimulus because of the inhibitory effects on the central nervous system and attentional focus (Crofford, 2015; Greenspan et al, 2007; Sarlani & Greenspan, 2002). One interesting note is that all 4 individuals in the study who were taking medications for anxiety or depression were all in the CS group, and to the best of our knowledge, the manner in which anti-depressants or anti-anxiety medications mediate or moderate EMG variables has not yet been assessed.

4.4.3. Limitations and Future Research

The results of this study indicate that there is no difference in muscle activation timing based on central sensitization group in females with PFP compared to pain-free females. There are several limitations to our study that are worth noting. The biggest limitation is sample size and distribution. We collected data from 20 females with PFP and all 20 demonstrated at least one sign of central sensitization. Our grouping plan was to group individuals based on having more evidence of central sensitization (two or more signs) and a group with zero or one sign of central sensitization. Allowing members of the NS group to experience one sign of central sensitization was an anticipatory strategy accounting for the fact that central sensitization is not dichotomous. There are no cutoff values that can be applied to quantitative sensory testing responses. It is also possible (and likely) that members of the NS group who experienced one

sign of sensitization could be peripherally sensitized, which could contribute to the non-significant differences between the CS and NS groups. Regardless, this grouping strategy, that left only 5 individuals in the NS group. We accounted for the possibility of unequal n's from a statistical standpoint, with the expectation based on previous research that about 2/3 of the sample would likely exhibit signs of central sensitization. Five participants in one group is still a very small number, so the results from the NS group should be extrapolated and interpreted with caution.

We determined PFP central sensitization status based on the mean values of the CON group. This strategy then left us with the issue that some members of the CON group could have also been able to be categorized as centrally-sensitized. While this is not ideal, this strategy was the best approach available given no established consensus for grouping (Greenspan et al, 2007). Females are two to nine times more likely to experience chronic pain conditions, so it is possible that this interpersonal variability within in the CON group is normal, based on our female-only sample (Fillingim, 2000; Unruh, 1996). Quantitative sensory testing has also been used to predict individuals who are at greater risk of chronic pain so the observed interpersonal differences within the CON group could be due to the predictive nature of the testing (Treede, 2019).

Interestingly, when assessing self-reported data, we could see a clear distinction between the CS and NS groups (Table 3), but assessment of the muscle function data was less obvious, with similar muscle activation timing across all groups.

Pain is considered a limitation of surface EMG, however, we observed similar temporal EMG characteristics across groups, suggesting that the effect of pain may have been minimal in our sample (Besomi et al, 2020). Several theories surrounding muscle activation, muscle force, and pain relationships have been proposed but none have been universally accepted (Besomi et

al, 2020). Some authors suggest muscle inhibition occurs in the presence of pain (Svensson, Houe, & Arendt-Nielsen, 1997; D. Turk, Melzack, R., 2011). Other authors suggest that pain increases muscle activity due to activation of excitatory signals and as a means of protecting the injured or painful body area (Hodges, 2011; Hodges & Smeets, 2015; Hodges & Tucker, 2011; Roland, 1986; D. Turk, Melzack, R., 2011). These theories are based on experimentally induced, nociceptive pain and none have demonstrated consistent results in the face of chronic musculoskeletal pain (Arendt-Nielsen, Graven-Nielsen, Svensson, & Jensen, 1997; Boudreau & Falla, 2014; Brindle et al, 2003; Graven-Nielsen, Arendt-Nielsen, Svensson, & Jensen, 1997; Graven-Nielsen, Svensson, & Arendt-Nielsen, 1997; Hodges, 2001; Hodges & Smeets, 2015; Hodges et al, 2016; Mista et al, 2016; Tucker et al, 2009).

This study is one of the first to assess relationships between muscle function and central sensitization status in individuals with PFP. Future research should continue to assess these relationships as they relate to PFP development, rehabilitation, and recovery. Specifically, our study only focused on the temporal aspects of muscle activation, but amplitudes and force have not yet been assessed as they relate to central sensitization. Additionally, future studies should continue to examine optimal grouping strategies for central sensitization. Other grouping strategies that have been assessed in the past include grouping based on TSP or CPM response (i.e. "responders" or "non-responders") but this strategy may be difficult to use in female samples as non-response is common even in pain-free females (Kemp et al, 2019; Kennedy et al, 2016). Other options could include grouping statistically based on tertiles or quartiles, but this can be difficult with multiple quantitative sensory testing responses to consider as a complete assessment of central sensitization characteristics. Last, while muscle function did not change across groups, we did observe clear differences in psychosocial characteristics of the CS and NS

groups including perceived knee function, pain intensity, pain catastrophizing, fear-avoidance, and pain self-efficacy. It is possible that one or a group of these factors may mediate relationships between central sensitization and muscle function and should continue to be assessed.

4.5. Conclusions

To our knowledge, this is the first study to assess whether central sensitization status relates to muscle function in females with PFP. Our results indicate that differences in muscle activation timing during a static task does not differ in females with PFP when grouped by central sensitization status or compared to pain-free females. Our findings add to the debate about the presence of altered quadriceps activation timing in females with PFP. Furthermore, our results did not support intra-muscular differences during a static task in the centrally sensitized PFP groups.

Chapter V

Females With Centrally Sensitized Patellofemoral Pain Exhibit Delayed Peak Quadriceps Activation But Not Altered Knee Kinematics During Stair Descent

5.1. Introduction

Patellofemoral pain (PFP) describes a common orthopedic condition consisting of insidious onset of pain around or behind the patella during prolonged sitting, stair ambulation, and exercise (Willy et al, 2019). PFP is over two times more prevalent in women than men (Boling et al, 2010; Smith, Selfe, et al, 2018). Long-term outcomes of PFP are poor, as pain persists in over 50% of participants included in longitudinal studies, and recurs in 70-90% of cases (Lankhorst et al, 2016; Stathopulu & Baildam, 2003). Current treatment recommendations are grounded in the pathomechanical model of PFP (Powers et al, 2017; Willy et al, 2019). The pathomechanical model frames PFP as elevated patellofemoral joint loading that activates patellofemoral nociceptors. Dysfunctional lower extremity neuromuscular and biomechanical factors are theorized to lead to this elevated joint loading, however, the model does not account for any factors impacting pain such as psychosocial factors or sensitization of the nervous system that is commonly observed with chronic musculoskeletal pain (Powers et al, 2017; M. S. Rathleff, Petersen, et al, 2016).

The protective response theory is a pain-movement model acknowledging that pain can develop in a variety of ways and is impacted by a number of factors including suboptimal tissue loading, central sensitization of pain, and psychosocial factors (Hodges & Smeets, 2015). As pain changes over time, altered neuromuscular control within and between muscles can lead to biomechanical changes. These biomechanical factors may serve a short-term protective purpose, but if these biomechanical changes continue, long term movement consequences can occur

(Hodges & Smeets, 2015). Several elements of altered pain and motor function included in this model have been observed in individuals with PFP.

One factor that can impact pain is central sensitization. Central sensitization describes an altered functional state of the pain system, characterized by increased responsiveness of nociceptive neurons (Arendt-Nielsen, Morlion, et al, 2018; "International Association for the Study of Pain Terminology," 2021). Manifestations of central sensitization include pain hypersensitivity due to subthreshold activation of central nociceptive neurons, and an imbalance in central pain inhibition and facilitation mechanisms (Arendt-Nielsen, Morlion, et al, 2018; Woolf, 2011). Signs of central sensitization can be assessed using quantitative sensory testing (Chimenti et al, 2018; Lluch Girbes et al, 2013). This increased response to noxious inputs may affect sensorimotor communication, which can alter neuromuscular control and muscle function (Hodges & Smeets, 2015; Noehren et al, 2016; M. S. Rathleff, Petersen, et al, 2016). Recent meta-analyses support the notion that at least a subset of individuals with PFP demonstrate signs of central sensitization but few studies have examined female-only samples despite documented sex differences on quantitative sensory testing in the population (Greenspan et al, 2007). Moreover, little is known about the relationships between central sensitization, muscle function, and biomechanics. These relationships could inform our understanding of PFP development and persistence (Bartholomew et al, 2019; De Oliveira Silva, Rathleff, et al, 2019; Sigmund et al, 2020).

Central sensitization indicates amplified afferent signals, so a delay in muscle activation could be the result of altered neuromuscular communication. Individuals with PFP exhibit altered neuromuscular function, but relationships between central sensitization and neuromuscular function have not yet been determined. Signs of altered neuromuscular function

in individuals with PFP include reorganization of the motor cortex, altered sensorimotor communication, and delayed vastus medialis (VM) activation compared to the vastus lateralis (VL) and to control groups (Aminaka et al, 2011; Boling et al, 2010; Cowan et al, 2001; Cowan et al, 2002; Diekfuss et al, 2021; Te et al, 2017). Delayed VM activation onset has been debated, though, as it is commonly reported during weightbearing and functional tasks but not during static, non-weightbearing tasks. Determining whether subgroups of females with centrally-sensitized and non-centrally sensitized PFP exhibit differences in VM or VL activation could help us better understand relationships between central sensitization and muscle function.

Altered kinematics are commonly associated with PFP development and compensation. Increased knee abduction is considered a pathomechanical component theorized to increase lateral patellofemoral joint reaction forces and has been associated with increased pain intensity (Powers et al, 2017; Scholtes & Salsich, 2020). Reduced knee flexion is considered a compensatory movement pattern of PFP, as less knee flexion would reduce patellofemoral joint loading (C. J. Barton et al, 2009; Brechter & Powers, 2002; de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & Azevedo, 2015; Nakagawa et al, 2012a; Nakagawa, Serrao, Maciel, & Powers, 2013; Powers et al, 1999; Salsich et al, 2001; Salsich et al, 2012; Salsich & Perman, 2013). Determining whether females with PFP grouped by central sensitization status exhibit differences in knee kinematics during a functional task would improve our understanding of relationships between central sensitization and movement patterns.

Examining the relationships between centrally sensitized pain in PFP, neuromuscular function, and knee kinematics may improve our understanding of PFP etiology. If central sensitization affects sensorimotor communication, stimulus response delays may occur, which

could alter the time it takes to achieve peak muscle activation. This delayed activation could alter quadriceps motor control during a functional, weight-bearing task.

5.1.1. Purpose, Specific Aims, and Hypotheses

The purpose of this study was to determine whether quadriceps muscle function and knee kinematics differed in females with PFP grouped by central sensitization status and compared to a healthy control group. The primary aim was to determine whether muscle activation timing would differ during a functional task (stair descent) when grouped by central sensitization status. We hypothesized that the centrally sensitized (CS) PFP group would exhibit slower muscle activation responses to a stimulus compared non-centrally sensitized (NS) PFP and healthy control (CON) groups. We also hypothesized that the CS group would exhibit later VM activation relative to the VL. Our second aim was to determine whether knee kinematics would be altered based on central sensitization status during stair descent. We hypothesized that the CS group would exhibit lower peak knee flexion and higher peak knee abduction compared to NS and CON groups.

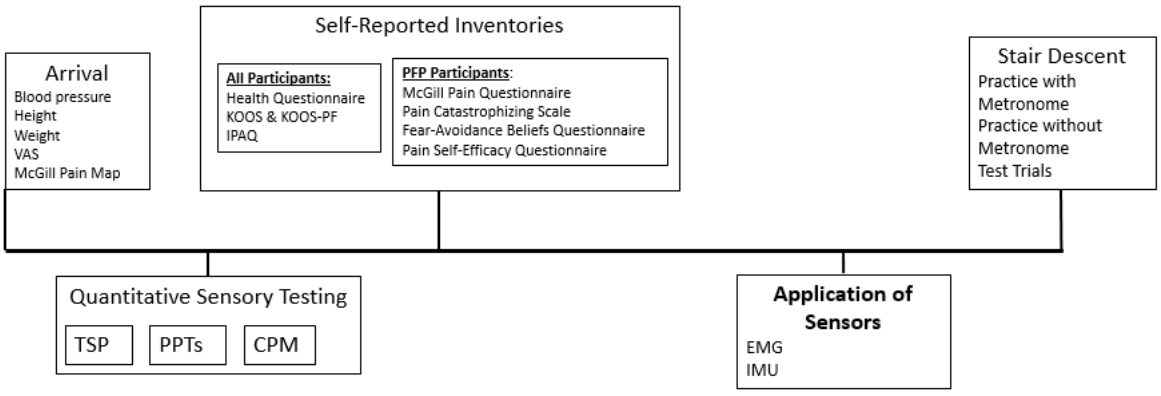


Figure 13: Study Protocol (3). Participants arrived, underwent quantitative sensory testing, followed by self-reported inventories, application of EMG and IMU sensors, and took part in the stair descent task.

5.2. Methods

5.2.1. Study Design and Protocol

Data collection for this cross-sectional observational study took place in the university neuromechanics laboratory. Participants arrived for a single session in the laboratory lasting 55 minutes. Data were collected from the affected (or most painful) side for the PFP group, and care was taken to ensure similar right-left distributions in the pain-free group. To characterize the sample, several clinical measures were completed (Figure 12). Quantitative sensory testing was completed for all participants as a means of grouping the PFP participants based on central sensitization status, followed by completion of several self-reported inventories to characterize the sample. Following these inventories, muscle activation response times and knee kinematics were recorded simultaneously during stair descent.

5.2.2. Participant Characteristics

Thirty-three participants (20 PFP, 13 CON) were recruited from local college campuses and the surrounding community, including clinics, athletic training facilities, gyms, public spaces, public recreational events, and online recruitment from recreationally athletic clubs and local public groups. Recruitment took place from November 2020 through September 2021. Demographic and self-reported data are presented by group in Table 5.

Participants were excluded if they had a hearing impairment or language barrier, any neurological condition affecting sensation or movement, current lower back, hand, or lower extremity pain, an injury to the lower back, hand, or lower extremity in the previous 6 months, history of surgery to either lower extremity, history of patellar dislocations or subluxations, were currently pregnant, had a chronic pain condition other than knee pain, they experienced adverse

reactions to cold in the past, had history of hypertension, or had implanted metal in the body (Maclachlan et al, 2020; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017; Zhao et al, 2012). Due to enrollment and data collection occurring between November 2020 and September 2021, all federal, state, local, and campus protocols related to COVID-19 were followed. Participants who were at high-risk of contracting COVID-19 were excluded from participation.

Table 5. Demographics & Self-Reported Data by Group (Mean ± SD) or Median (IQR)

Measure	CS Group	NS Group	CON Group	p-value
Age (y)	29.9 ± 7.4	27.2 ± 5.9	28.0 ± 7.0	0.688
Height (cm)	165.9 ± 5.5	169.2 ± 7.2	166.0 ± 9.6	0.671
Weight (kg)	64.5 ± 8.2	73.1 ± 11.6	69.3 ± 7.5	0.212
Body Mass Index	23.5 ± 3.5	25.5 ± 3.5	25.1 ± 2.6	0.532
Symptom Duration (mo)	24 (5, 120)	5 (5, 68)	NA	0.168
KOOS- Overall	67.2 ± 10.1	82.6 ± 10.4	98.5 ± 1.98	<0.001[a]
KOOS- PF	57.8 ± 14.5	84.9 ± 9.9	98.6 ± 2.7	<0.001[a]
IPAQ (Total MET-min)	7578.9 ± 6320.9	7373.7 ± 7282.3	8591.5 ± 5970.4	0.894
Pain Catastrophizing Scale	11.8 ± 7.8	5.0 ± 4.2	NA	0.025[b]
FABQ-Knee	26.1 ± 7.8	13.6 ± 8.8	NA	0.029
PSEQ	50.5 ± 7.3	58.6 ± 5.0	NA	0.019[b]
McGill Pain Questionnaire (Summed Rank)	23.6 ± 11.9	18.4 ± 6.9	NA	0.242
McGill Body Pain Map (pixel area, cm^2)	3107.9 ± 7637.9	1708.5 ± 1795.7	NA	0.52
VAS- Baseline	20.4 ± 16.6	5.0 ± 11.2	NA	0.04[b]
VAS- Stair Descent Baseline	30.9 ± 20.1	14.8 ± 22.7	NA	0.209
VAS- Post-Stair Descent	27.7 ± 21.6	5.4 ± 7.9	NA	0.003[b]
% of Unilateral/ Bilateral Symptoms	20% / 80%	100% / 0%	NA	NA

Abbreviations: IQR= Interquartile Range; CS=Centrally Senstized; NS= Non-centrally Sensitized; CON= control; KOOS=Knee Injury and Osteoarthritis Outcome Score; KOOS-PF= KOOS-Patellofemoral Subscale; IPAQ= International Physical Activity Questionnaire; FABQ-Knee= Fear-Avoidance Behavior Questionnaire for the knee; PSEQ= Pain Self-Efficacy Questionnaire; VAS=Visual Analog Scale; NA= Not Assessed. a= Significant differences between each group at the p<0.0001 value. b= Significant differences between CS and NS groups at the p=0.05 value.

Participants were examined using video calls to rule out knee conditions other than PFP, and to ensure the knee health of the pain-free individuals. Individuals in the PFP group were included if: they had non-traumatic onset of knee pain around or behind the patella(e), experienced pain with 2 or more of the following: squatting or kneeling, stair ambulation, sitting for long periods of time, or during or after physical activity such as running or jumping (Crossley et al, 2016). Upon arrival at the laboratory, participants were screened for high blood pressure due to the potential for vasovagal symptoms with ice immersion (Zhao et al, 2012). None of the blood pressure screenings required exclusion based on this screening.

5.2.3. Instrumentation and Procedures

5.2.3.1. Self-Reported Inventories. All participants completed a self-reported questionnaire regarding current health status, knee injury and treatment history, history of depression and anxiety, and medication use were collected using a health questionnaire (Appendix E). Self-reported knee function was collected using the Knee Injury and Osteoarthritis Score (KOOS) and associated patellofemoral subscale (KOOS-PF). Physical activity levels were reported using the International Physical Activity Questionnaire (IPAQ). The PFP group also completed the following pain-related inventories: McGill Pain questionnaire and body pain map, the Pain Catastrophizing Scale, the Fear-Avoidance Beliefs Questionnaire for the Knee (FABQ-Knee), and the Pain Self-Efficacy Questionnaire (PSEQ; Appendix E-G for more details on all self-reported inventories).

5.2.3.2. Quantitative Sensory Tests. All quantitative sensory tests were conducted by the same examiner on the affected side or the side with worse symptoms in the PFP group. Test

limb side (i.e. right or left) were similarly distributed across the PFP and healthy groups (30% left leg, 70% right leg assessed in both the CON and PFP groups).

TSP was assessed using the monofilament method (300g nylon filament, Baseline, White Plains, NY, USA). Temporal summation was assessed by applying the monofilament perpendicular to the center of the teste d patella until bending of the monofilament was observed (Figure 4). This application was repeated at one-second intervals for a series of 10 applications. Participants were provided a stack of paper Visual Analog Scales (VASs) and were asked to mark their current pain on a VAS form and flip to the next blank VAS between monofilament applications. The average of the second through fourth applications (VAS I) and the average of the eighth through tenth applications (VAS II) was used for analysis. TSP response was defined as VAS II - VAS I, in alignment with other studies for this type of analysis (Holden et al, 2018).

PPTs were assessed using a computerized pressure algometer (Algomed, Meddoc, Israel) at a pressure delivery rate of 30kPa/s with a $1cm^2$ round rubber tipped applicator (Figure 5). PPTs were assessed at each of four locations: the center of the patella, 3 cm medial to the medial patellar border, 3 cm lateral to the lateral patellar border, and on the middle phalanx of the 3^{rd} finger on the contralateral hand. Two repetitions of PPTs were recorded at each site and the average of each site was used for analysis, consistent with other study protocols (Holden et al, 2018; M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017; M. S. Rathleff et al, 2013). Reliability of the PPT measurement was good to excellent for all test sites for the lead researcher (0.88-0.92).

CPM was assessed using the cold pressor test (Figure 6). The cold pressor test was performed by assessing PPTs at each site (in the aforementioned manner and locations), and were repeated while the contralateral foot and ankle were submerged in an ice water immersion.

The ice water immersion temperature was maintained at 7°C using a water circulation and temperature control device. The average for each site for each of the two time points (baseline and during ice immersion) was calculated. CPM response was defined as the percent difference from baseline to ice immersion and this was used for analysis.

5.2.3.3. Surface Electromyography. Surface electromyography (EMG) of the VM and VL were recorded using Noraxon MyoMotion 3.14 (Scottsdale, AZ, USA). Prior to data collection, the skin was prepared with coarse gauze and an alcohol wipe. Square 7/8" x 7/8" Ag/AgCl electrodes with 20mm interelectrode distance were placed on the VL and VM according to SENIAM guidelines (Figure 11). To place the VM and VL electrodes, the participant will be positioned supine on a table with a bolster under the knee. The electrode will be placed at 80% (to the distal end) of the line between the anterior superior iliac spine (ASIS) and medial joint line of the knee in the direction of the fibers. The VL electrode will be placed at 2/3 the distance from the ASIS to the lateral angle of the patella ("Surface Electromyography for Non-Invasive Assessment of Muscles Project," 1999). Self-adhesive tape secured the electrodes and sensors in place to reduce the amount of movement artifact.

Data were recorded at 1500KHz with analog-to-digital conversion. EMG amplitudes were rectified, providing the root mean squared value for a 50ms moving window. Additional smoothing of the signal was not conducted to ensure that onset time was properly identified.

SRT was defined as the time from the audible cue until the onset of EMG activity at the start of the task for each muscle. PRT was defined as the time from the audible cue until peak activation of stance phase for the second step during stair descent. EMG files were visually assessed for SRT and PRT to ensure accuracy and reduce the risk of false identification of onset (or lack of onset), consistent with prior research and current consensus (Besomi et al, 2020;

Hodges & Bui, 1996). SRT and PRT were recorded using surface electromyography (Noraxon MyoMuscle 14.0, Scottsdale, AZ) of the VM and VL.

5.2.3.4. Motion Analysis. Peak knee flexion and abduction angles were recorded during stance phase of the stair descent. Movement of the pelvis and lower extremity was captured in

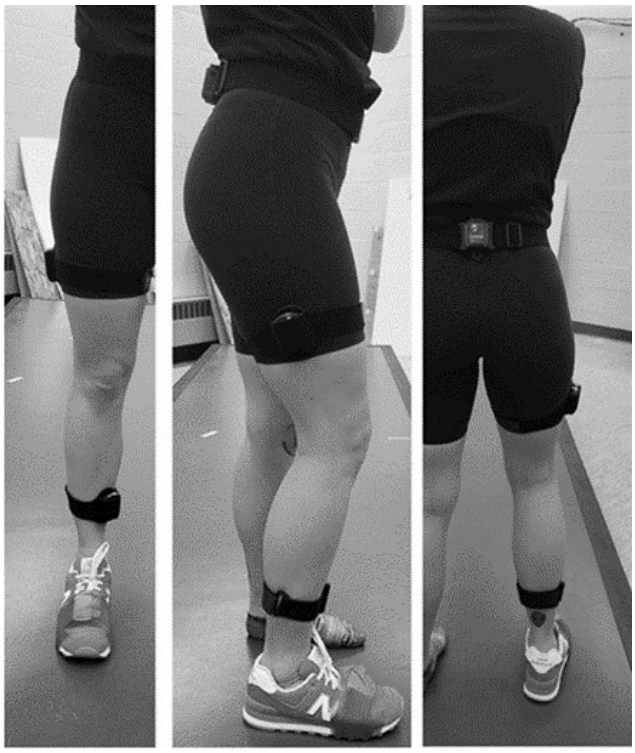


Figure 14: IMU Sensor Locations (Noraxon MyoMotion 3.14) at the pelvis, lateral thigh, medial shin, and top of the foot.

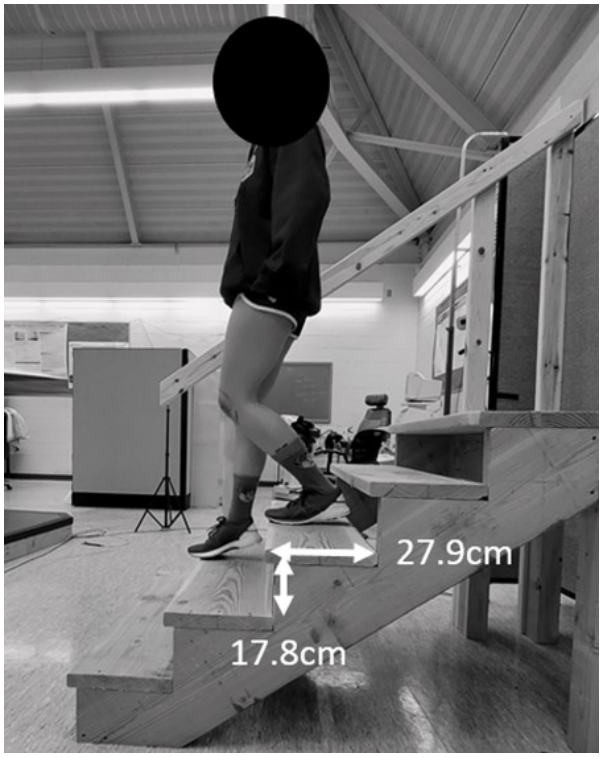


Figure 15: Stair Descent Task and Stair Dimensions. Figure represents an example of maximum knee flexion angle at the end of stance phase of the descent.

3D using an inertial measurement unit (IMU) system (Noraxon MyoMotion 14.0, Scottsdale, AZ) which recorded synchronously with the aforementioned surface EMG. Motion sensors were placed over the pelvis, lateral mid-thigh, and distal 1/3rd of the shank, and the top of the foot, in accordance with manufacturer recommendations (Figure 14). Kinematic data were filtered within the MyoMotion system using a quaternion orientation and sensor fusion of the gyroscope and accelerometer data, which mathematically filters out noise and corrects drift and gimbal lock

errors. Segment coordinate systems are anatomically based, where positive values represent knee flexion and abduction. Joint angles will be calculated using Euler angles and are decomposed using a Cardan sequence [x-y-z; (Sinclair, Taylor, Edmundson, Brooks, & Hobbs, 2012).

5.2.3.5. Stair Descent Task. The participant was asked to descend a 5-step wooden staircase at a rate of 96 beats per minute (bpm), leading with the test leg. Participants practiced three times with the aid of a metronome to aid in their understanding of the rate of step descent. Then, the metronome sound was removed, but the researcher watched a visual cue to ensure that the participant maintained proper pacing. The participant was then asked to relax completely at the top of the staircase and wait for the audible cue that served as the start of each test trial. The audible cue was delivered using a keystroke, which embedded the cue automatically and synchronously within the Noraxon system. They were instructed to descend as soon as they heard the cue and to stop once they reached the bottom of the stairs. Arm swing was not controlled or standardized to encourage natural motion.

Stair dimensions were 17.8cm (height) x 27.9 (depth) with a platform at the top (Figure 15). An attached handrail was present for safety, but if the handrail was touched, the trial was repeated. During descent, the participant's test leg contacted the steps three times during the total descent. The stance phase of the second step was used for data extraction of PRT-VL, PRT-VM, and peak knee flexion and knee abduction joint angles. Additionally, SRT was assessed for the VM and VL during this task. The average of the three trials for each variable were recorded and used for analysis.

5.2.3.6. Central Sensitization Status Grouping. After all data analysis was completed, participants were grouped based on their quantitative sensory testing results. Participants with PFP were included in the CS group if they met two of the following criteria: 1) TSP response of

>10mm compared to the mean CON group TSP response, 2) lower CPM response of the mean CON group CPM, and/or 3) remote PPTs that are lower than the mean CON group by 0.25 or greater standard deviation. These criteria were derived from expected differences between PFP and CON females based on a recent systematic review (M. S. Rathleff, Petersen, et al, 2016; M. S. Rathleff et al, 2017; Sigmund et al, 2020). The NS group was comprised of participants with PFP who did not meet the 2/3 criteria above.

5.2.4. Statistical Analysis

Participant characteristics and self-reported data were analyzed using descriptive statistics. Group characteristics were compared using Welch's tests for normally distributed data. When only the CS and NS groups were compared and non-normally distributed data were observed, Mann-Whitney U tests were conducted.

A multifactorial (e.g. within-between) repeated measures approach was selected to account for the anticipated within-subject correlations of the EMG and kinematic data (Atkinson, 2002; Atkinson & Nevill, 2001).

Two repeated measures ANOVAs were conducted comparing SRT and PRT during stair descent between groups. Muscle (VM, VL) was the within-subjects factor and group (CS, NS, CON) was the between-subjects factor. Tukey post-hoc analysis was used to identify group differences. A multivariate ANOVA was conducted to determine whether peak knee flexion and knee abduction joint angles differed by group (CS, NS, CON). Partial η^2 values were calculated in SPSS to assess the between-group effects. J. Miles and Shevlin (2001) provide rules for interpretation of the Partial η^2 value for ANOVA models that were applied (small effect= 0.01, moderate effect= 0.06, large effect= 0.14).

5.3. Results

5.3.1. Participant Characteristics

The three groups (CON, CS, NS) did not differ based on age, height, weight, or BMI (Table 5). The CS group reported higher pain intensity during baseline and after stair descent compared to the NS group ($F(1,18)= 5.602$, $p= 0.029$). Neither typical pain intensity with stairs nor symptom duration (mo) was significantly different between the CS and NS groups. Eighty percent of the CS group experienced bilateral pain, while 100% of the NS group experienced only unilateral knee pain. The CS group reported greater perceived dysfunction (on overall KOOS and KOOS-PF scales), higher pain catastrophizing responses, more fear-avoidant beliefs, and lower pain self-efficacy than the NS group. Meanwhile, physical activity levels, overall McGill scores, and total pain area on the McGill body pain map, and typical pain with stair walking did not differ between CS and NS groups. Mean demographic and self-reported data can be found in Table 5. More self-reported and demographics results can be found in Appendices G-I.

5.3.2. Muscle Function

5.4.2.1. PRT. PRT data met all assumptions of the repeated-measures ANOVA. There was no significant group-by-muscle interaction ($F(2,30)= 1.17$, $p=0.324$) or main effect for muscle ($F(1,30)= 0.11$, $p= 0.745$). A significant between-group effect was observed ($F(2,30)= 11.92$, $p< 0.001$) with a large between-group effect (Partial $\eta^2= 0.443$), indicating that the CS group demonstrated later peak activation response times to the CON group regardless of muscle. No differences in peak activation response times were observed between the CS and NS groups, or the NS and CON groups (Table 5).

5.3.2.2. SRT. Non-normality was observed in SRT data, so a Logx transformation was conducted prior to the analysis. There was no significant group-by-muscle interaction (F(2,30)= 1.31, p=0.286). No main effect of muscle was observed (F(1,30)= 0.151, p= 0.700), nor were there any significant between group differences were observed (*F*(2,30)= 2.01, p= 0.151) with a moderate between-group effect (Partial η^2= 0.118). However, due to the small sample size in the NS group and the transformation of the data, the clinical relevance of this finding is debatable.

5.3.3. Knee Kinematics

5.3.2.3. Knee Kinematics. Non-normality was observed in both knee flexion and knee abduction joint angles, so a Log transformation was conducted prior to the analysis. There were no significant between-group differences for knee flexion (F(2,30)= 1.85, p=0.175) or knee abduction (F(2,30)= 2.92, p=0.069). Effect sizes for between-group differences for knee flexion were moderate (Partial η^2= 0.110) and for knee abduction were large (Partial η^2= 0.163). However, we encourage caution with the effect size interpretation due to the small sample size for the NS group and the transformation of the data for the analysis.

Table 6. Movement Variables by Group During Stair Descent (Mean ± SD)

Variable	CS Group	NS Group	CON Group	All Participants
EMG				
SRT - VL (s)[a]	-0.353 ± 0.31	-0.188 ± 0.29	-0.417 ± 0.12	-0.353 ± 0.25
SRT - VM (s)[a]	-0.293 ± 0.27	-0.257 ± 0.21	-0.451 ± 0.13	-0.350 ± 0.23
PRT - VL (s)	3.230 ± 0.13[c]	3.164 ± 0.35	2.81 ± 0.23[c]	3.06 ± 0.29
PRT- VM (s)	3.239 ± 0.22[c]	3.071 ± 0.39	2.86 ± 0.24[c]	3.06 ± 0.31
Kinematics				
Knee Flexion Angle (°)[a]	4.5 ± 0.09	4.5 ± 0.06	4.5 ± 0.05	4.5 ± 0.08
Knee Abduction Angle (°)[a,b]	5.2 ± 0.48	5.1 ± 0.23	5.0 ± 0.01	5.2 ± 0.10

Abbreviations: SD=Standard Deviation; CS= Centrally Sensitized; NS= Non-centrally sensitized; CON= Control; EMG= Electromyography. [a]= These variables were log-transformed due to non-normality during analysis. b= 0° represents neutral. values >0° represent knee abduction, values < 0° represent knee adduction. c= The CS group has significantly later VL nd VM PRT compared to the CON group (p<0.001).

5.4. Discussion

5.4.1. Key Findings

Central sensitization has the potential to alter sensorimotor communication, affecting neuromuscular function (Diekfuss et al, 2021; Te et al, 2017). Altered neuromuscular control can lead to changes in inter- and intra- muscular function, which can alter kinematics during a functional task (Hodges & Smeets, 2015; Hodges & Tucker, 2011). The purpose of this study was to determine whether neuromuscular or kinematic differences occurred during a functional task between females with PFP based on central sensitization and compared to pain-free females. This is one of the first studies examining relationships between muscle function, kinematics, and central sensitization in females with PFP and our hypotheses were partially supported. The CS group exhibited delayed VL and VM peak activation during stair descent relative to the CON group, but no between-group differences were observed for VM or VL activation onset, peak knee flexion and peak knee abduction angles.

Delayed VM and VL peak activation in the CS group compared to the CON group may be indicative of muscular inhibition. According to the protective response theory, muscular inhibition could be the product of altered sensorimotor function, cortical reorganization, or the product of central inhibition and is a precursor to altered kinematics (Diekfuss et al, 2021; Hodges & Smeets, 2015; Te et al, 2017). Delayed VM activation onset is theorized in the pathomechanical model to increase lateral patellar translation or tilt but there is no mention of delayed VL activity compared to pain-free individuals (Powers, 2000a; Powers et al, 2017). Our findings are in agreement with several authors that did not report temporal differences in VM and VL activation during stair and step descent tasks (Aminaka et al, 2011; Brindle et al, 2003; Cavazzuti et al, 2010; Powers et al, 1996). None of these studies examined central sensitization

as a part of the research question. Only one female-only sample was assessed yielding similar outcomes to our study (Powers, Perry, Hsu, & Hislop, 1997). Time to peak activation was only assessed in one study and no differences between PFP and control groups were observed. In that study, males and females were included in the sample with a slightly younger mean age compared to our study (Cavazzuti et al, 2010). Time to VM and VL peak activation may be delayed during stair descent in individuals with central sensitization, but more research is needed to confirm whether sex or age play a role in this finding.

We did not observe differences in muscle activation onset in response to a stimulus. Briani et al (2016) observed delayed VMO activation relative to the VL during stair descent, but only in a subgroup of females with PFP reporting high physical activity levels. In the moderately active PFP group, no differences were observed in activation onset between VM and VL. In our sample, 14 females with PFP were categorized by IPAQ criteria as highly active (11 CS, 3 NS) along with 10 CON group individuals were also in this group. Only three participants (one per group) were considered inactive and six were considered minimally active (3 CS, 1 NS, 2 CON). While we did not statistical analyze our results according to physical activity level, our non-significant activation onset and high number of highly active participants suggests it would not be likely in our sample.

Step height and tempo of descent could also impact stance side knee flexion angle and muscle activation required to perform controlled lowering of the contralateral leg. We constructed stairs in accordance with current U.S. building codes (17.8cm height and 27.9cm depth) and standardized descent timing to 96 beats per minute (bpm) in accordance with previous studies (Bolgla, Malone, Umberger, & Uhl, 2008; Cowan et al, 2001; Crossley, Cowan, et al, 2004; "United States General Site and Building Codes," 2018). Step heights in other

investigations have ranged from 17cm to 21cm heights and 22 to 30.5cm depth (Aminaka et al, 2011; Brindle et al, 2003; Cavazzuti et al, 2010; Cowan et al, 2001; Powers et al, 1997). Only one author reported standardizing the timing of the stair descent at the same rate we selected (96 bpm) while the others all assessed self-selected paces (Cowan et al, 2001). Only one author of a self-selected pace study conducted a post-hoc analysis to determine whether stride rate or cadence were different (Powers et al, 1997). Self-selected pacing is problematic during temporal assessment of EMG variables because if the step or stride rate during the task are not similar across participants, delays in activation onset time or time to peak activation may be the product of different gait characteristics and not pain-related muscle inhibition (Cowan et al, 2001). Altered peak activation in the CS group supports intra-muscular changes during functional movement in the protective response theory, but also needs to be interpreted in the context of kinematic variables to understand whether these changes play a role in altered movement.

During stair descent, peak knee flexion and abduction joint angles are most likely to occur at the end of the stance phase, when controlled lowering of the body's center of gravity from the stance leg to the next lower step occurs. We observed delayed peak activation of both the VM and VL, but not VM-to-VL differences in activation onset in response to a stimulus that are often reported in individuals with PFP (Boling et al, 2006; Cowan et al, 2001; Cowan et al, 2002). This indicates that the CON group pre-activated the VM and VL prior to peak knee flexion but the CS group did not exhibit the same pre-activation. Peak knee flexion and abduction joint angles were similar across all groups (Figure 16) indicating that the change in peak vasti activation did not affect knee kinematics. The CON group was also the only group to activate the VM prior to peak abduction angle, though pre-activation only lasted 0.1s and is unlikely to have clinical significance. The NS group did not differ from either group for peak

knee angles, however, peak VM and VL activation means fell between the CS and CON groups, which could indicate a pattern that onset of PFP delays peak activation but when CS occurs, these changes become significantly different. This shift to later peak activation is important because peak quadriceps activation provides both feedforward and feedback information about peak knee angles, improving knee stability during functional tasks (Peng, Fey, Kuiken, & Hargrove, 2016). Therefore, peak activation that is temporally closer to maximal knee flexion could lead to a less controlled stair descent. Reduced anticipatory activation could lead to higher loading rates, higher pain intensity, and higher movement-related fear (Briani et al, 2018; de Oliveira Silva, Barton, et al, 2019; de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & Azevedo, 2015). While we did not assess movement-related fear or loading rates in this study,

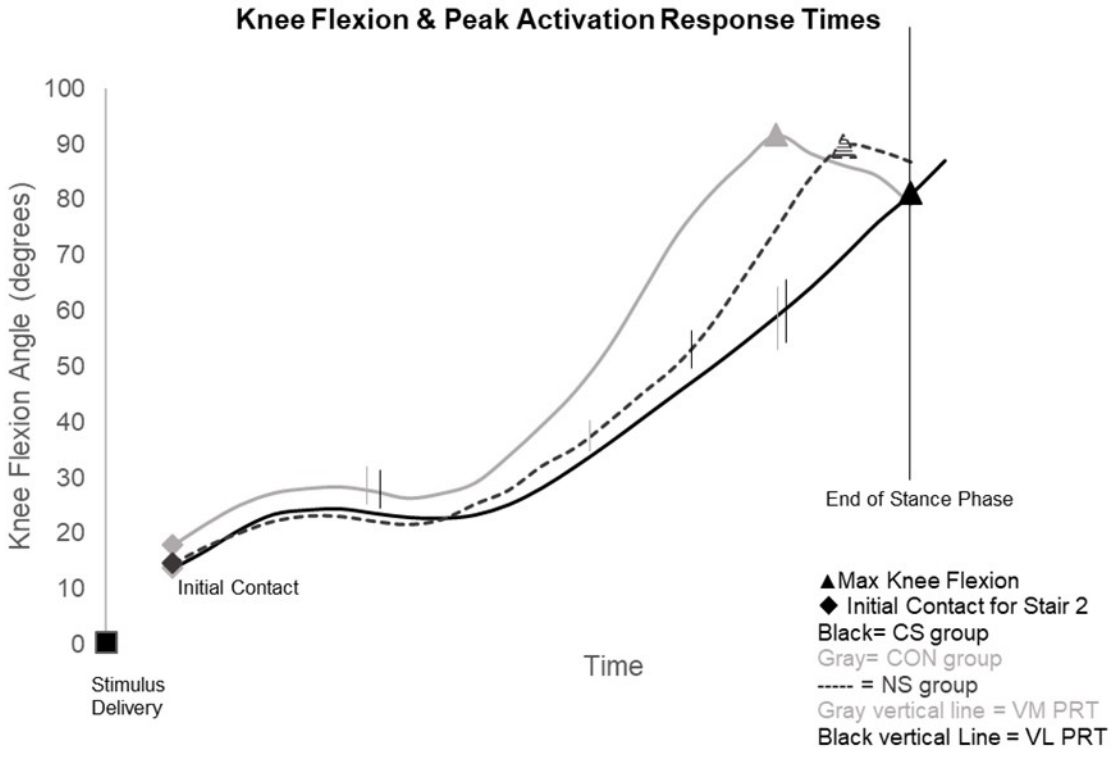


Figure 16: Knee Flexion Angles and Peak Activation Response Times During Stance Phase of Stair Descent. Note that the CON group activates the VM and VL earlier in stance phase than the NS and CS groups, and that the CS group activates the VM and VL just prior to maximum knee flexion.

our CS group did report higher fear-avoidant beliefs, lower perceived function, and increased pain after stair descent compared to the NS group.

In the pathomechanical model, reduced knee flexion is presented as a means of reducing patellofemoral joint compression and loading (Powers et al, 2017). In the protective response model, reduced knee flexion is explained as the reduction of total knee range of motion in order to (theoretically) protect the joint from further perceived damage and reduce pain (Hodges, 2011; Hodges & Smeets, 2015). Regardless of the rationale, reduced knee flexion and lower knee extensor moments have been inconsistently observed in individuals with PFP (Brechter & Powers, 2002; Crossley, Cowan, et al, 2004; Powers et al, 1999). We observed 4.5° less knee flexion between the CS and CON groups, but only 1.8° less between the NS and CON groups. Crossley, Cowan, et al (2004) observed PFP groups with 6.0° less peak knee flexion during stair walking, which was significantly less than the control group. It is worth noting that a larger but unbalanced sample size was present in that study with 48 males and females with PFP and 18 controls (Crossley, Cowan, et al, 2004). Powers et al (1997) did not observe differences in peak knee flexion angle, but did not report group means to offer comparison. Visual comparison of our knee flexion time series graphs (Figure 15) were similar to both of these studies, with both depicting slightly higher and (non-significantly) earlier peak knee flexion in the healthy group (Crossley, Cowan, et al, 2004; Powers et al, 1997).

It has been suggested that when cadence is controlled, between-group differences in knee flexion during stair descent are more likely than when cadence is not standardized (C. J. Barton et al, 2009). In order to ensure the consistency of our temporal EMG variables, we standardized stair descent at the same cadence (96 bpm) as previous studies but did not observe between-group differences (Bolgla et al, 2008; Cowan et al, 2001; Crossley, Cowan, et al, 2004). While

we cannot assume that cadence control did not impact our knee joint angles, we can conclude that it did not impact the significance of our kinematic results.

Peak knee abduction angles in our study did not differ based on central sensitization status. In fact, our entire sample tended to have a neutral abduction angle during stance phase with a tendency to move into increased adduction angles as opposed to knee abduction. In addition, peak knee abduction typically occurred at the beginning of stance phase for all groups, and in the CS and NS groups it occurred prior to VM and VL peak activation. This indicates that the VM and VL may not activate in anticipation of peak knee abduction but as a response to altered frontal plane knee angles during stair descent.

Increased peak knee abduction is inconsistently reported during stair ambulation for individuals with PFP (Bolgla et al, 2008; Graci & Salsich, 2015; Myer, Ford, Di Stasi, et al, 2010; Noehren et al, 2012; Salsich et al, 2001; Salsich et al, 2012; Scholtes & Salsich, 2020). Our results are in line with prior studies suggesting that women with PFP may demonstrate less peak knee abduction during stair walking compared to angles observed during single-leg squatting and landing (Bolgla et al, 2008; Herrington, 2014). In fact, our mean knee abduction angle was fairly neutral and 65% of the PFP group (38% CON group) demonstrated a mean frontal angle representing knee adduction or a neutral frontal plane position. This is similar to findings of Bolgla et al (2008) who reported knee varus in both control and PFP groups with greater knee varus angles in the PFP group during stair descent. In both studies, as in ours, cadence was standardized to 96 bpm. This was important for our timing analysis, however, studies that do not standardize timing across participants appear to demonstrate higher peak knee abduction angles (C. J. Barton et al, 2009). This could indicate a difference in preferred

kinematic strategy when cadence is not controlled that may be closer to the participants typical gait pattern.

Peak abduction angles are also influenced by altered movement patterns throughout the kinetic chain. Therefore, it is possible that the lack of increased knee abduction angles at the knee could indicate altered trunk, hip, or ankle movement patterns (Powers et al, 2012). We did not assess kinematics at other joints and cannot speculate what these patterns would have been for our sample. Bolgla et al (2008) suggested that a more neutral or adducted gait pattern could be a compensation in order to avoid a movement pattern associated with higher pain intensity. In our study, the CS group had significantly higher pain intensity after stair walking compared to the NS group but pain intensity was still relatively low at baseline and after stair descent (see Table 3 for means). We did not see different knee abduction angles across groups, but the CS group did report higher pain after stair descent along with higher fear-avoidance beliefs, so it is possible that these factors led to increased pain perception that was not the result of altered movement patterns. Since stair walking is a common symptom of PFP and is often unavoidable during activities of daily living, relationships between pain expectation and intensity, central sensitization, and kinematics should continue to be explored.

We were only able to identify one other study investigating relationships between central sensitization and lower extremity kinematics for individuals with PFP (de Albuquerque, Liebano, Biasotto-Gonzalez, Lopes Ferreira, & Lucareli, 2021). Grouping and analysis was conducted in a different manner, making study comparisons difficult. We grouped our participants based on central sensitization status by comparing quantitative sensory testing results between PFP and control group, while the other authors analyzed a single PFP group to identify associations between quantitative sensory testing results and movement patterns. The PFP group in that study

also did not exhibit impaired CPM or enhanced TSP compared to a control group, so it is possible that the sample could be considered peripherally sensitized, as opposed to centrally sensitized. Lower PPTs at local and remote sites were reported, but this could also indicate peripheral sensitization and not central effects (de Albuquerque et al, 2021). There is no current standardization for grouping procedures for central sensitization. Standardized analytic protocols would limit the ambiguity involved in interpreting quantitative sensory testing data as it relates to group membership (Kennedy et al, 2016). Other suggested methods of grouping have included quantitative sensory testing comparisons to healthy groups and grouping based on CPM-responder versus non-responder status. A CPM non-responder would be an individual who demonstrates increased pain but lower or no change in PPTs during the conditioning stimulus, whereas a responder would indicate increased pain with higher PPTs. In our study, every PFP participant demonstrated at least 1 CPM non-response across the four test sites, and 54% of the CON group included CPM non-responders as well. This highlights the potential effect of sex and indicates the grouping based on CPM response may not be appropriate for female-only samples.

We selected kinematic variables that have been associated with pain in participants with PFP (Crossley, Cowan, et al, 2004; Salsich et al, 2012). In the comparison study, a movement deviation profile score was created from lower extremity lateral step-down kinematic data that was assessed for correlations with each of the quantitative sensory testing variables (de Albuquerque et al, 2021). No significant association between quantitative sensory testing and the kinematic score were observed. The movement deviation profile used in the study has been validated for walking gait, and has been previously reported in lateral step-down analysis, but reliability and validity information for the step-down task was not presented (G. J. Barton,

Hawken, Scott, & Schwartz, 2012; Lopes Ferreira et al, 2020). More studies are needed before relationships between central sensitization, muscle function, and kinematics can be assessed.

The CS group exhibited delayed peak VM and VL activation relative to the CON group, but activation onset times and knee kinematics were similar across groups. The altered intramuscular function presented in the protective response theory was partially supported by this study, but only for peak response times. The hypothesis that altered muscle function would lead to kinematic changes was not supported, though the protective response theory does specify that biomechanical changes are a long-term consequence of altered muscle function. In order to update the pathomechanical model, the idea that central sensitization of PFP can alter peak muscle function should be considered. Future studies need to be conducted in order to better understand these relationships in order to update the evidence-based model. Clinicians should consider that restoration of effective CPM and TSP have been identified as signs of self-reported recovery (Holden et al, 2020; Holden et al, 2018; M. S. Rathleff, Roos, et al, 2016). Future clinical research should examine whether restored quantitative testing could lead to recovered muscle function and motor control during stair descent.

5.4.2. Potential Confounders

Pain intensity and perceived function can impact biomechanics (de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & Azevedo, 2015; Scholtes & Salsich, 2020). In this study, pain intensity levels were lower than previously published work. The CS group reported significantly lower pain intensity and lower perceived knee function at baseline compared to the NS group. Because there were no differences between knee kinematics, it is unlikely these factors affected our results.

The CS group also reported significantly higher pain catastrophizing, fear-avoidance beliefs, and lower pain self-efficacy, indicating the potential for adverse psychosocial factors. It is unclear from this dataset whether these negative psychosocial responses the cause or the result of altered central pain processing or as a predisposition for it. Maclachlan et al (2020) did not observe significant relationships between similar psychosocial factors and quantitative sensory testing in a large group of individuals with PFP. One key difference between that study and ours was the inclusion of both males and females in the sample, which can affect both sets of variables. Future studies should continue to explore these relationships between psychosocial variables and signs of central sensitization in females with PFP.

5.4.3. Limitations and future research

The multifactorial nature of the variables included in this study is one limitation of the study. Pain itself is a biopsychosocial factor and a number of variables can influence the reporting pain intensity at baseline, post-movement, and during quantitative sensory testing. We collected information regarding self-reported depression and anxiety and medications for these conditions (previously reported). We also collected information regarding previous and ongoing rehabilitation and treatment strategies, current stress levels, and a number of psychosocial variables.

There is debate about the extent to which EMG reading are trustworthy in the presence of pain (D. Turk, Melzack, R., 2011). Individuals with pain have exhibited higher, lower, and no difference relative to pain-free controls (Arendt-Nielsen et al, 1997; Graven-Nielsen, Svensson, et al, 1997; Hodges, 2001; Mista et al, 2016; Svensson et al, 1997; Tucker et al, 2009). The aim of this study was not to determine amplitude differences but to identify whether timing differences occurred between groups, as onset and peak activation could lead to altered motor

control during a functional task. In addition, some authors have identified lower knee flexion and higher knee abduction angles as movement patterns that provoke pain in individuals with PFP (de Oliveira Silva, Briani, Pazzinatto, Ferrari, Aragao, & Azevedo, 2015; Graci & Salsich, 2015; Salsich et al, 2012). In our study, PFP participants reported relatively low pain intensity levels at baseline and after stair descent, so this could have affected some of our non-significant findings. It is unclear whether our muscle function or kinematic results will be generalizable to individuals with higher pain intensity levels.

Body fat percentage, movement, and pain can introduce additional artifact or noise into the EMG signal (Besomi et al, 2019). While we did not exclude participants based on body fat percentage or measure it, we did exclude participants with BMI > 30 from participation (Prior et al, 2014). Any subcutaneous fat over the muscle could provide resistance to surface EMG signals, though, so this is a limitation. Movement artifact can also affect surface EMG signals (Besomi et al, 2020; Besomi et al, 2019). The subjects were not moving during the MVIC in the second study, but they were asked to descend stairs during the third study. Several other authors have identified muscle activation onset and duration during stair descent in participants with PFP so there is precedent for assessing surface EMG during stair-walking on individuals experiencing pain (Aminaka et al, 2011; Boling et al, 2006; Brindle et al, 2003; Cowan et al, 2001; Powers et al, 1997). Lastly, there is disparity in the literature regarding whether pain actually affects surface EMG recordings. Several theories suggest that pain may increase an individual's baseline muscle activity, but others refute this (D. Turk, Melzack, R., 2011). The current CEDE guidelines consider pain a limitation when assessing surface EMG (Besomi et al, 2020)

We did not use fine-wire EMG because our variables of interest were for the whole VM and VL response and not individual motor unit recruitment or firing rate. When drawing

conclusions for surface EMG, we are supposing that increased muscle activation is the result of increased motor unit activity or summation of motor unit activity, however, this is a less direct method of assessment, so it is a limitation of our methods (Besomi et al, 2020). Assessment of motor unit discharge, recruitment, or firing rates may get closer to the idea of a "central" motor system issue as it relates to central sensitization, but these methods are more invasive and we chose to examine the larger muscle activation. Several authors have identified motor unit discharge and firing rates as they relate to PFP which may be useful reading if that variable is of interest in future studies (Gallina, Hunt, Hodges, & Garland, 2018; R. Mellor & P. W. Hodges, 2005).

Knee kinematics and surface EMG were collected during the second step for the test leg while descending the stairs during the third study. When descending the set of five stairs, the test leg would have contacted a stair three total times. During pilot testing, we observed limited flexion and abduction range of motion while moving from the top platform to the first step, and limited range of motion and different mechanics while completing the last step. The second step offered us the largest range of motion (and therefore, the most likely timeframe to observe potential changes in range of motion) and most consistent stepping pattern. Therefore, we confined the timeframe during the stepping task when we would observe knee joint angles and surface EMG to the stance phase of the second step. This led to longer time between the stimulus and peak activation in our study compared to previous studies that used a within-subject temporal marker (e.g. time from foot contact until peak activation, etc.) but it may provide more consistency between-participants (Cowan et al, 2001; Crossley, Cowan, et al, 2004). In addition, some of our participants exhibited peak knee flexion after the end of stance phase while transitioning to the second step, so this more controlled and consistent assessment method may

still be missing important temporal markers within the sample and deserves further investigation.

Time to peak activation was a unique variable. Many studies have examined activation onset and duration of activation, but few have identified time to peak activation in groups with PFP (Brindle et al, 2003; Cavazzuti et al, 2010). We hypothesized that motor control of stair descent could be influenced by activation onset, but could also be influenced by the time it takes the quadriceps (VM and VL) to achieve peak activation. Ideally, peak activation would be achieved prior to peak motion (i.e. joint angles) to offer the best control. We saw evidence of this in the CON group but not in the PFP groups. Since magnitude of peak joint angles were our variables of interest and not temporal assessment of kinematics, we did not further examine this phenomenon. Assessing temporal characteristics of kinematics as they relate to muscle activation timing could offer additional insight into motor control of joint angles.

Lastly, the kinematic assessment itself has several limitations. When the lower extremity is modeled, the segments are assumed to be rigid; however, we know that tissue deformation makes complete rigidity during weightbearing motion impossible (Cappozzo, Catani, Leardini, Benedetti, & Croce, 1996). We also did not assess the kinematic effect on the patellofemoral joint itself, which is the joint experiencing the pain and therefore, a key variable of interest. The kinematic factors selected were hypothesized to mechanically load the patellofemoral joint, thereby increasing nociception but assessing tibiofemoral kinematics does not itself offer insight into patellofemoral kinematics (Powers 2017). The knee is also a linked segment, moving as a lever between the ankle and hip, which were not assessed in this study. Changes in hip, ankle, or foot motion would affect the knee position, and we cannot make assumptions about any of these segments based on the data in this study (Powers et al, 2012). Further assessment of central sensitization as it relates to proximal or distal motor control are warranted.

While our results are promising, we also observed a relatively small, unbalanced sample. Due to campus policy, we also had to impose additional exclusionary criteria to protect potential participants during the COVID-19 pandemic. This led to excluding more potential participants. Future studies including larger sample sizes should continue to consider sex as a grouping variable or only assess a single sex cohort in order to ensure the trustworthiness of the results and to align with current consensus (Greenspan et al, 2007). We also grouped our central sensitization after all data had been collected. This allowed a semi-blinding to occur, as we did not know until all results were completed which PFP participants would be included in the CS or NS groups (but we were aware of their PFP status). This post-hoc grouping plan made it difficult to obtain an equal sample size. Future studies should consider other analytic methods of grouping based on central sensitization status. The results of this study would indicate that grouping based on CPM-responders versus non-responders may not be an effective strategy for females with PFP.

5.5. Conclusions

The results of this study support delayed time to VM and VL peak activation in females with centrally-sensitized PFP compared to pain-free females but not kinematic or activation onset differences. These results indicate that central sensitization may affect more than just pain intensity or duration. Clinicians should consider that enhanced pain facilitation and impaired inhibition could lead to altered peak quadriceps activation during stair descent. Restoration of effective pain modulation has been demonstrated (Holden et al, 2020; Holden et al, 2018; M. S. Rathleff, Roos, et al, 2016), but rehabilitation strategies that go beyond lower extremity factors and seek to restore pain modulation may be necessary in order to see long-term success.

Chapter VI

Conclusions

6.1. Introduction

The aims of this study were to determine whether females with PFP demonstrated signs of central sensitization compared to pain-free females, to determine whether muscle function differed based on central sensitization status during a static task, and whether muscle function or kinematics would differ based on central sensitization status during a functional task. We hypothesized that females with PFP would demonstrate altered pain processing compared to the pain-free group. We also hypothesized that muscle function would be altered based on central sensitization status during a static MVIC, and both muscle function and knee kinematics would differ based on central sensitization status during stair walking. Our hypotheses were partially supported. Females with PFP demonstrated signs of central sensitization including enhanced TSP and inefficient CPM response, resulting in dysfunctional pain modulation. The nociceptive element of PFP has been somewhat elusive despite an abundance of research exploring pathomechanical factors. What most of this research neglects is the physiology behind the development of insidious pain onset. When peripheral nociceptors become sensitized, they are activated at subthreshold levels. This indicates that if patellofemoral loading was the initial factor driving nociception that over time it would take incrementally less loading before pain was sensed. When central nociceptive neurons become sensitized, they can activate spontaneously or at subthreshold levels so that when loading occurs, it creates a centrally-driven response. This enhanced pain facilitation along with the impaired descending central pain inhibition leads to a net product of pain. If effective pain facilitation and inhibition mechanisms are not restored, PFP will persist because the underlying mechanisms has not been affected. PFP recurrence is also

possible, even after a period of rest or reduced loading, because once loading (or other nociceptive activation) would lead to a centralized pain response at earlier and lower thresholds.

Current clinical practice guidelines for PFP management indicate that modalities should not be used in PFP treatment in favor of movement retraining to reduce patellofemoral joint loading and strengthening the core and lower extremity (Willy et al, 2019). The implication of this suggestion is that altered biomechanics and muscle function are the "underlying cause" of PFP, as outlined in the pathomechanical model. The results of this study indicate that central sensitization of the pain system may be an additional underlying factor that may not allow for complete recovery (i.e. high recurrence or persistence). Moreover, effective pain modulation can be restored, but it may require a rehabilitation strategy aimed at central somatosensory function and not simply biomechanical factors. Exercise and transcutaneous electrical nerve stimulation (TENS) are two mechanisms that have demonstrated the ability to restore efficient central pain inhibition and effective pain facilitation mechanisms (Chimenti et al, 2018; Hodges, 2011). It is important to note that as we use "exercise" here does not have to be knee-focused exercise, as exercise itself has central effects on the pain system.

Muscle function during a static task did not differ when grouping participants by central sensitization status, but peak activation response times were delayed during a functional task. The implication of these results, in alignment with previous research, is that weight-bearing tasks may elicit different motor strategies and different recruitment of motor units in order to accomplish a functional or dynamic movement. During weight-bearing activities, muscles are not solely responsible for movement through a range of motion but have an added element of joint and postural stability. These results may also indicate that some other factor related to movement may be responsible for the difference in activation strategy, as it is not observed

during a maximal, controlled isometric task. Altered peak activation timing during stair descent may have led to a less controlled stair descent, with the CS demonstrating shorter peak activation response times prior to maximal knee flexion compared to the control group. The NS group also exhibited peak response times that were between the CS and CON groups. While we cannot infer causal mechanisms due to our cross-sectional design, it is an interesting finding that warrants further examination to determine whether muscle function changes are related to changes in the pain system.

Despite altered peak activation during stair walking, activation onset did not differ by central sensitization group in response to a stimulus during static or dynamic tasks. Post-hoc analysis demonstrated slower SRT for all participants during the stair task as opposed to the MVIC task. This indicates longer sensory processing times prior to muscle activation during the task. This could be the result of attending to other movement factors such as postural control, or accurately contacting the first step. It could also be the result of the additional timing constraint (96bpm) imposed during the task that altered typical movement patterns. During the MVIC, these additional movement elements were not required so the participant was only asked to attend to the auditory cue and producing a maximal contraction. The increased complexity of the stair ambulation task could change their perception of task demands which could affect stimulus response time, pain intensity, or perceptions of pain self-efficacy that could be task-specific.

Peak knee flexion and abduction angles did not differ based on central sensitization during a stair walking task. Increased knee abduction has been associated with higher pain intensity levels during movement tasks, while reduced knee flexion is considered a compensation to avoid increased patellofemoral joint loading. Though neither of these angles were different across groups, we did observe that the VM and VL were activated earlier in the CON group

while the CS group activated both VM And VL just prior to the moment of maximum knee flexion This could indicate less control of the motion, or even less perceived control of the motion.

Overall, these results indicate that females with PFP do exhibit signs of central sensitization and that, when grouped based on central sensitization status, peak quadriceps activation is delayed during a weight-bearing, functional task (stair descent). Clinicians and researchers should be aware of central sensitization as a mechanism with the potential to affecting pain onset, persistence, recurrence, and on movement outcomes in females with PFP.

6.2. Impact on Clinicians

Quantitative sensory testing can help clinicians identify dysfunctional pain modulation in the nervous system (Arendt-Nielsen, Morlion, et al, 2018). Clinical assessment methods are available to clinicians but training and education are required to understand these methods and their clinical use. Clinicians need to understand different types of pain (i.e. nociceptive, neuropathic, nociplastic), and how treatment strategies differ between and within each of these. Clinicians also need a foundation of understanding central and peripheral sensitization of pain, as these are implicated in most persistent musculoskeletal pain conditions, or as subgroups of patients with these conditions. Understanding the nervous system response and how to restore effective pain modulation is a step toward offering more efficient and successful treatment (Chimenti et al, 2018; M. S. Rathleff, Petersen, et al, 2016; Sluka, 2016).

Current treatment strategies suggested in the PFP Clinical Practice Guidelines (Willy et al, 2019) include movement retraining, strengthening the core, hips, and thighs of patients with PFP. This excludes a range of treatment methods that could be successful in subgroups with

central sensitization such as biofeedback, manual therapies, transcutaneous electrical nerve stimulation, treatments aimed at restoring somatosensory function, and pain education (Willy et al, 2019). This does not suggest that all of these treatments will be successful in patients with PFP, but they further investigation as they related to subgroups with centrally sensitized nervous systems.

Individual assessment of patient-reported outcomes and quantitative sensory testing is essential. Relationships between negative psychosocial factors (e.g. pain catastrophizing) and quantitative sensory testing have been documented. We also observed significant differences in perceived knee function, pain intensity, pain catastrophizing, fear-avoidance beliefs, and low pain self-efficacy between CS, NS, and CON groups. Though we cannot determine causality from our study design, this indicates potential relationships between these psychosocial factors and central sensitization that should be explored further.

Pain inhibition and facilitation mechanisms can be restored, and restoration of these factors has been identified as a sign of self-reported recovery in females with PFP (Holden et al, 2020; Holden et al, 2018; M. S. Rathleff, Roos, et al, 2016). If negative pain responses and/or coping strategies are observed, referral to a healthcare professional trained in cognitive-psychosocial strategies should be coordinated so the patient received consistent messaging regarding pain, coping with pain or dysfunction, and perceived causes of pain. Patient perspectives regarding the negative impact of nocebic language use by clinicians has been reported in chronic musculoskeletal pain, and echoed during interviews with PFP patients (Rossettini, Carlino, & Testa, 2018; Smith, Moffatt, et al, 2018; Smith et al, 2019).

Clinicians should consider evaluating quantitative sensory testing in females with PFP, especially TSP and CPM response. Clinical assessment only requires a pressure algometer for

PPTs, which vary in price and amount of training; standard nylon monofilaments for TSP assessment; and an ice bath or second noxious stimulus for CPM. Clinicians need to consider the potential effect of central sensitization on peak muscle function, particularly during functional tasks. Due to the multifactorial nature of all of the included variables, clinicians should consider a patient-centered approach to PFP that incorporates assessing and restoring pain modulation mechanisms as well as muscle function during functional tasks.

6.3. Impact on PFP Research

Females with PFP exhibited impaired CPM response and facilitated TSP response relative to the pain-free group. This indicates that females with PFP demonstrate signs of central sensitization. Specifically, inefficient descending central pain inhibition and enhanced central pain facilitation responses were observed, but neither local or widespread pain hypersensitivity were observed. If females with PFP experience facilitated pain signals and impaired pain inhibition, the net effect could be increased or persistent pain. Current models of PFP etiology do not account for central sensitization as a means of producing insidious nociceptive signaling or by inducing a central response to noxious stimulation. If indeed the pathomechanical model is correct in identifying elevated patellofemoral joint loading as a nociceptive factor, it is possible that repetitive or prolonged patellofemoral joint loading could create a central-mediated pain response. This centrally-mediated pain response may be more resistive to traditional treatment and rehabilitation efforts, as they are not typically designed restore central pain modulation. Pain mechanism-based approached to rehabilitation exist and have gained appreciation in other chronic musculoskeletal pain conditions, so it may be time to begin exploring these in individuals with PFP. We concur with authors who suggest that the pain in PFP is a combination

of nociceptive and nociplastic characteristics (Maclachlan et al, 2020). This impression is common in other chronic musculoskeletal pain conditions (Arendt-Nielsen, Morlion, et al, 2018; Correa, Costa, de Oliveira, Sluka, & Liebano, 2015; Osgood et al, 2015; Staud, 2012). It may be appropriate to compare central and peripheral pain characteristics across conditions to develop pathological and etiological models that are broader than individual diagnoses.

During a stair descent task, later VM and VL peak activation was observed in females with centrally sensitized PFP compared to the pain-free group with no subsequent differences in peak knee joint angles. Later peak quadriceps activation could indicate reduced motor control during the stair descent. While this altered activation was not observed in conjunction with altered knee kinematics, they could relate to group differences in negative psychosocial variables in the CS group. Further exploration of these associations is needed before conclusions can be reached. Altered quadriceps muscle function was only observed during the functional task, which could indicate that either the dysfunction only occurs during more complex movement patterns, or that other factors involved in the stair descent task play a role in later peak activation.

Females with centrally sensitized PFP did not demonstrate quadriceps muscle function differences compared to those with fewer signs of sensitization or pain-free females during quadriceps MVIC. Neither onset time nor peak VM-to-VL activation were altered based on central sensitization. When compared with the other findings of the study, this may indicate that central sensitization status may affect muscle function during weightbearing functional tasks but not during static or open kinetic chain tasks.

Researchers should continue to explore these biopsychosocial factors by assessing relationships between neuromuscular control, lower extremity kinematics, central and peripheral sensitization, and psychosocial variables. Additional knowledge of these relationships can

continue to impact understanding the etiology of PFP onset and pain persistence, and inform new rehabilitation models. Furthermore, we echo the sentiments of de Oliveira Silva et al (2016) who called for pathomechanical models to consider factors beyond of lower extremity (i.e. proximal, distal, and local) biomechanical variables.

6.4. Future Research

In the protective response model, a range of potential sensorimotor adaptations to persistent pain or threat of pain are presented (Figure 2), many of which have been observed in individuals with PFP. Hodges and Smeets (2015) also included twelve potential motor behavior adaptations observed in individuals experiencing persistent pain ranging from changes in muscle coordination to avoiding functional activities. Many of these behaviors have been observed in PFP and are included in the pathomechanical model [Figure 1; (Powers et al, 2017)]. Fitting the pathomechanical model of PFP into the larger framework of the protective response model may be useful in identifying nociceptive responses, as well as motor and biomechanical adaptations to peripheral or central sensitization. An example of this is identified in Figure 15, but a number of unknowns still exist to fit the models together.

First, we could not identify any studies where hamstring-quadriceps co-activation were assessed in individuals with PFP. In other knee conditions, the antagonist-agonist relationship is foundational. In PFP patients, however, the VM-to-VL and gluteal muscle relationships have been assessed more frequently. The agonist-antagonist relationship would provide information that could allow us to understand motor behavior around the tibiofemoral joint, which could help us better understand PFJ kinematics. When hamstring-quadriceps co-activation occurs, the knee typically has reduced total range of motion, especially in tasks with fewer constraints (i.e. single-

leg squatting, etc.). This could allow researchers to better identify preferred motor behavior patterns that could lead to a short-term protective response or long-term consequences, if they can be related to altered kinematics or kinetics.

Sitting is another common motion in which PFP is commonly reproduced, but the biomechanical rationale is not well understood (Collins et al, 2016). Some authors have suggested that individuals with sitting pain may have other distinguishing features that indicate greater severity of the condition (Collins et al, 2013). What makes sitting pain so difficult to understand is that the patella should be compressed within the trochlear groove during sitting (i.e. flexion) so there would be less patellar mobility during sitting. Powers et al (Powers, 2000b) suggests that sitting pain could be related to higher compressive force within the PFJ, or that deformation of the retropatellar cartilage may induce nociception. However, consider that insidious pain at rest could be due to spontaneous or subthreshold activation of (central or peripheral) nociceptive neurons due to a centrally sensitized nervous system and central sensitization might help demystify sitting pain in PFP (Latremoliere & Woolf, 2009; Woolf, 2011).

The hip and ankle control may even be more important to understanding biomechanical outcomes at the knee. It has been suggested that females with PFP exhibit gluteal muscle inhibition (medius and maximus) which may be related to central sensitization status, however, to our knowledge this theory has yet to be tested (Glaviano, Bazett-Jones, & Norte, 2019). A study set up in a similar manner assessing gluteal activation timing may provide further insight during functional tasks, as the gluteal muscles provide postural control in addition to advancement of the leg during gait (Boling et al, 2006). The foot and ankle are additionally responsible for transmitting ground reaction forces up the kinetic chain, and some authors have

argued that placement and motor control of the foot may related to tibiofemoral mechanics, which can therefore alter PFJ kinematics (Powers, Chen, Reischl, & Perry, 2002). Identification of the muscles and joint affected during typically painful tasks would improve both pathomechanical and protective response models as they relate to individuals with PFP.

Furthermore, authors of the pathomechanical theory introduce several kinematic and kinetic factors in which sex differences may exist, including the idea of elevated PFJ loading itself (Powers et al, 2017). We also know that sex differences in quantitative sensory testing are widely observed. Therefore, when assessing relationships between central sensitization, motor function, and altered kinematics, it may be imperative to consider sex of the participant (or group) in the analysis. Thus far, many authors assessing quantitative sensory tests in PFP patients have examined females and males in the same analysis or have examined females without the presence of males, but no direct sex comparisons have been observed (Sigmund et al, 2020). Additionally, several biomechanical studies have accounted for potential sex differences, but this has led to fewer assessments of males with PFP and when males are included, sex is not typically accounted for in the statistical analysis (Glaviano & Saliba, 2018; Noehren et al, 2016; Scholtes & Salsich, 2020). It is possible that males and females just have different overall PFP experiences that need to be accounted for, but studies comparing biomechanical and neuromuscular outcomes on the basis of sex differences in PFP are lacking and should be further examined.

Integration of the pathomechanical model into the protective response framework may provide an opportunity to better understand how central sensitization, neuromuscular, biomechanical, and psychosocial variables come together. Though more information is needed on the interactions between these factors, an example of this framework is provided in Figure 17.

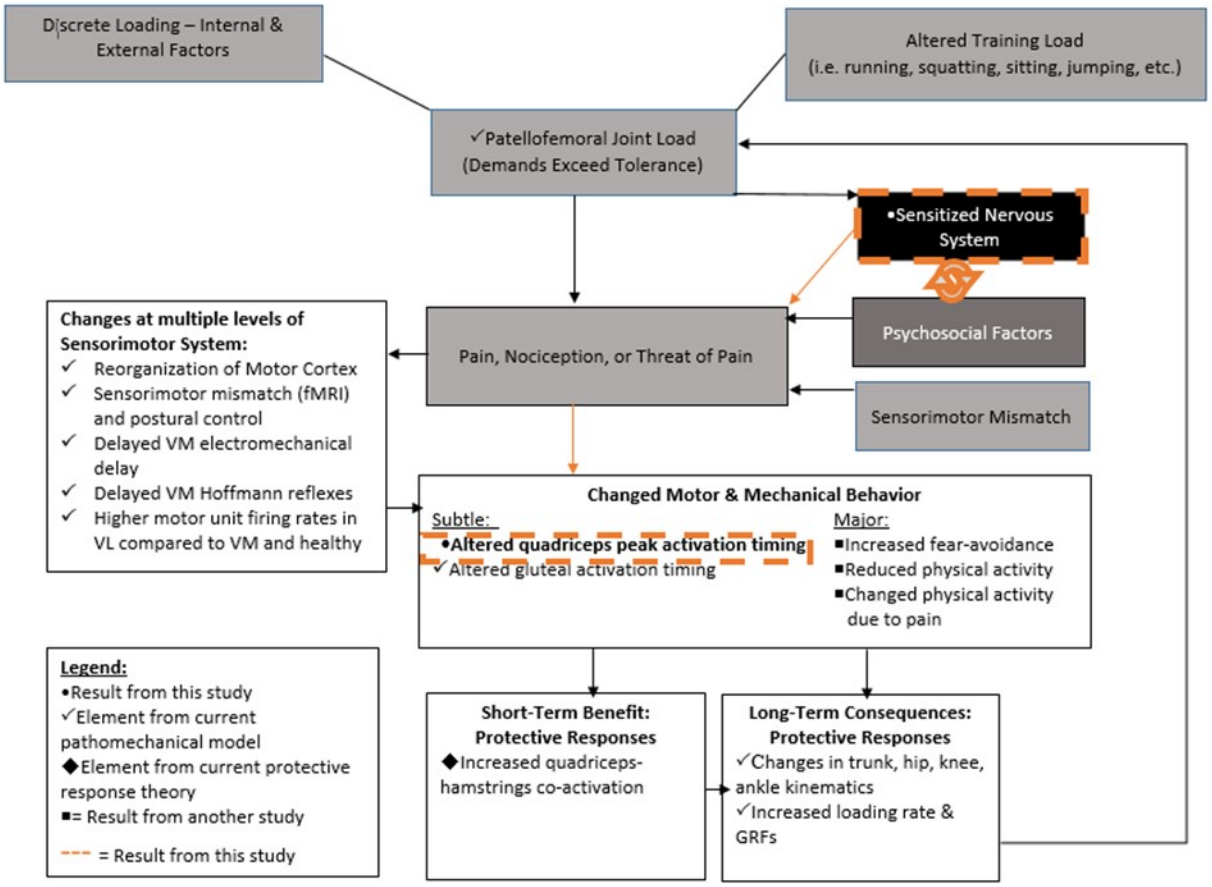


Figure 17: Protective response framework for PFP. Includes elements from the protective response theory, pathomechanical theory, this study, and other research that relate to factors that have been explored compared to the original protective response theory (Esculier, Maggs, Maggs, & Dubois, 2020; Glaviano, Baellow, & Saliba, 2017; Hodges & Smeets, 2015; Powers, Witvrouw, Davis, & Crossley, 2017)

6.5. Conclusion

Females with PFP demonstrated signs of central sensitization including enhanced TSP and inefficient CPM response. Muscle function during a static task did not differ based on central sensitization status, but peak activation response times were delayed during a functional task. Activation onset response to a stimulus did not differ based on central sensitization during a stair walking task. Intramuscular differences presented as part of the protective response model were only partially supported, with delayed VM and VL peak activation in the CS group during a functional task but not during an MVIC. Likewise, no group differences in kinematics were

observed in this study. The variables included are only a small portion of the potential variables that could be affected, and further exploration is warranted to determine the nature of the relationships between central sensitization, neuromuscular function, and biomechanical variables.

It is imperative to better understand adaptive responses to pain within the nervous system and to further explore neuromuscular and kinematic outcomes as they relate to these changes. As we better understand altered central pain modulation, it is critical to explore pain relief options that promote restoration of central pain modulation. Clinicians should be educated on current pain assessment and pain modulation restoration models, and researchers should continue to consider central sensitization as (at least) a subgroup of PFP when exploring neuromuscular and biomechanical factors.

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APPENDICES

Appendix A: Screening Form

SCREENING FORM

Hello. The purpose of this phone call is to determine whether you meet the inclusion criteria for our study. Please answer each question honestly. If you have trouble understanding any of the questions or with the English language, please let me know.

PARTICIPANT ID _____AGE: _____ DATE: _____

EXCLUSION CRITERIA:

Do you have any neurological conditions affecting sensation (i.e. diabetic neuropathy, etc.)?	Y	N
Do you have any conditions or reactions to the cold (e.g. cold allergy, Reynaud's, etc.)	Y	N
Do you have any chronic pain conditions (i.e. arthritis, low back pain, fibromyalgia, etc)?	Y	N
Do you know or have you ever been diagnosed with high blood pressure?	Y	N
Have you experienced injury to the lower body (other than your knee pain) or back in the past 6 months?	Y	N
Have you ever dislocated or subluxed your kneecap?	Y	N
Have you ever had knee surgery?	Y	N
Do you have any implanted metal?	Y	N
Are you currently experiencing any pain (other than your knee) to your lower extremity, back, or hand?	Y	N
Are you currently pregnant?	Y	N

SCREENING:

ARE YOU CURRENTY EXPERIENCING ANY PAIN IN EITHER KNEE?

YES NO

IF **YES**, <u>CONSIDER FOR PFP GROUP</u> BY ANSWERING THE FOLLOWING:

Did a traumatic injury cause the pain in your knee?	Y	N
Have you ever injured the ligaments, meniscus, or cartilage in your knee?	Y	N
Have you ever been diagnosed with Osgood-Schlatter's or Sinding-Larson-Johansson syndrome?	Y	N
Do you have pain with any of the following?		
-Squatting or kneeling?	Y	N
-Walking up or down stairs (or both)?	Y	N
-Sitting for long periods of time?	Y	N
-During or after physical activity (running, jumping)	Y	N
Do you have pain in one or both knees?	One	Both
Which knee is (most) painful?	R	L

HOW LONG HAVE YOU HAD THIS PAIN IN YOUR KNEE? _____WEEKS MONTHS YEARS

Based on these criteria, you are / are not eligible for a free knee examination to determine whether you qualify for this study. If eligible: We would like to schedule this examination, and, if you are eligible, we can conduct testing on the same day. Testing takes approximately 2 hours and we would ask that you wear loose-fitting shorts. If you do not own shorts, we can provide shorts in the lab. You will also be provided sneakers for testing once you arrive to the lab. We ask that on the day of the examination and testing, you take part in your normal daily routine including sleep, nutrition, and caffeine intake. However, we would ask you to refrain from taking any pain medication or anti-inflammatories for 24 hours prior to the exam and testing day, and that you refrain from any therapeutic intervention such as rehabilitation exercises, ice, heat, etc. If you have recently changed any prescription medications, we will delay testing until you have been on these medications for at least 2 weeks with no changes. This will ensure that our examination and testing information collected are accurate.

Appendix B: Virtual Examination Form

PHYSICAL EXAMINATION FORM

PARTICIPANT ID: _____ DATE: _____

KNEE EXAMINATION

Now, we are going to go through a virtual knee examination. For this, I will ask you to point to or poke specific parts of your knee to see if they are painful, and at the end, I will ask you to go through a few movements to see whether they reproduce your pain. Do you have any questions before we get started?

DATE: _____

Have you taken any pain medications in the past 24 hours?		Y	N
If yes, were these for your knee pain?	N/A	Y	N

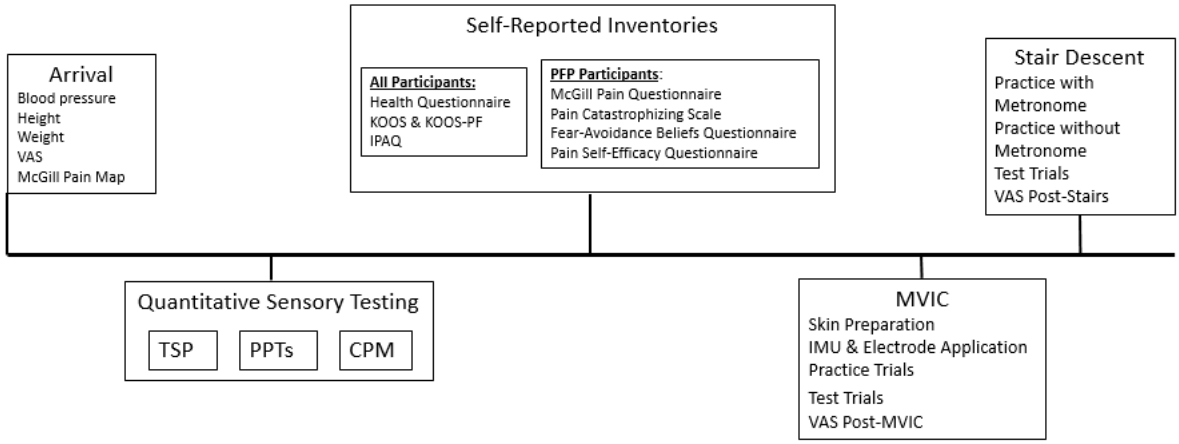
EXAMINATION FINDINGS:

PAIN IN PERIPATELLAR OR RETROPATELLAR AREA?	Y	N
PAIN WITH PALPATION OF PATELLAR FACETS?	Y	N
PAIN WITH PALPATION OF THE IT BAND OR GERDY'S TUBERCLE?	Y	N
PAIN OVER JOINT LINE?	Y	N
EVIDENCE OF OSGOOD-SCHLATTER'S OR SINDING-LARSON-JOHANNSON?	Y	N
PAIN WITH PALPATION OF IT BAND?	Y	N
PAIN WITH PALPATION OF PATELLAR TENDON?	Y	N
PAIN WITH PALPATION OF PES ANSERINE?	Y	N
PAIN WITH SINGLE-LEG SQUATTING?	Y	N
PAIN WITH DOUBLE LEG SQUATTING?	Y	N

Results: **Included** **Excluded**

Based on the results of this examination, you are **able / not able** to be included in the study. If you are interested, the study takes place in 2 parts that can occur on the same day. Part 1 involves sensory testing and questionnaires, and Part 2 involves movement testing. Are you still interested in participating? Yes / No If yes, we will schedule a time to complete testing. The total time of the study is about 65 minutes. The total time you would be in close contact (within 6 feet) with a researcher would be less than 15 minutes of that total timeframe. We would ask you to wear running shorts. There is a locker room available in the lab for you to change if needed. Sneakers will be provided to you when you arrive. We do ask that you refrain from taking medications for your knee pain for 24 hours prior to your arrival at the lab. If you are unable to do that, please let us know when you arrive that you have taken medication for your knee pain so we can record it. Do you have any other questions at this time?

Appendix C: Complete Dissertation Protocol Timeline



Appendix D: Visual Analog Scales

Visual Analog Scale- Current Pain

Place a vertical line on the line below, indicating the level of your current pain

No pain _____ Worst Pain Imaginable

Walking Down Stairs Pain

Place a vertical line on the line below, indicating the worst pain you experience walking down stairs.

No pain _____ Worst Pain Imaginable

Appendix E: Qualtrics Questionnaires for Control Group

(In order: Health Form, KOOS, KOOS-PF, IPAQ)

Health Questionnaire Instructions.

Many things, including daily activities and habits such as sleep, nutrition, stress, menstrual cucle, medications, and history of depression and/or anxiety can affect pain levels. The objective of this form is to collect information to help us control for these habits. Please provide accurate reposnses on this questionnaire.

Please check all the boxes that correspond with medications or drugs you are currently taking that are related to your knee pain:

- ☐ Anti-inflammatories (i.e. Ibuprofen, Advil, Aleve, etc.)
- ☐ Over-the-counter pain relievers (i.e. Acetaminophen,Tylenol, etc.)
- ☐ Pain-relieving topical ointments, gels, or creams
- ☐ Prescription pain relievers or corticosteroids (e.g. Codeine, Fentanyl, Hydrocodone, Vicodin, Norco, etc.)
- ☐ Other/Not Listed (please describe in the box below):
- ☐ I am not currently taking any medications related to my knee pain.

Can you describe any evaluation and/or treatment that has been provided for your knee pain by checking any/all corresponding boxes below, or providing your own response in the "Other" box? **(Select all that apply)**

- [ ] I have been evaluated by a healthcare professional for my knee pain.
- [ ] I am currently receiving treatment or participating in rehabilitation for my knee pain.
- [ ] I have previously received treatment or have participated in rehabilitation for my knee pain.
- [ ] I have not received treatment or participated in rehabilitation for my knee pain.
- [ ] I tried treatment or rehabilitation for my knee pain but it was not successful.
- [ ] Other (please describe in the box below):

←

→

Do you have previous experience with ice water immersion (i.e. cold whirlool therapy, ice baths, polar plunges, or slush buckets)? NOTE: This does NOT need to be related to treatment for your knee pain.

- Yes
- No

← →

If you awswered that you have previous experience with ice water immersion, how frequently have you used this method (choose one option below):

- Daily
- Weekly
- Monthly
- Yearly
- Once in a while
- Less than 3 times (total)

Stress

On the following line, please indicate the level of stress you currently feel where the left end of the line represents no stress and the right end of the line represents the worst imaginable stress.

No Stress Worst Imaginable Stress

Current Stress

Done

Have you ever been diagnosed with depression?

- Yes
- No

Have you ever been diagnosed with anxiety?

- Yes
- No

Are you currently taking medications related to either depression and/or anxiety?

Yes

No

Done

This question only generates when 1 of the 2 previous questions are answered YES.

What day of your menstrual cycle are you currently on (Day 1= the Day after your last period ended).

←

→

Please **STOP** and let the researcher know that you are starting the **KOOS forms**. The researcher will provide instructions and will be here to answer any questions that you have.

This survey asks for **your view about your knee**. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities. Please answer every question by checking the appropriate box and **you may only select ONE option for each question**. If you are unsure how to answer a question, please give the best answer you can or ask the researcher a question.

Answer these questions thinking of your knee symptoms during the **LAST WEEK**.

1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
○	○	○	○	○

2. Do you feel grinding, hear clicking, or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
○	○	○	○	○

3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
○	○	○	○	○

4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
○	○	○	○	○

5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
○	○	○	○	○

Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

6. How severe is your knee stiffness after first waking in the morning?

None	Mild	Moderate	Severe	Extreme
○	○	○	○	○

Done

7. How severe is your knee joint stiffness after sitting, lying, or resting later in the day?

None	Mild	Moderate	Severe	Extreme
○	○	○	○	○

1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
○	○	○	○	○

What amount of pain have you experienced in the **LAST WEEK** during the following activities:

	None	Mild	Moderate	Severe	Extreme
Twisting/Pivoting on your knee	○	○	○	○	○
Straightening knee fully	○	○	○	○	○
Bending the knee fully	○	○	○	○	○
Walking on a flat surface	○	○	○	○	○
Going up or down stairs	○	○	○	○	○
At night while in bed	○	○	○	○	○
Sitting or lying	○	○	○	○	○
Standing upright	○	○	○	○	○

This section describes your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experiences in the LAST WEEK due to your knee.

	None	Mild	Moderate	Severe	Extreme
Descending Stairs	○	○	○	○	○
Ascending Stairs	○	○	○	○	○
Rising from Sitting	○	○	○	○	○
Standing	○	○	○	○	○
Bending to the floor/pick up an object	○	○	○	○	○
Walking on a flat surface	○	○	○	○	○
Getting in/out of your car	○	○	○	○	○
Going shopping	○	○	○	○	○
Putting on socks/ stockings	○	○	○	○	○
Rising from bed	○	○	○	○	○
Taking off socks/ stockings	○	○	○	○	○
Lying in bed (turning over, maintaining knee position)	○	○	○	○	○
Getting in/out of bath	○	○	○	○	○
Sitting	○	○	○	○	○
Getting on/ off toilet	○	○	○	○	○
Heavy domestic duties (moving heavy boxes, scrubbing floors, etc.)	○	○	○	○	○
Light domestic duties (cooking, dusting, etc.)	○	○	○	○	○

This section describes your ability to be active on a higher level. For each of the following activities, please indicate the degree of difficulty you have experienced in the **LAST WEEK** due to your knee.

	None	Mild	Moderate	Severe	Extreme
Squatting	○	○	○	○	○
Running	○	○	○	○	○
Jumping	○	○	○	○	○
Twisting/pivoting on your injured knee	○	○	○	○	○
Kneeling	○	○	○	○	○

1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
○	○	○	○	○

2. Have you modified your life style to avoid activities potentially damaging to your knee?

Not at all	Mildly	Moderately	Severely	Totally
○	○	○	○	○

3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
○	○	○	○	○

Patellofemoral Subscale

What amount of knee pain have you experienced in the **LAST WEEK** during the following activities? Please give the **best** answer you can, even if you are unsure about an item.

If you haven't done this activity because of medical advice or pain, please check Extreme.

	None	Mild	Moderate	Severe	Extreme
Rising from sitting (including getting out of the car)	○	○	○	○	○
Kneeling	○	○	○	○	○
Squatting	○	○	○	○	○
Heavy household activities (including carrying and lifting)	○	○	○	○	○
Hopping/ jumping	○	○	○	○	○
Running/ jogging	○	○	○	○	○
After sport and recreational activities	○	○	○	○	○

Done

Patellofemoral Subscale

The following question concerns your quality of life over the **PAST WEEK**.

1. Have you modified your sport or recreational activities due to your knee pain?

Not at all	Mildly	Moderately	Severely	Totally
○	○	○	○	○

← →

4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
○	○	○	○	○

Patellofemoral Subscale

The following question concerns the amount of joint stiffness you have experienced during the **LAST WEEK** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

1. How severe is your knee stiffness after exercise?

None	Mild	Moderate	Severe	Extreme
○	○	○	○	○

Patellofemoral Subscale

2. How often do you experience knee pain after stopping activity?

Never	Monthly	Weekly	Daily	Always
○	○	○	○	○

Patellofemoral Subscale Pain

3. How often does pain limit your activity?

Never	Monthly	Weekly	Daily	Always
○	○	○	○	○

STOP. Tell the researcher that you are starting the **IPAQ.** The researcher will provide you with instructions.

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **LAST 7 DAYS**. Please answer each question even if you do not consider yourself to be an active person.

Please think about the ativites you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise, or sport.

Think about all the **vigorous** and **moderate** activities you did in the **LAST 7 DAYS**.

- **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.
- **Moderate** activities refer to activities that take moderate effort and make you breathe somewhat harder than normal.

Job-Related Physical Activity

This first section is about your work. It includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

Job-Related Physical Activity

1. Do you currently have a job or do unpaid work outside your home?

- Yes ○
- No ○

The next questions are all about the physical activity you did in the **LAST 7 DAYS** as part of your paid or unpaid work. This does not include travling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs as part of your work?
Think about only those physical activities that you did for at least **10 minutes at a time**.

- About ___ days per week (place answer in the box provided) ○
- [ ]
- No vigorous job-related physical activity ○

4. Again, think about only those physical activities that you did for at least **10 minutes** at a time. During the **LAST 7 DAYS,** on how many days did you do **moderate** physical activiites like carrying light loads **as part of your work**? Please do not include walking.

- ___ days per week (enter answer in the box provided) ○
- [ ]
- No moderate physical activity ○

6. During the **LAST 7 DAYS**, on how many days did you **walk** for at least **10 minutes** at a time as part of your work? Please do not count walking that you did to travel to or from work.

___ days per week (enter answer in box provided ○

No job-related walking ○

7. How much time did you usually spend walking as part of your work?

___ hours per day (enter answer in the box provided)

___ minutes per day (enter answer in the box provided)

PART 2: Transportation Physical Activity

These questions are about how your traveled from place to place, including to places like work, stores, movies, and so on.

Transportation

8. During the LAST 7 DAYS, on how many days did you travel in a motor vehicle like a train, bus, car, or tram?

- ___days per week (enter answer in the box provided) ○
- [ ]
- No traveling in a motor vehicle. ○

Now, think about the **bicycling and walking** you have done to travel to and from work, to do errands, or to go from place to place.

10. During the **LAST 7 DAYS**, on how many days did you **bicycle** for at least **10 minutes** at a time to go from place to place?

- ___days per week (enter answer in the box provided) ○
- [ ]
- No bicycling from place to place. ○

13. How much time did you usually spend on one of those days walking from place to place?

___hours per day (enter answer in the box provided)

___minutes per day (enter answer in the box provided)

Done

Part 3: Housework, House Maintenance, and Caring for Family

This section is about some of the physical activities you might have done in the last 7 days in and around your home, like housework, yard work, general maintenaince work, and caring for your family.

14. Think about only the activities that you did for at least **10 minutes** at a time. During the **LAST 7 DAYS**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

___ days per week

No vigorous activity in the garden or yard

15. How much time did you usually spend on one of those days doing vigorous physical activities in the garden or yard?

___ hours per day

___ minutes per day

16. Again, think about only those physical activities that you did for at least **10 minutes** at a time. During the **LAST 7 DAYS,** on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

___ days per week

No moderate activity in the garden or yard.

18. Once again, think about only those physical activities that you did for at least **10 minutes** at a time. During the **LAST 7 DAYS**, on how many days did you do **moderate** physical activities like carying light loads, washing windows, scrubbing floors, and sweeping **inside your home**?

___ days per week (enter answer in the box provided)	○
No moderate activity inside the home.	○

19. How much time did you usually spend on one of those days doing moderate physical activities inside your home?

___hours per day

___minutes per day

Part 4: Recreation, Sport, and Leisure-Time Physical Activity

This section is about all the physical activiites that you did in the LAST 7 DAYS solely for recreation, sport, exercise, or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **LAST 7 DAYS**, on how many days did you **walk** for at least **10 minutes** at a time in your **leisure time**?

___days per week (enter answer in the box provided)

No walking in leisure time

22. Think about only those physical activities that you did for at least **10 minutes** at a time. During the **LAST 7 DAYS,** on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

__ days per week (enter answer in the box provided) ○

No vigorous activity in leisure time ○

23. How much time did you usually spend on one of those days doing vigorous physical activities in your leisure time?

___ hours per day

___ minutes per day

24. Again, think about only those physical activities that you did for at least **10 minutes** at a time. During the **LAST 7 DAYS**, on how many days did you do **moderate** physical activiites like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

___ days per week (enter answer in the box provided) ○

No moderate activity in leisure time ○

Part 5: Time Spent Sitting

The last questions are about the time your spend sitting while at work, at home, while doing coursework, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

___ hours per day

___ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

___ hours per day

___ minutes per day

Appendix F: Qualtrics Questionnaires for PFP Participants

(McGill Pain Questionnaire, PSEQ, PCS, and FABQ)

Please **STOP** and inform the researcher that you are now at the **McGill Pain Questionnaire**.

The researcher will provide you with instructions on completion of this portion of the questionnaire:

1. For each question, please **select the ONE word** that best describe your pain. Click "None of these" if none of the words in that question describe your pain. One box must be selected for each question, even if it is the "None of these" box.
2. For the Present Pain Inventory question, please indicate your current pain intensity at this moment.
3. In the Temporal Pain Characteristics questions, please indidicate which of the words best describes how your pain changes over time.
4. You may provide additional comments in the comments box but this is not required, nor will they be "scored" in any way. Your responses may be used for a qualitative analysis, if appropriate or unique to your experience but these responses will be anonymous (i.e. no identifying characteristics will accompany the quote).

If you have any questions after these instructions are read, please ask them at any time.

Pain Subscale 1: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Flickering ○
- Quivering ○
- Pulsing ○
- Throbbing ○
- Beating ○
- Pounding ○
- None of these ○

Pain Subscale 2: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Jumping
- Flashing
- Shooting
- None of these

Pain Subscale 3: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Pricking
- Boring
- Drilling
- Stabbing
- Lancinating
- None of these

Done

Pain Subscale 4: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Sharp
- Cutting
- Lacerating
- None of these

Pain Subscale 4: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Sharp ○
- Cutting ○
- Lacerating ○
- None of these ○

Pain Subscale 5: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Pinching ○
- Pressing ○
- Gnawing ○
- Cramping ○
- Crushing ○
- None of these ○

Pain Subscale 6: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Tugging ○
- Pulling ○
- Wrenching ○
- None of these ○

Pain Subscale 7: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Hot ○
- Burning ○
- Scalding ○
- Searing ○
- None of these ○

Pain Subscale 8: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Tingling ○
- Itchy ○
- Smarting ○
- Stinging ○
- None of these ○

Pain Subscale 9: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Dull ○
- Sore ○
- Hurting ○
- Aching ○
- Heavy ○
- None of these ○

Pain Subscale 9: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Dull
- Sore
- Hurting
- Aching
- Heavy
- None of these

Pain Subscale 10: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Tender
- Taut
- Rasping
- Splitting
- None of these

Pain Subscale 10: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Tender ○
- Taut ○
- Rasping ○
- Splitting ○
- None of these ○

Pain Subscale 11: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "Neither of these"

- Tiring ○
- Exhausting ○
- Neither of these ○

Pain Subscale 12: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "Neither of these"

- Sickening ○
- Suffocating ○
- Neither of these ○

Pain Subscale 13: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Fearful ○
- Frightful ○
- Terrifying ○
- None of these ○

Pain Subscale 14: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Punishing ○
- Gruelling ○
- Cruel ○
- Vicious ○
- Killing ○
- None of these ○

Pain Subscale 15: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "Neither of these"

- Wretched ○
- Blinding ○
- Neither of these ○

Done

Pain Subscale 16: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Annoying ○
- Troublesome ○
- Miserable ○
- Instense ○
- Unbearable ○
- None of these ○

Pain Subscale 17: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Spreading ○
- Radiating ○
- Penetrating ○
- Piercing ○
- None of these ○

Pain Subscale 18: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Tight ○
- Numb ○
- Drawing ○
- Squeezing ○
- Tearing ○
- None of these ○

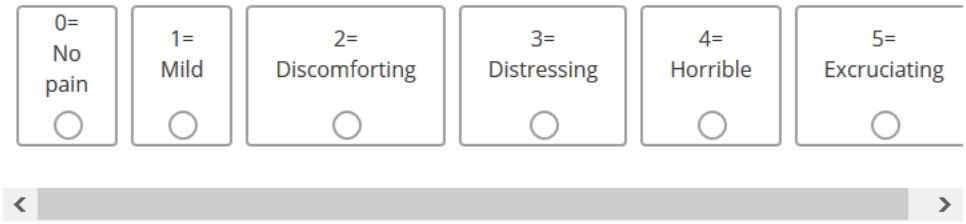
Pain Subscale 19: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

- Cool ○
- Cold ○
- Freezing ○
- None of these ○

Pain Subscale 20: Select the description that best describes your pain. If none of the descriptors match your pain experience, please select "None of these"

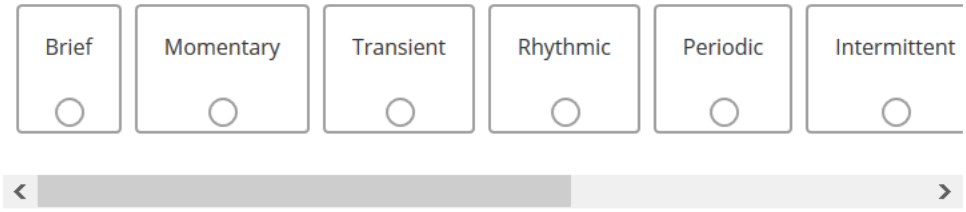
- Nagging ○
- Nauseating ○
- Agonizing ○
- Dreadful ○
- Torturing ○
- None of these ○

Present Pain Intensity: Please select the number that best describes your pain at this moment.

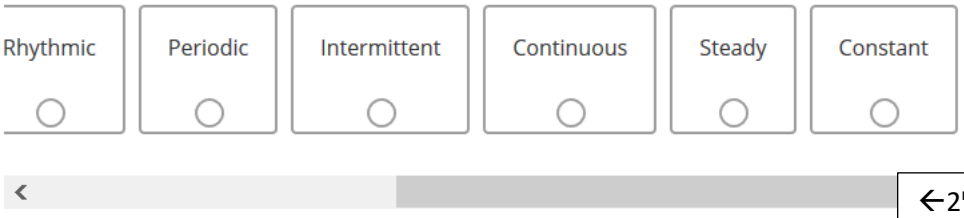


Done

Temporal Pain Characterstics: Select the description that best describes your pain. If none of the descriptors match your pain experience.



Temporal Pain Characterstics: Select the description that best describes your pain. If none of the descriptors match your pain experience.



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STOP.

Tell the researcher that you are starting the **PCS.**

The researcher will give you instructions and will be available if you have any questions during this survey.

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint, or muscle pain. People are often exposure to situations that may cause pain such as illness, injury, dental procedures, or surgery.
We are interested in the types of thoughts and feelings that you have while you are in pain. Listed below are 13 statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.
0=not at all, 1= to a slight degree, 2= to a moderate degree, 3= to a great degree, 4= all the time.

	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 worry all the time about whether the pain will end.	◯	◯	◯	◯	◯
2. I feel I can't go on.	◯	◯	◯	◯	◯
3. Its terrible and I think its never going to get any better.	◯	◯	◯	◯	◯
4. Its awful and I feel that it overwhelms me.	◯	◯	◯	◯	◯
5. I feel I can't stand it anymore.	◯	◯	◯	◯	◯
6. I become afraid that the pain will get worse.	◯	◯	◯	◯	◯
7. I keep thinking of other painful events.	◯	◯	◯	◯	◯
8. I anxiously want the pain to go away.	◯	◯	◯	◯	◯
9. I can't seem to keep it out of my mind.	◯	◯	◯	◯	◯
10. I keep thinking about how much it hurts.	◯	◯	◯	◯	◯
11. I keep thinking about how badly I want the pain to stop.	◯	◯	◯	◯	◯
12. There's nothing I can do to reduce the intensity of the pain.	◯	◯	◯	◯	◯
13. I wonder whether something serious may happen.	◯	◯	◯	◯	◯

STOP.

Tell the researcher you are starting the **PSEQ.** The researcher will provide instructions and will be here to answer questions.
For this questionnaire, we are interested in learning more about how confident you are when dealing with painful situations. Please rank the level of confidence you have relating to each of the statements.

	0- Not Confident At All	1= Mostly Not Confident	2= Somewhat Not Confident	3=Neither Confident Nor Not Confident	4=Somewhat Confident	5= Mostly Confident	6=Completely Confident
1. I can enjoy things, despite the pain.	◯	◯	◯	◯	◯	◯	◯
2. I can do most of the household chores (e.g. tidying up, washing dishes, etc.) despite the pain.	◯	◯	◯	◯	◯	◯	◯
3. I can socialize with my friends or faily members as often as I used to do, despite the pain.	◯	◯	◯	◯	◯	◯	◯
4. I can cope with my pain in most situations.	◯	◯	◯	◯	◯	◯	◯
5. I can do some form of work, despite the pain ("work" includes housework, paid, and unpaid work).	◯	◯	◯	◯	◯	◯	◯
6. I can still do many of the things I enjoy doing, such as hobies or leisure activity, despite the pain.	◯	◯	◯	◯	◯	◯	◯

7. I can cope with my pain without medication.	◯	◯	◯	◯	◯	◯	◯
8. I can still accomplish most of my goals in life, despite the pain.	◯	◯	◯	◯	◯	◯	◯
9. I can live a normal lifestyle, despite the pain.	◯	◯	◯	◯	◯	◯	◯
10. I can gradually become more active, despite the pain.	◯	◯	◯	◯	◯	◯	◯

STOP.

Tell the researcher you are now on the **FABQ.** The researcher will provide instructions and be here to answer any questions you have.

Here are some of the things which other patients have told us about thier pain. For each statement, please select any number from 0 to 6 to say how much physical activities such as bending, lifting, walking, or driving would affect *your* knee pain.

	Completely Disagree			Unsure			Completely Agree
	0	1	2	3	4	5	6
1. My pain was caused by physical activity.	◯	◯	◯	◯	◯	◯	◯
2. Physical activity makes my pain worse.	◯	◯	◯	◯	◯	◯	◯
3. Physical activity might harm my knee.	◯	◯	◯	◯	◯	◯	◯
4. I should not do physical activities which (might) make my pain worse.	◯	◯	◯	◯	◯	◯	◯
5. I cannot do physical activities which (might) make my pain worse.	◯	◯	◯	◯	◯	◯	◯
6. My pain was caused by my work or by an accident at work.	◯	◯	◯	◯	◯	◯	◯
7. My work aggravated my pain.	◯	◯	◯	◯	◯	◯	◯
8. I have a claim for compensation for my pain.	◯	◯	◯	◯	◯	◯	◯
9. My work is too heavy for me.	◯	◯	◯	◯	◯	◯	◯
10. My work makes or would make my pain worse.	◯	◯	◯	◯	◯	◯	◯
11. My work might harm my knee.	◯	◯	◯	◯	◯	◯	◯
12.I should not do my normal work with my present pain.	◯	◯	◯	◯	◯	◯	◯
13. I cannot do my normal work with my present pain.	◯	◯	◯	◯	◯	◯	◯
14. I cannot do my normal work till my pain is treated.	◯	◯	◯	◯	◯	◯	◯
15. I do not think that I will ever be back to my normal work within 3 months.	◯	◯	◯	◯	◯	◯	◯
16. I do not think that I will ever be able to go back to that work.	◯	◯	◯	◯	◯	◯	◯

Appendix G: Self-Reported Inventory Methods & Results

G.1. Methods

Perceived knee function was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the KOOS patellofemoral subscale (KOOS-PF). The KOOS included five subsections: symptoms, pain, activities of daily living, function in sport and recreation, and quality of life. All items were rated on 5-point scales (0= never to 4=always with 2 reverse-worded questions) or (0=none, 4=extreme). The subscale scores are then added together and a total score of 100 indicates no problems and a score of 0 indicates extreme problems (Appendix F).. The KOOS-PF subscale, an 11-item subscale related to stiffness, pain, and knee-related quality of life was used to report perceived function relating to PFP. The scoring schema is the same for the KOOS-PF subscale as the original KOOS. The KOOS and KOOS-PF have excellent test-retest reliability [ICC=0.86, respectively; (Crossley, Bennell, et al, 2004)]. Only one study reported that the minimal clinically important difference for the KOOS in individuals with PFP is 8 points but it is important to note that the study sample was adolescent athletes (Ferreira et al, 2018).

Participants reported physical activity for the past week on the International Physical Activities Questionnaire (IPAQ). The IPAQ provides metabolic-minutes for three levels of physical activity (vigorous, moderate, and walking) and one level of sedentary behavior (sitting) across different situational factors. The IPAQ is a valid and reliable measure of self-reported physical activity (Craig et al, 2003).

The Pain Catastrophizing Scale (PCS) was used to identify any catastrophizing responses to pain (Quartana, 2009). The PCS is a 13-items scale ranking responses on a 5-point Likert (0=not at all, 4=all the time). Higher scores indicated higher levels of catastrophizing. The PCS

has held up to confirmatory factor analyses in a variety of populations including chronic pain patients, both sexes, and across age and cultural groups (Quartana, 2009).

The FABQ-Knee [Appendix F (Glaviano & Saliba, 2016)] was used to identify fear-avoidance beliefs. The FABQ-Knee is a 16-item inventory with 2-subscales: a work-related subscale and a physical activity-related subscale. Participants rated responses on a scale from 0 to 6, (0 =completely disagree, 3= unsure and 6=completely agree for a series of statements about their pain. Higher scores indicated more fear-avoidance beliefs but minimal clinical important difference has not been reported for groups with PFP.

Participants rated their confidence dealing with painful situations on the Pain Self-Efficacy Questionnaire (PSEQ). The PSEQ is an 10-item inventory ranking confidence on a scale from no confidence to complete confidence for each situation (Miles et al, 2011). Higher scores indicated higher pain self-efficacy (Appendix F). The PSEQ has good internal consistency and construct validity (Miles et al, 2011), but minimal clinical important difference have not been reported in groups with PFP.

Pain characteristics were reported using the McGill Pain Questionnaire. Participants report perceptions of pain by ranking sensory, affective, evaluative, and miscellaneous domains by selecting characteristics that best describe the pain from a list of 78 descriptors (Appendix F). Each descriptor within each domain is assigned a rank value. All rank values are then summed and the total is called the pain rating index (Melzack, 2005). Participants were also asked to shade in areas of pain with a pen and paper. The shaded area was calculated for each side and the sum of the pixel area from both sides was analyzed using ImageJ 1.53k software (National Institute of Health, USA).

G.2. Self-Reported Inventory Characterization of the Sample for Chapter III

All 20 participants reported experiencing pain during or following physical activity, while 18 experienced pain with squatting or kneeling, 17 reported pain with stair ambulation, and 15 reported pain with sitting. Of these, eight were topical, four were over-the-counter pain relievers, two were topical with three total respondents providing more than one medication response. Eleven of 20 (55%) of the PFP group reported seeking evaluation and/or rehabilitation from a healthcare provider. Of those 11, only 4 were currently taking part in rehabilitation programs. Of the seven individuals were sought healthcare but were not currently engaged in rehabilitation programs, four considered their rehabilitation "failed," while one was discharged and provided a home exercise regimen. One additional individual reported receiving periodic chiropractic adjustments to the spine to treat her knee pain.

The most commonly prescribed treatment or rehabilitation strategy was thigh or quadriceps strengthening (8/11), followed by hip and core muscle strengthening (7/11) and cold therapy (6/11), taping or bracing (6/11), and manual therapies (5/11). Other reported treatments included electric stimulation for pain (3/11), heat therapy (2/11), as well as ultrasound, biofeedback intervention, dry needling, iontophoresis, and foot and ankle mobility and strengthening (each of these were 1/11 reporting).

Our participants reported a wide range of pain descriptors on the McGill Pain Questionnaire in every subcategory (Figure 8). One hundred percent of participants reported at least one descriptor in the sensory and evaluative categories, 95% reporting at least one miscellaneous-sensory descriptor, and 45% of participants reporting at least one affective descriptor. The two subcategories with the greatest number of *descriptors* marked were sensory (115 responses over 31 descriptive terms), and miscellaneous-sensory (i.e. radiating, spreading,

numb, etc.) with 47 responses across 10 descriptors (Appendix H). The five most common responses were: annoying (80% of the sample reporting), nagging (75%), aching (70%), sharp (60%), and tender (60%).

G.3. Self-Reported Inventory Characterization of the Sample- Chapters V and VI

G.3.1. PFP Symptoms

The CS group had median symptom duration of 60.9 months (IQR= 5, 120 months), while the NS group reported median symptom duration of 5 months (IQR= 5, 68 months) which was not significantly different (p=0.168). Seventy-three percent of the sample reporting worst pain in the right knee and 27% experiencing pain the left. Sixty percent of CS groups reported bilateral symptoms, while 100% of the NS group experienced unilateral symptoms (Appendix H). Fifty-three percent of the CS group and 60% of the NS group reported regularly taking some form of medication for their knee pain. NSAIDs were the most common in both groups (33% and 60% in the CS and NS groups, respectively), followed by over-the-counter analgesics and topical medications. Eleven of 20 (55%) of the PFP group reported seeking evaluation and/or rehabilitation from a healthcare provider. All participants in both CS and NS groups reported experiencing pain during or following physical activity, and all of the NS participants reported pain with squatting. Eighty percent of the NS group and 73% of the CS groups reported pain with sitting.

G.3.2. Current or Prior Treatment

Eleven participants total reported prior evaluation or treatment by a healthcare provider. Of those 11, only 7 were in the CS group and 4 in the NS group. Three of the four respondents

who indicated that they were currently engaged in treatment were in the CS group. The most common treatments in the CS group were hip and core strengthening, thigh and quad strengthening, and wearing a knee brace or compressive sleeve (each with 2/3 responses). In the NS group, only 1 person reported taking part in rehabilitation but it was similar to the CS group, with the addition of manual therapy techniques (exact type not specified), cryotherapy, and heat therapy. Of the 7 participants who were no longer taking part in treatment, 4 considered their rehabilitation programs "failed," while 1 was discharged with a strengthening (hip/core and thigh/quadriceps) strengthening program that they self-discontinued. The most common treatments that were considered "failed" included manual therapy (5/7 reporting), thigh/quadriceps strengthening (5/7 reporting), and cryotherapy (4/7 reporting). Other reported treatments in the "failed" contingent included electrical stimulation (1/7), biofeedback (1/7), heat therapy (1/7), ultrasound (1/7), and hip/core strengthening (2/7), and chiropractic adjustments of the lower back to relieve knee pain (1/7, CS group).

G.3.3. Pain Characteristics

Our participants reported a wide range of pain descriptors on the McGill Pain Questionnaire in every subcategory. The frequency within each dimension of pain by central sensitization status and the most common descriptors selected by central sensitization group are reported in Figures 14-15. Only 1/5 participants in the NS group reported 1 affective descriptor, where 15 participants reported 17 affective descriptors in the CS group. In the miscellaneous-sensory category (i.e. numb, radiating, spreading, etc.) the CS group reported 33 responses while the NS group reported 13 responses. While 100% of participants in each group reported sensory and evaluative descriptors, the CS group reported 88 responses in the category, while the NS

group reported 27 sensory responses, and 15 (CS) and 5 (NS) evaluative responses. Eighty percent of the CS group experienced bilateral pain, while 100% of the NS group experienced only unilateral knee pain. Sixty percent of the CS group experienced pain for longer than 6 months, while only 40% had pain for 6 months or less. We observed the opposite relationship for the NS group (40% had pain longer than 6 months, while 60% experienced pain for 6 months or less). Symptom duration (mo) was not significant between the CS and NS groups.

The CS group reported higher co-morbidities of depression (40%) and anxiety (53%) compared to the NS group (40% depression, 20% anxiety), and CON group (7% and 23%, respectively). Of these, 4 individuals in the CS groups reported currently taking mental health medications, while none in the CON or NS groups reported taking medications for these conditions. The CS group reported higher stress at the time of testing (36.4 ± 26.9) than the NS (40.2 ± 21.7) and CON groups (25.4 ± 21.8) on a 100mm VAS, but this was not significantly different (p=0.366).

Appendix H: Supplemental Tables

(Not included in primary analysis)

Table 7. Quantitative Sensory Testing (Mean ± SD)

Test	CS Group	NS Group	CON Group	p-value	effect size (η^2)
TSP Difference (VAS)	8.7 ± 7.3[a,b]	0.11 ± 4.6[b]	1.88 ± 2.6[a]	0.02	0.325
PPT Lateral	314.6 ± 134.8	281.5 ± 90.2	359.9 ± 90.2	0.272	0.065
PPT Center	360.3 ± 142.7	360.3 ± 142.8	378.3 ± 126.3	0.6	0.027
PPT Medial	279.8 ± 93.1	302.5 ± 132.7	302.8 ± 123.6	0.847	0.011
PPT Hand	292.9 ± 136.8	360.3 ± 54.4	345.4 ± 149.3	0.324	0.047
CPM Lateral (% Difference)	-9.5 ± 20.6	14.4 ± 17.3	-0.6 ± 21.9	0.081	0.147
CPM Center (% Difference)	-11.1 ± 28.3[c]	8.3 ± 7.85	20.1 ± 26.7[c]	0.023	0.257
CPM Medial (% Difference)	2.9 ± 37.9	11.7 ± 36.1	8.0 ± 20.22	0.875	0.012
CPM Hand (% Difference)	-11.6 ± 19.3[d]	-7.8 ± 21.9	15.9 ± 27.8[d]	0.041	0.255

[a]=TSP was signficantly higher in the CS group compared to CON groups (p=0.008)

[b]= TSP was significantly higher in the CS group compared to NS (p=0.015)

[c]= CPM at center of the patella was significantly lower in the CS group compared to the CON group (p=0.009)

[d]= CPM at the hand was significantly lower in the CS group compared to the CON group (p=0.011)

Appendix I: Supplemental Figures for Self-Reported Data

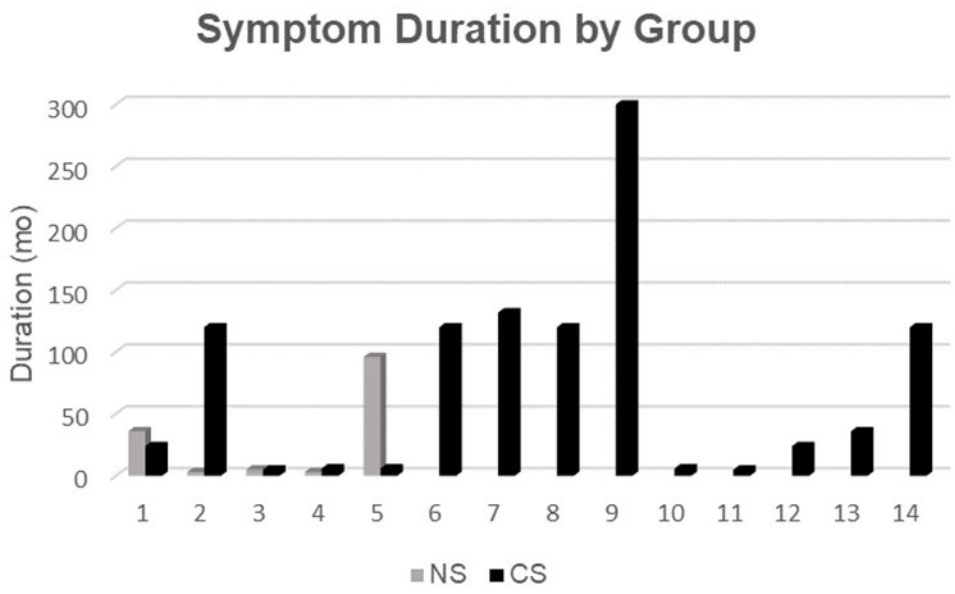

Figure 17: Symptom Duration by Central Sensitization Group

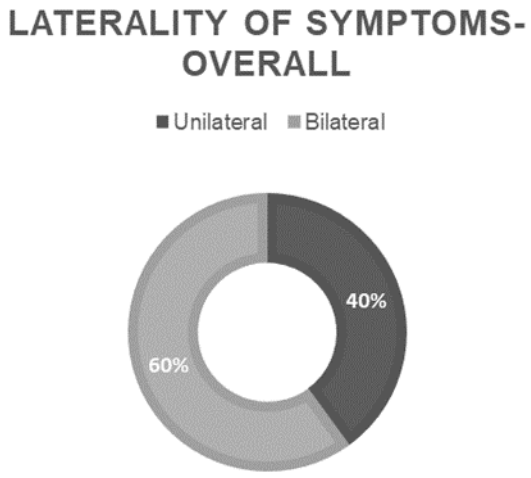

Figure 18: Laterality of Symptoms for Entire PFP Group

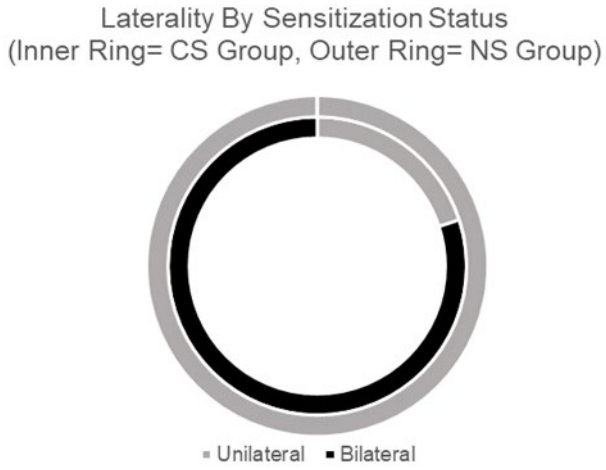

Figure 19: Laterality of Symptoms by Central Sensitization Group

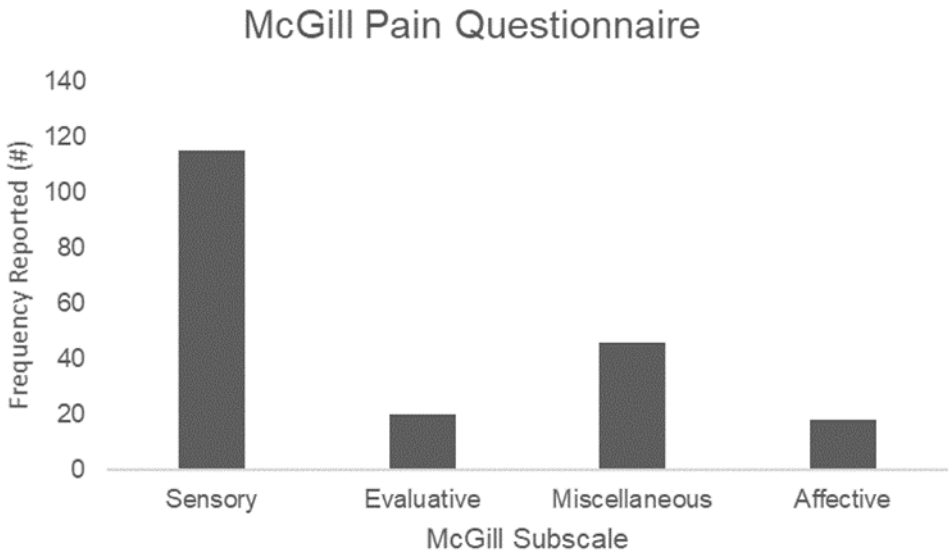

Figure 20: McGill Pain Questionnaire Distribution of Domains for Entire PFP Group

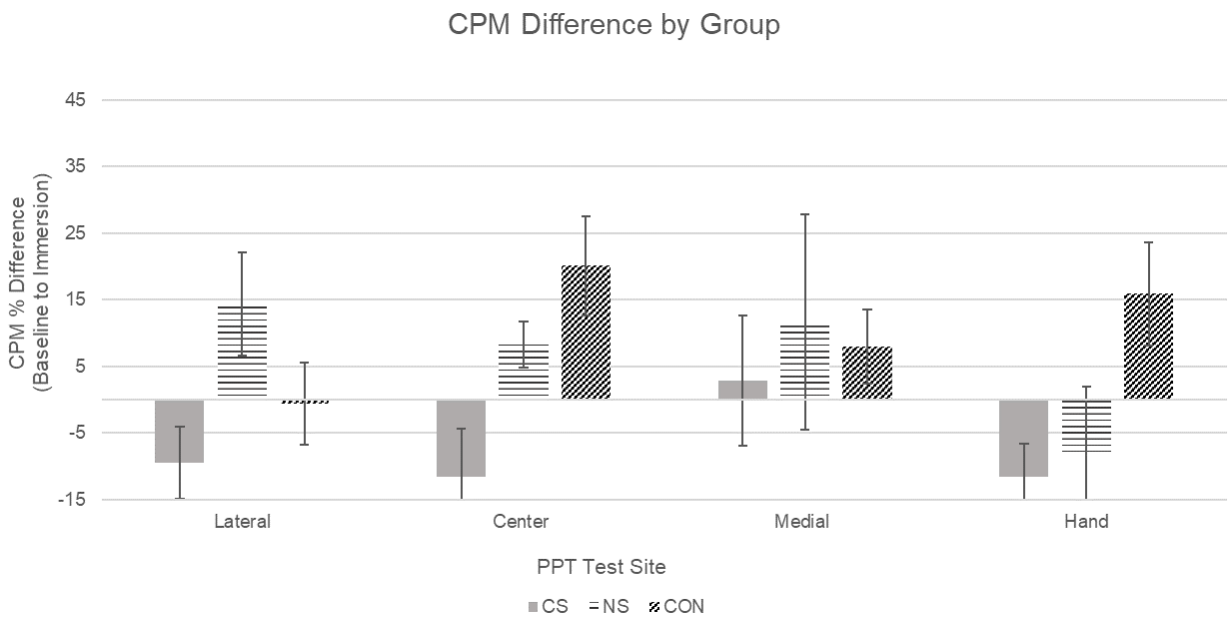

Figure 21: CPM Differences by Central Sensitization Group

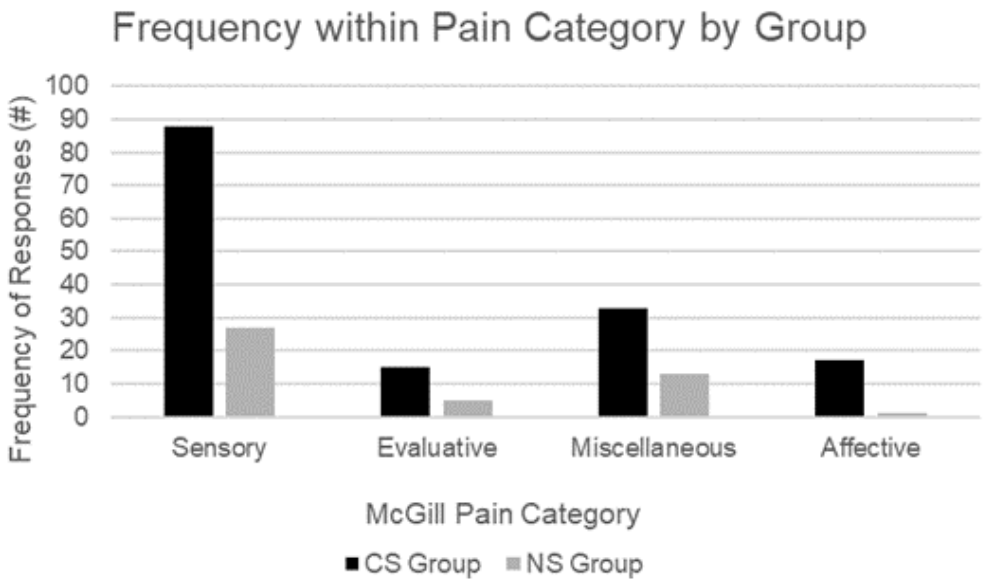

Figure 22: McGill Pain Questionnaire Pain Domain by Central Sensitization Group

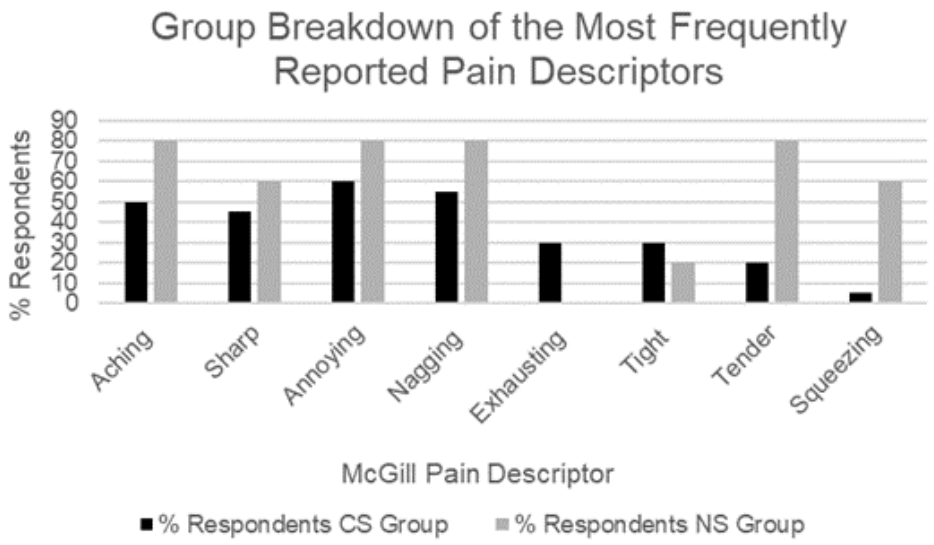

Figure 23: McGill Pain Questionnaire Most Frequently Reported Descriptors by Group

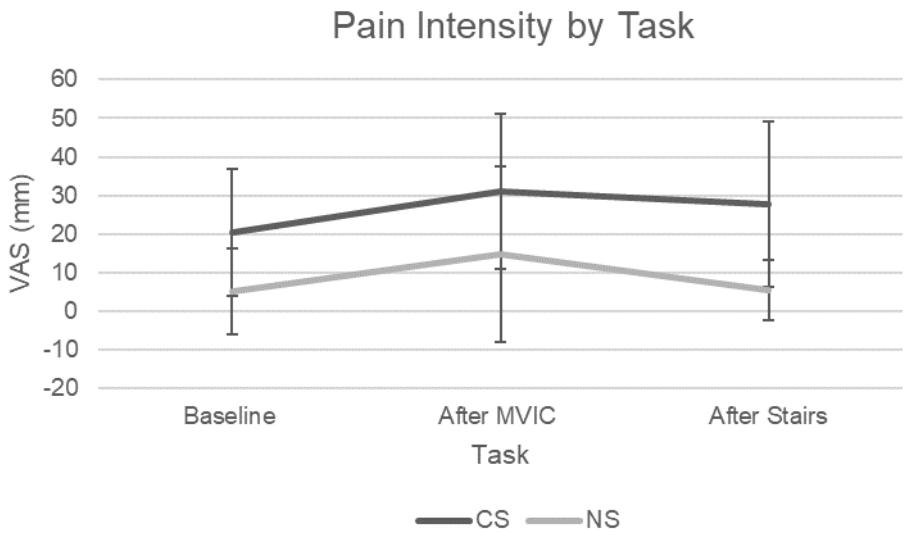

Figure 24: Pain Intensity By Task for by Sensitization Group

Curriculum Vitae

Kemery J. Sigmund, MS, LAT, ATC, NASM-PES

CURRENT POSITION

Assistant Professor of Health & Human Performance
Exercise Physiology
Concordia University Wisconsin
Mequon, Wisconsin

EDUCATION

2021	Ph.D.	Kinesiology Primary Cognate Area: Biomechanics Secondary Cognate Area: Sport Psychology PhD Minor: Statistics University of Wisconsin-Milwaukee, Milwaukee, Wisconsin
2008	M.S.	Kinesiology- Athletic Training Focus in Biomechanics Illinois State University, Normal, Illinois
2004	B.A.	Athletic Training English- Writing Minor Hope College, Holland, Michigan

EXERCISE SCIENCE & ATHLETIC TRAINING CREDENTIALS

2013-Current	L.A.T.	Wisconsin Department of Safety & Professional Services Athletic Training Licensure (#1568-39)
2013	PES	National Academy of Sports Medicine Performance Enhancement Specialist
2004-Current	A.T.C.	Board of Certification (#100402040) Athletic Training Certification, ATC Credential

Section I: Positions, Teaching, Advising, & Mentoring

Concordia University Wisconsin (Mequon, Wisconsin)

- Assistant Professor of Health & Human Performance, Exercise Physiology Program
    - Instructor for 6 courses, all new course development
    - Advised average of 10 students per year
    - Developed a human movement laboratory including procurement and bidding materials, semester scheduling, and maintenance

Concordia University Wisconsin (Mequon, Wisconsin)

- Coordinator of Clinical Education, Assistant Professor of Health & Human Performance Athletic Training Program,
    - Instructed 10 courses
    - Developed 6 new courses
    - Advised average of 10 graduate & undergraduate students per year
    - Chaired 6 thesis committees in the Master of Science in Athletic Training program
    - Advised 1 Deloss-Brubaker Student Writing Contest Winner (sponsored by the National Athletic Trainers' Association)- Best Literature Review
    - Prepared 6 Annual Reviews for the Commission on Accreditation of Athletic Training Education (CAATE)
    - Prepared 2019 Self-Study and participated in 2020 CAATE Accreditation Site Visit

Marietta College (Marietta, Ohio)

- Assistant Professor of Sports Medicine, Athletic Training Program
    - Instructed 12 courses
    - Developed 1 new course
    - Advised 24 students
    - Received a College-wide Advising Award
    - Mentored 2 Honor's Thesis projects and 10 undergraduate research projects per year in the Athletic Training and Health Science majors
    - Mentored 1 Deloss-Brubaker Student Writing Contest Winner (sponsored by the National Athletic Trainers' Association)- Best Original Research Project

Section II: Scholarly Activity

RESEARCH FOCUS

- Relationships between pain mechanisms with altered motor function and biomechanics in patients with chronic musculoskeletal conditions
  - Surface electromyography (EMG) and force analyses
  - Inertial Measurement Unit and 3D motion capture for biomechanical analysis
  - Quantitative sensory testing
  - Psychosocial contributions to chronic musculoskeletal conditions

PUBLICATIONS

Peer Reviewed Journals

- Sigmund KJ, Hoeger Bement MK, Earl-Boehm JE. (2021). Exploring the pain in patellofemoral pain: A systematic review and meta-analysis examining signs of central sensitization. *Journal of Athletic Training,* 56 (8), doi:10.4085/1062-6050-0190.20
- Sigmund, KJ, Earl-Boehm, JE. (2020). Force and EMG comparison between a weight-bearing clinical assessment of hip strength assessment and non-weight-bearing tasks. *Journal of Sports Medicine and Allied Health Sciences,* 6(2): 1-9.
- Sigmund, KJ & Marchetti, DP. (2014). Os Odontoideum in a collegiate softball player: A case review. *Athletic Training and Sports Health Care Journal,* 7(2): 70-74.

Collaborator

- Vicenzino B, Rathleff MR, Holden S, Maclachlan L, Smith B, Arvinen-Barrow M, de Azevedo F,... van Middelkoop M. (2020). Clinical and research priorities on pain and psychological features in individuals who have patellofemoral pain: An international Delphi consensus study of patients and health care professionals. *British Journal of Sports Medicine, (in press).*

Abstracts

- Sigmund, K.J., Hoeger Bement, M.K., & Earl-Boehm, J.E. (2020). Central Sensitization in Patellofemoral Pain: A Systematic Review & Meta-Analysis. Journal of Athletic Training.
- Sigmund, K.J., Arvinen-Barrow, M., & Earl-Boehm, J.E. (2016). A Prospective Investigation into injury occurrence and college athletes' perceptions of susceptibility to sport-related injury. Journal of Athletic Training

Unpublished Academic Work

- Twining (Sigmund), KJ. (2008). Shoulder range of motion and glenohumeral translation characteristics in collegiate softball pitchers. Unpublished thesis. Illinois State University, Normal, IL.

PRESENTATIONS

- Sigmund, K.J. Central Sensitization in Patellofemoral Pain: A Systematic Review & Meta-Analysis. Presented at the National Athletic Trainers' Association Annual

Symposium and Meeting. Atlanta, GA. June 25, 2020. **This meeting was changed to a virtual format**

- Sigmund, K.J., Hoeger Bement, M.K., Earl-Boehm, J.E. Better Understanding the Pain in Patellofemoral Pain: A Systematic Review & Meta-Analysis. Presented at the International Patellofemoral Pain Research Retreat. Milwaukee, WI. Oct. 3, 2019.
- Sigmund, K.J., Earl-Boehm, J.E. EMG and Force Analysis of a Weightbearing Hip Strength Assessment Task. Presented at the International Patellofemoral Pain Research Retreat. Milwaukee, WI. Oct. 1, 2019.
- Sigmund, K.J., Earl-Boehm, JE. EMG and Force Analysis of a Weightbearing Hip Strength Assessment Task. Presented at the University of Wisconsin-Milwaukee College of Health Science Research Symposium. May 3, 2019.
- Sigmund, K.J., Earl-Boehm, JE. EMG and Force Analysis of a Weightbearing Hip Strength Assessment Task. Presented at the National Athletic Trainers' Association Annual Symposium and Meeting. Las Vegas, NV. June 26. 2019.
- Sigmund, K.J. Pain: More than a 4-letter Word. Presented at the Wisconsin Athletic Trainers' Association Annual Clinical Symposium. Stevens Point, WI. April 6, 2019.
- Sigmund, K.J. A Prospective Investigation into injury occurrence and college athletes' perceptions of susceptibility to sport-related injury. Rapid Fire Presentation. National Athletic Trainer's Association Annual Symposia & Convention, Baltimore, Maryland. June 26, 2016.
- Sigmund, K.J. (2014). Os Odontoideum in a collegiate softball player. Free Communications Presentation. National Athletic Trainer's Association Annual Symposia & Convention, Indianapolis, Indiana. June 24, 2015.
- Sigmund, K.J., Wile, K, and Lusky, A. (2012). Glenohumeral Range of Motion and Scapular Positioning Characteristics in Collegiate Rowers. Oral Presentation at Ohio Athletic Trainer's Association Annual Meeting, Dublin, OH. May 2014.
- Sigmund KJ, Lazorik D, Hamilton P. *Women's Leadership in Athletics.* Invited to speak: Discussion Panel at the Women in Leadership Conference. Marietta, OH. April 2010.
- Twining (Sigmund), KJ. *Shoulder Range of Motion and Glenohumeral Translation Characteristics in Collegiate Softball Pitchers.* Thesis- Original Research, Illinois State University. Presented at 2007 Illinois State University Research Symposium.

POSTER PRESENTATIONS & FREE COMMUNICATIONS- ADVISOR

- Reinke, H., Swoboda, C., Thorpe, J.L., Sigmund, K.J. Relationships between shoulder proprioception, core activation, and perceived shoulder function in overhead athletes. Presented at the Wisconsin Athletic Trainers' Association Annual Meeting & Symposia. Stevens Point, WI. April 4, 2019.
- Gratz, B., VanDamme, C, Gotzler, A., Sigmund, K.J. The effects of kinesiotape on rounded shoulder posture. Presented at the Wisconsin Athletic Trainers' Association Annual Meeting & Symposia. Stevens Point, WI. April 4, 2019.
- Eichhorst, E.,Thorpe, JL, Sigmund, K.J.. Comparison of King-Devick and ImPACT baseline scores in collegiate athletes. Presented at the Wisconsin Athletic Trainers' Association Annual Meeting & Symposia. Wisconsin Dells, WI. April 12, 2018.
- Macioch, A., Wetzel, K., Sigmund, K.J., Thorpe, J.L. (2018). Concussion baseline testing: the effect of gender, mental toughness, and depressive symptoms on baseline

scores. Presented at the Wisconsin Athletic Trainer's Association Annual Meeting & Symposia. Wisconsin Dells, Wisconsin. April 12, 2018.

- McLeod, L., McKay, A., Sigmund, K.J., Thorpe, J.L., and Gotzler, A. (2018). Relationships between Core Strength and Proprioception. Presented at the Wisconsin Athletic Trainer's Annual Meeting & Symposia. Wisconsin Dells, Wisconsin. April 12, 2018.

FUNDING

- **University of Wisconsin-Milwaukee College of Health Science Graduate Student Research Grant Award, PI (Student)**
  $2,000 for Project: Conditioned Pain Modulation Responses in Females with Patellofemoral Pain and Pain-free Females
- **National Athletic Trainers' Association Doctoral Research Grant (#1819DGP06), PI (Student)**
  $2,500 for Project: Conditioned Pain Modulation Responses in Females with Patellofemoral Pain and Pain-free Females
- **Wisconsin Athletic Trainers' Association Research Grant (PI)**
  $2,000 for Project: Conditioned Pain Modulation Responses in Females with Patellofemoral Pain and Pain-free Females

INVITED GUEST LECTURER

- **Marquette University, PHTH 7530: Pain Mechanisms & Treatment (annual)**
  Relationships between Chronic Musculoskeletal Pain & Movement
- **Concordia University Wisconsin, MSES 550: Seminar in Exercise Science**
  The Interaction of Pain and Movement
- **Concordia University Wisconsin, MSAT 530 Psychosocial Aspects of Athletic Training**
  Lessons from the Field: The Importance of Biopsychosocial Approach to Athletic Training Practice
- **Concordia University Wisconsin, MSAT 380, Therapeutic Modalities (annual)**
  Biopsychosocial and Neurophysiological Aspects of Pain
- **Concordia University Wisconsin, MSAT 510, General Medical Conditions & Pharmacology (annual)**
  Recognition, Auscultation & Percussion, and Management of Cardiac, Lung, Thorax & Abdominal Conditions

MEDIA

- WTAP Ohio Evening News, Parkersburg, West Virginia (2011): *Concussions in Sport*

MEETING ORGANIZATION & PLANNING COMMITTEES

- Organized a 100-participant Zoom Call for Clinical Coordinators and Program Directors from across the US to discuss alternative options for clinical education delivery in response to COVID-19 (SARS-COV-2)
- Founding member of the Marietta College Undergraduate All-Scholar's Day Committee

- Founding member of the Marietta College First Year Experience Peer Mentorship Program & Committee
- Don Drumm Renovation Planning Commitee

AWARDS

- University of Wisconsin-Milwaukee College of Health Science Research Presentation Award- 3nd Place, May 3, 2020
- Excellence in Advising Award, Marietta College, February 2012
- Alpha Lambda Delta Academic Excellence in Teaching Award, Marietta College, April 2011

Section II: POSITIONS, TEACHING, ADVISING, & MENTORING

ACADEMIC POSITIONS AND PROFESSIONAL EXPERIENCE

2021-present Assistant Professor of Health & Human Performance
Exercise Physiology Program
Concordia University Wisconsin
Mequon, Wisconsin

2014-2021 Clinical Education Coordinator
Assistant Professor
Athletic Training Program
Department of Health & Human Performance
Concordia University Wisconsin

2009-2014 Assistant Professor
Head Athletic Trainer
Department of Sports Medicine
Marietta College

2008-2009 Assistant Professor
Assistant Athletic Trainer
Athletic Training Program
Department of Sports Medicine
Marietta College

TEACHING EXPERIENCE

Concordia University Wisconsin (Mequon, Wisconsin)

2020-present **HHP 373:** Motor Development

2020-present **HHP 371:** Exercise Physiology

2020-present **HHP 375:** Biomechanics

2020-present **HHP 280:** Sport Psychology
Course re-design and development with case-based approach

2020-present **MSES 540:** Applied Kinesiology
Graduate course design and development with focus on application

2020-2021 **MSAT 520: Basic Statistics for Athletic Trainers**
Course Development
Developed Classroom and lab assignments with an active learning focus

2017-2021 **MSAT 600: Thesis**
Independent and group advising during the Thesis project

2015-2021 **MSAT 569: Research Design**
Thesis & Capstone Coordinator for MSAT Program

2014-2020 **MSAT 301: Rehabilitation Techniques in Athletic Training**
Implemented novel Case Building approach to incorporate evidence-based practice
and active learning techniques

2014- 2021 **MSAT 289: Seminar in Athletic Training (formerly HHP 289)**
Arranged weekly guest speakers to introduce students to sports medicine current events topics

2014-2019 **MSAT 115: Medical Terminology for Healthcare Professions**
Online Course Management

2014-2016 **HHP 493: Senior Seminar in Athletic Training**

2014-2018 **MSAT 376/378: Recognition and Evaluation of Orthopedic Injuries II with Lab**
New Course Development at the graduate level

2015 **HHP 491: Practicum V in Athletic Training**

2015 **HHP 312: Administration and Organization in Athletic Training***
Co-instructor: Katherine Liesener

2014 **HHP 492: Practicum VI in Athletic Training**

Marietta College (Marietta, Ohio)

- Primary instructor for courses in CAATE-accredited Athletic Training Program with a 3-year BOC first-time passing rate (2010-2013) of 95%
- Developed a Mentor Program for Athletic Training student organization

- Served as Research advisor for multiple students per year for original research studies involving human subjects

2012-2014 **SPTM 499: Motor Learning and Development**
New Course Development for Independent Study with a culminating final project

2009-2014 **SPTM 484, 485, 486: Introduction to Research & Design, Research Design I & II**
SPTM 214: Lower Extremity Assessment Lab
SPTM 311/313: Advanced Assessment of the Head & Spine and Lab

2008-2014 **SPTM 328: Practical Biomechanics**
Re-designed Practical Biomechanics course

2009-2011 **FYS 101: First Year Seminar: Introduction to Sports Medicine Healthcare Providers**
Served for 2 years in the First Year Experience program (2009-2010)

2008-2010 **SPTM 210: Fundamentals of Athletic Training**
SPTM 290: Personal Health
SPTM 211/213: Lower Extremity Assessment and Lab