TRAINING ENDOGENOUS PAIN MODULATION: EFFECTS ON RESTING-STATE FUNCTIONAL BRAIN CONNECTIVITY IN HEALTHY VOLUNTEERS

By

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To my grandfather, who showed me persistence, strength, will, and devotion

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LIST OF ABBREVIATIONS

A-MH	A-mechanoheat
ART	Artifact detection tool
BRS	Brief resilience scale
dmPFC	Dorsomedial prefrontal cortex
DOMS	Delayed onset muscle soreness.
PMC	Pain modulatory capacity
QST	Quantitative sensory testing
RD	Repeated delayed onset muscle soreness
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
ICN	Intrinsic connectivity network
ICA	Independent components analysis
MCC	Mid-cingulate cortex
mPFC	Medial prefrontal cortex
MP-RAGE	Magnetization-prepared rapid gradient echo
MVC	Maximum voluntary contraction
NAc	Nucleus accumbens
NRS	Numeric rating scale
PAG	Periaqueductal gray
PCS	Pain catastrophizing scale
PEVAS	Pain experience visual analogue scale

rACC	Rostral anterior cingulate cortex
REDCap	Research electronic data capture
rmPFC	Rostromedial prefrontal cortex
ROI	Region of interest
RVM	Rostroventral medulla
sgACC	Subgenual anterior cingulate cortex
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SMN	Sensorimotor network
TSSP	Temporal summation of second pain
UF	University of Florida
vmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

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Standard analgesic treatments aim to achieve states of no pain or minimal pain variability. These agents often display marginal success in relieving chronic pain and may result in maladaptive neurophysiological changes. Evidence suggests that repeated exposure to painful stimuli results in increased pain modulation via engagement of anti-nociceptive brain regions. It was hypothesized that repeated exposure to clinically-relevant pain stimuli [delayed onset muscle soreness (DOMS)] would result in increased pain resilience via decreased pain sensitivity and functional neuroplasticity underlying greater pain modulatory capacity (PMC). A mixed between-within-subjects design was used to identify neuroplasticity following repeated DOMS of the biceps muscles. 23 healthy subjects (mean age=32.52, SD=17.11; 17 female) completed baseline and follow up resting-state fMRI and quantitative sensory testing (QST) visits 40 days apart. Subjects were randomized to two groups: A Repeated DOMS Group (RD Group) that received four, weekly DOMS inductions and a Control Group that received one induction at baseline. Daily pain ratings were collected for seven days post-induction, and quantitative sensory testing (QST) metrics were

collected at baseline and follow up. fMRI data were preprocessed with SPM12. Using the CONN toolbox, regional functional connectivity (FC) was estimated among areas involved pain modulation including the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC). Seed-to-whole-brain FC was estimated among areas involved in anti-nociception and sensory processing, the subgenual anterior cingulate cortex (sgACC) and sensorimotor network (SMN), respectively. Changes in FC were compared between groups. The RD Group displayed significant reductions in post-DOMS pain ratings and significant changes were observed in thermal QST measures. Significant group-by-time interactions were observed in NAc-mPFC functional connectivity ($p = 0.03$), and in SMN connectivity with the dorsomedial, ventromedial, and rostromedial prefrontal cortices ($p_{height}<0.001$ uncorrected, $p_{cluster}<0.05$ FDR), suggestive of greater neural adaptation in the RD Group. Changes in SMN-PFC connectivity correlated with reductions in post-DOMS depression, anger, anxiety, and fear. Results suggest that repeated exposure to clinically-relevant pain stimuli results in substantial functional, neural adaptations among brain regions involved in pain modulation. Repeated exposure to clinically-relevant pain may serve as a mechanism to increase PMC via inhibition of emotional valuation of painful stimuli.

CHAPTER 1
INTRODUCTION

Chronic pain is a significant public health concern in the U.S., affecting 100 million Americans and resulting in annual expenditures of over $600 billion per year from lost productivity and healthcare costs [38]. Standard analgesic treatments result in avoidance of the experience of pain via inhibition of inflammatory factors or modulation of opioid-dependent signaling. That is, the assumed goal of many existing treatments is to achieve a state of no pain or minimal pain fluctuation. While existing analgesic agents are successful in certain cases (e.g. acute pain), these agents typically display limited utility and success rates of only 30-40% [19] in chronic pain, or pain that persists for greater than three to six months [95]. Significant evidence to suggests that both short- and long-term exposure to exogenous opioids may impair endogenous pain modulatory functioning [73] and that these impairments may persist following opioid discontinuation. For example, exogenous opioids are known to produce a progressive lack of response to opioid agents, hypersensitivity to painful stimuli [51], and both peripheral and central nervous system inflammation [73]. Exposure to exogenous opioids may produce long-term pro-nociceptive activation, leading to a state of “latent pain sensitization,” and greater potential for pain chronicity [73]. This evidence suggests that attempts to achieve a pain-free state through exogenous agents paradoxically increases pain vulnerability. In light of this, it is proposed that attempts to eliminate pain experiences or reduce pain variability contribute to diminished endogenous capacity to modulate pain by limiting opportunities for natural pain modulatory adaptation. Efforts to increase endogenous pain modulatory capacity (PMC), thereby fostering resilience to subsequent pain episodes, may provide insights for novel intervention development.

Resilience and Pain

The study of resilience offers important concepts in understanding adaptation to pain episodes. Resilience encompasses phenomenological qualities displayed by resilient individuals, the processes involved in achieving adaptive outcomes, and motivational factors related to the pursuit of meaning or purpose [71]. As such, a distinction exists between resilience resources, trait-like personality factors that promote resilient coping, and resilience mechanisms, cognitive, affective or behavioral processes that mediate outcomes after stress [91]. The outcomes achieved by resilience process are contextually dependent and may include recovery and return to equilibrium, maintenance of meaningful or valued pursuits despite stressor presence, reintegration or growth following stressor cessation, or capacity to respond with greater efficiency or effectiveness to future stressors [91]. Physiologically, resilience has been linked to allostasis: the physiological processes, alterations, and temporary dysfunctions necessary to regulate and maintain organism functioning during stress [e.g. efficient mobilization and termination of stress responses [76]. Conversely, vulnerability has been described as as an as over-generalization of stress related fear responses, which may be linked to avoidance behaviors, stability of trauma-related memories [33], and physical and emotional dysfunction [27]. Though resilience and vulnerability do interact, they do not exist on a continuum but rather operate as two unique factors influencing context-specific outcomes [21]. As such, although numerous psychological and physiological processes underlie resilience. Motivational, cognitive and affective factors are particularly salient to pain resilience.

Within the context of pain, resilience refers to factors that facilitate adaptive responses that may mitigate pain-related distress and or facilitate meaningful outcomes

in the face of pain [1]. It is notable that, depending on the degree or type of injury, only 10-50% of individuals develop persistent pain [27]. This suggests that resilience to pain is the norm in ecological settings. Experimentally, many studies suggest there is a link between resilience processes and adaptive pain outcomes. For example, individuals scoring high on measures of general resilience demonstrate higher pain tolerance and greater habituation to painful stimuli [36,84,86]. According to the Broaden and Build Theory [69], the emotional complexity experienced during pain has direct implications on one's ability to identify effective and efficient coping resources. As such, individuals who are able to maintain accurate appraisals of hedonic tone, and as a result, experience both positive and negative emotions during pain pain, tend to utilize more effective coping strategies. Additionally, catastrophizing, a cognitive process characterized by pain-related rumination and magnification, results in cognitive narrowing, which may prevent individuals from engaging in novel coping behaviors and may promote the maintenance of ineffective control or avoidance coping strategies [90,91]. Additionally, individuals who display greater levels of catastrophizing exhibit decreased habituation to painful stimuli [87], diminished activity in pain modulatory regions of the brain, and increased activity in regions of the brain involved in attention [81]. Conversely, positive emotion and self-efficacy may promote individuals to explore alternate coping strategies, seek additional resources or social support in managing pain. Ong, et al (2010) proposed that resilient individuals display less pain catastrophizing and that this relationship is mediated by the experience of positive emotions. Therefore, resilience to pain is related to both the range and variability of cognitive and affective pain-related experiences.

Resilience and Pain Modulatory Adaptation in the Central Nervous System

Although numerous systems are involved in resilience processes, the mesocorticolimbic system may be particularly involved in adaptive pain responses [97]. This system, which includes regions such as the medial prefrontal cortex (mPFC), amygdala, nucleus accumbens (NAc), hippocampus, and ventral tegmental area (VTA), is involved in assigning value to the environment, encoding prediction errors for aversive and appetitive stimuli, and the regulation of learning and motivated behavior. The mPFC may be particularly involved in regulating emotional responding to pain and stressful events. The ventral aspect of the mPFC (vmPFC) inhibition of amygdala-mediated fear responses may promote adaptive behavior such as identification of appropriate coping mechanisms [33], efficiency in responding to changing stimulus qualities (e.g. from innocuous to threatening [49,50], while connectivity among these regions may predict stress and fear responses. Alterations in vmPFC functional connectivity and vmPFC degeneration have been implicated in poor outcomes in chronic pain patients [31]. Connectivity among the NAc and mPFC may be particularly salient for pain modulation. The NAc, rich in opioidergic and dopaminergic pathways, is involved in assigning hedonic value and anticipating stimulus valence. In a study of thermal pain modulation, subjects were asked imagine thermal stimuli as more or less pain (i.e., up regulate or down regulate). The degree subjects were able to successfully regulate pain perceptions was mediated by connectivity among the mPFC and NAc [108]. In clinical settings, decreased NAc-mPFC functional connectivity was predictive of successful recovery following an episode of subacute back pain [10]. Animal models suggest that pain modulation achieved by prefrontal activation is mediated by the NAc, which projects to the periaqueductal gray (PAG) and brainstem, and indirectly to the

thalamus via the palladium and substantia nigra [52]. Therefore, interactions among medial cortical and limbic structures are salient to pain modulation and resilience to acute pain episodes.

Given these findings and the processes subsumed in the mesocorticolimbic system, Vachon-Presseau, et al. (2016) conceptualized adaptive responding to pain in the in terms of cortical inhibition of emotional over-valuation of pain stimuli. The authors suggested that the near constant, normal flow of nociceptive information from the periphery is rarely brought to awareness due to cortical gating [97]. Injury or acutely painful events may surpass the threshold of normal gating and result in one of two primary responses: cortical suppression of pain-related limbic system activity to decrease emotional valuation of pain, or increased emotional valuation of pain and subsequent reorganization of gating circuitry. Lack of inhibitory, cognitive control results in emotional over-valuation of nociceptive information, such that overtime the brain responds to painful stimuli as an increasingly emotional experience. This is consistent with previous accounts of pain chronicity as a state of continuous learning with minimal forgetting of the emotional or motivational value of pain stimuli [5]. Resilience then refers to appropriate mobilization of cortical inhibition to prevent emotional over-valuation of pain stimuli.

Fostering Resilience and Capacity to Modulate Pain

Challenges may be necessary to “toughen” individuals or physiological systems to develop resilience to future stressors [77,79]. Specifically, stress inoculation theories posit that previous, moderate levels of exposure to stressors promotes adaptive and resilient responding to future stressors [77]. In the context of pain, healthy individuals who experienced a moderate number of adverse life events reported lower levels of

catastrophizing, pain intensity, and negative affect following an experimental pain task [80]. Additionally, chronic pain patients who report moderate levels of previous adverse events experience better outcomes in terms of disability, healthcare utilization, and disability status [78]. Perceived control has been proposed to underlie this phenomenon, and differences in perceived control or pain-related self-efficacy may distinguish those who may or may not become sensitized to pain [92]. As such, interventions designed to increase resilience via graded exposure to and recovery from painful stimuli may be a possible vector for the development of new treatments.

Research suggests that short-term, repeated exposure to painful stimuli results in increased involvement of anti-nociceptive brain regions during pain processing. In an investigation of pain habituation-related brain processes, Bingel and colleagues (2007) found and replicated (2008) that eight, daily exposures to a 20-minute thermal pain paradigm resulted in substantial decreases in pain ratings at follow up compared to baseline (i.e., successful habituation). Functional magnetic resonance imaging (fMRI) results displayed decreased activation in the thalamus, insula, and secondary somatosensory cortex (SII), regions involved in pain processing, and increased activation in the subgenual anterior cingulate cortex (sgACC), a region involved in endogenous pain modulation through opioid and other pathways. This finding suggests successful adaptation of the pain modulatory system to promote resilient outcomes (e.g. decreased disruption of normal functioning due to a painful stimulus). In a subsequent study [70], habituation was not significantly diminished after opioid antagonist, naloxone, induction, which suggests that habituation-related pain modulation is not directly mediated by endogenous opioids though indirect opioid involvement is possible.

Individual differences in sgACC functional connectivity at rest may also be associated with differences in pain modulatory capacity [100].

Prior research confirms that habituation-related neural adaptations are evident at rest. Riedl, et al. (2011) assessed neural adaptation of intrinsic connectivity networks (ICNs) at rest following 11 days of consecutive thermal pain exposure. ICNs map temporally coherent, low-frequency (>0.1 Hz) signal fluctuations among functionally and, or anatomically connected regions of the brain at rest [22,109]. Following repeated pain exposure, the authors found evidence of vmPFC recruitment into the sensorimotor ICN (SMN), a network comprised of regions involved in the processing of sensory stimuli. The degree of vmPFC-SMN coherence obtained was also predictive of the magnitude of habituation. The authors postulated that following through habituation-related learning, the vmPFC served an anticipatory function to modify the valuation of incoming pain stimuli. These studies suggest that habituation is associated with increased involvement of pain modulatory brain regions in pain processing. These results also indicate that through repeated exposure to painful stimuli, it is possible to increase PMC.

Given the potential to train increased PMC in experimental settings, exposure to and recovery from clinically-relevant pain stimuli will likely produce more ecologically valid adaptation. Among chronic pain patients, musculoskeletal pain is one of the most common complaints [56,89], and it is one of the most common causes of activity limitation and medication consumption [7]. Our group has successfully developed and validated acute, exercise-induced, pre-clinical pain models using delayed onset muscle soreness (DOMS) [17,18,25,26,40]. This model induces clinically meaningful pain

intensity levels, self-reported, disability, and interference in most subjects. Additionally, with these models the mechanism and site of injury can be controlled, resulting in sample homogeneity that cannot be obtained with clinical populations. In this protocol, damage is caused to muscle fibers through the performance of eccentric (lengthening) actions in muscles unaccustomed to such forces, causing mechanical disruption of protein filaments and a secondary inflammatory response [37]. Pain, hyperalgesia, allodynia, weakness, and edema can result secondary to sensitization of muscle nociceptors following exposure to mediators of the inflammatory process [6,42]. Symptoms resolve naturally within several days to two weeks [23,30]. Notably, it is well-established that in subsequent bouts of DOMS, there is a significant reduction in subsequent pain intensity and sensitization. Although the mechanisms for these changes are currently unclear [47], similar neural processes may underlie theses and habituation-related adaptation. Additional research is needed to determine whether central pain modulatory systems play a role in adaptation following repeated exposure to clinically-relevant pain such as DOMS.

There is compelling evidence that treatments aimed at achieving a pain-free state may hamper endogenous pain modulatory mechanisms [73]. Additionally, individuals who have greater pain-related self-efficacy, which can be developed through previous instances of successful recovery from pain, display greater resilience to subsequent pain episodes. Experimentally, repeated exposure to painful stimuli results in perceptions of decreased pain intensity, potentially through functional or structural adaptations pain-related neural networks [15,72,94]. Therefore, repeated exposure to clinically-relevant pain may result in increased PMC, as evidenced by functional neural

adaptation and decreased pain sensitivity at sites proximal and distal to the initial injury. The present study sought to examine the neural correlates of adaptation following exposure to and recovery from multiple bouts of DOMS with the following three aims: 1) Assess the role of the nucleus accumbens-medial prefrontal cortex pathway in pain adaptation, 2) Evaluate the effects of repeated exposure to musculoskeletal pain on the coherence among specific pain-related brain regions and networks, and 3) Evaluate how negative and positive psychosocial factors influence neural adaptability after repeated exposure to musculoskeletal pain. It was hypothesized that following repeated bouts of DOMS 1) Subjects would display decreased NAc-mPFC functional connectivity, suggestive of increased PMC, and that individuals with less NAc-mPFC coherence at baseline would demonstrate greater adaptation in QST metrics, 2) Subjects would exhibit greater coherence among the sgACC and pain-related brain regions [PAG, rostroventral medulla (RVM), insula, primary somatosensory cortex (SI), and SII], and greater coherence among the vmPFC and SMN, and that these changes would correspond with changes in pain sensitivity, and 3) Individuals exhibiting greater self-reported resilience at baseline would exhibit greater changes in v/mPFC connectivity, and individuals exhibiting greater catastrophizing at baseline would exhibit lesser changes in sgACC functional connectivity.

CHAPTER 2
METHODS

A mixed between- within-subjects design was used to test the adaptation of functional brain connectivity during resting-state fMRI following repeated exposure to musculoskeletal pain. The present study assessed the correspondence of changes in resting-state connectivity with changes in measures of experimental and clinically-relevant pain. The influence of psychosocial variables on these changes was also assessed.

Participants

Healthy subjects aged 18 and older were recruited. Potential subjects were excluded if they met any of the following criteria: 1) Previous participation in a conditioning program specific to the biceps in the past 6 months, 2) Any report of wrist/hand, elbow, or shoulder pain in the last 3 months, 3) Any chronic medical conditions that may affect pain perception (e.g., diabetes, high blood pressure, fibromyalgia, headaches), kidney dysfunction, muscle damage, or major psychiatric disorder, 4) Consumption of any drugs (e.g., alcohol, theophylline, tranquilizers, antidepressants) that may affect pain perception or hydration status 24 hours before participation in the final testing session, 5) Use of caffeine 4 or less hours before testing session, 6) Use of any intervention (including but not limited to medication, massage, and stretching) for symptoms induced by pain training for the duration of the study, 7) Recent illness, 8) Positive result on pre-MRI metal screening or pregnancy test because of contraindication for the MRI environment, and 9) Any participant with metal in the head, neck, or abdominal cavity.

Procedure

Participants were randomized to one of two groups: 1) repeated DOMS + quantitative sensory testing (QST) + MRI scanning or 2) single-DOMS + QST + MRI scanning. Study procedures were specified for each group as follows below:

Group 1: Participants in group 1 (Repeated DOMS; RD group) participants completed a total of five sessions. At the first session, participants underwent anatomical and functional MRI scanning, completed self-report measures, biceps palpation and girth measurement, quantitative sensory testing (QST), maximum voluntary contraction (MVC) assessment, and the DOMS-inducing protocol at their randomly assigned elbow flexor muscles (dominant or non-dominant). Specific procedures for each are outlined below. Every 7-14 days for the next 30 days, participants repeated the DOMS protocol on the elbow flexor muscles opposite to those that were exercised at the previous session for a total of four DOMS inductions. For example, if a participant was randomized to receive DOMS at the dominant elbow flexor muscles at Session 1, they then received DOMS at their non-dominant elbow flexor muscles at Session 2, DOMS at the dominant elbow flexor muscles at Session 3, and DOMS at the non-dominant elbow flexor muscles at Session 4. Therefore, both the dominant and non-dominant elbow flexors muscles were exercised twice during the course of the study. Additionally, during Session 5, participants underwent follow up anatomical and functional MRI scanning, and QST and MVC assessment. Participants completed daily pain measures that documented pain intensity and quality in the week following each DOMS induction. Daily measurements were acquired through the University of Florida (UF) Research Electronic Data Capture (REDCap) system. See Figure 2-1 for study design schematic.

Group 2: Group 2 participants (Control Group) completed a total of two sessions. At Session 1, participants underwent anatomical and functional MRI scanning, completed self-report measures, biceps palpation and girth measurement, quantitative sensory testing (QST), maximum voluntary contraction (MVC) assessment, and the DOMS-inducing protocol at their randomly assigned dominant or non-dominant elbow flexor muscles. During Session 2, they completed follow up assessments of anatomical and functional MRI, and QST and MVC assessment 40 days after the initial testing session (Figure 2-1).

Isometric Strength and DOMS-Inducing Exercise Protocol

Maximum voluntary contraction (MVC) of elbow flexion strength was tested using a Biodex System Isokinetic Dynamometer (Biodex Medical Systems, Shirley, NY). The subject was seated within the testing apparatus (Figure 2-2) with a stabilizing strap attached proximal to the elbow joint. The subject moved through their available range of motion in elbow flexion and extension. The device was then locked into place and the subject was instructed to build up force while holding onto the grip handle of the machine. Once peak effort was achieved, the subject was instructed to relax, the device was released and the subject returned to a neutral position. A research assistant who was trained in the use of the Biodex exercise equipment conducted this test and subsequent exercise protocol.

To perform the dynamic fatiguing exercise bout, the subject was seated in the Biodex machine in order to isolate the dominant biceps muscle. The subject then performed the isometric strength test (described above). Following 60 seconds of rest after the isometric test, the subject completed through an exercise protocol consisting of

eccentric (elbow straightening/biceps lengthening) exercises intended to induce DOMS at the biceps. The Subject performed three sets of 15 repetitions at a speed of 60/60°/s. Isometric strength was then reassessed. RD Group participants completed this protocol at Sessions 1-4. Control Group participants completed this protocol only at Session 1.

Structural and Functional MRI Scanning

Anatomical and functional (fMRI) data were collected from each participant during baseline (Session 1) and follow up (RD Group Session 5 and Control Group Session 2). Sequentially, one high-resolution 3D anatomical MRI scan and one resting-state fMRI scan were performed.

Functional and structural MRI data were acquired with a research-dedicated whole-body Philips Achieva 3.0T scanner using a standard head 32-channel radiofrequency coil. High-resolution 3D anatomical images were collected using a T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) protocol (170 1mm axial slices; repetition time = 8.1ms, echo time = 3.7ms, flip angle = 8°, matrix = 240 × 240mm, field of view = 240mm), and functional images were collected using a T2-gradient echo planar imaging sequence capturing 33 contiguous axial slices of the whole brain parallel to the anterior commissure–posterior commissure plane (repetition time = 2000ms; echo time = 30ms; flip angle = 80°; 80 × 80 matrix; field of view = 240 × 240mm; $3mm^3$ isotropic voxels with 0mm slice gap).

Assessment Measures

Self-Report Questionnaires

All participants completed the following measures during Session 1. Measures of resilience- and vulnerability-related psychosocial variables were collected to determine the influence of these qualities on pain adaptation following repeated DOMS.

Demographic and Historical Information: Study participants completed a standard intake information form. Demographic data collected at initial evaluation included gender, age, employment status, marital status, educational level, and medical history.

The Pain Catastrophizing Scale (PCS) is a 13-item, 5-point Likert scale with higher scores indicating elevated levels of catastrophizing [93].

The Brief Resilience Scale (BRS) is a 6-item, 5-point Likert scale that assesses one's ability to recover from stressful or difficult life events [85,106].

Clinical and Experimental Measures

Palpation

Palpation of the to-be exercised biceps brachii occurred in both groups prior to the start of QST, and occurred in the RD Group during Sessions 2-4 before the initiation of DOMS to confirm no lingering pain from the previous DOMS induction.

Thermal and mechanical QST

Thermal pain testing: Study participants completed standard psychophysical pain testing using a contact thermode to deliver evoked, thermal pain stimuli (Medoc Thermal Sensory Analyzer, TSA-2001, Ramat Yishai, Israel). The range of stimulus intensities to be used (40-51°C) were presented beforehand in ascending one-degree steps to each subject. This procedure familiarizes subjects with the stimulus range, tends to obviate range effects in psychophysical scaling, and helps alleviate subject anxiety about the upper limit of stimulus intensities. In order to standardize the scaling instructions and to clarify the distinction between the sensory intensity and affective dimensions of pain, a standardized instructional set was used for all subjects. First pulse response (primarily A-delta fiber mediated function) and second pain (primarily C-fiber mediated function) were assessed. A Numerical Pain Rating Scale (NRS) was

used to record responses to each stimulus. The NRS consisted of a scale whose endpoints are designated as '0 - no pain sensation' and '100 - the most intense pain sensation imaginable.' In order to standardize the scaling instructions, standard instructions were used for all subjects.

Thermal pain threshold and tolerance: A continuous heat stimulus was delivered to the subject's dominant and non-dominant volar forearms. The stimulus started at 35°C and was increased at a rate of 0.5°C per second with subjects terminating the stimulus when the temperature reaches pain threshold ("When the sensation first transitions from heat to pain") and tolerance ("When the sensation becomes so strong you want to remove it from your skin"). The Participant rated the intensity of the stimulus at pain threshold and tolerance using the NRS. These procedures were repeated two times, and averages for threshold and tolerance were calculated.

Ramp and hold: Supra-threshold responses are believed to be representative of A-delta fiber mediated pain sensitivity and these responses were assessed at the dorsal calf via a ramp and hold protocol. The ramp and hold protocol consisted of four heat pulses each lasting five seconds and delivered five seconds from the end of the preceding pulse. Baseline temperature for each heat pulse was 35° C and increased at a rate of 10°C per second to a randomly determined end point of 45°C, 47°C, 49°C, or 51°C. The protocol was repeated twice and NRS ratings were recorded in response to these four temperatures. Average NRS ratings at each temperature were calculated.

Temporal summation of second pain: To assess temporal summation of second pain (TSSP), a train of six heat pulses was applied to the glabrous skin of the

dominant foot. An inter-stimulus interval of 2.5 seconds was used and the temperature of each heat pulse fluctuated from a baseline of 35°C to 48°C during each stimulus. Magnitude of TSSP was calculated as the difference between the last minus the first pulse.

After-sensations: To examine thermal heat after-sensations, participants were asked to rate the magnitude of their pain sensation following the train of six TSSP heat pulses. The participant was cued to rate his or her pain every 15 seconds after the last stimulus in the series of pulses. Ratings were obtained for 60s. These response ratings are known to be primarily C-fiber mediated and associated with endogenous pain modulation [65,67]. Magnitude of after-sensation was calculated as the difference between the first minus the last pulse.

Mechanical pressure testing: Pressure pain threshold was collected using mechanical pressure applied with a Wagner Digital Algometer (Wagner Instruments, Greenwich, CT). The tip of the dolorimeter was equipped with a rubber footplate of 1cm diameter. During pressure testing, force was slowly increased until the subject indicated that the sensation changed from pressure to pain (i.e. pain threshold). The subjects were asked to rate any pain with the same NRS as was described above. Pressure testing occurred at the previously exercised biceps muscle belly, to-be-exercised-that-session biceps muscle belly, bilateral hands (1st dorsal interosseous muscle) and between the first and second toe on the dorsal aspect of bilateral feet. Thresholds and ratings collected from the hand and feet were entered into statistical analyses.

Daily pain measures

RD Group participants were asked to complete the following daily pain ratings beginning the day after Session 1 and continue until their participation in the study is

complete (Session 5). These daily pain measures were used to: 1) Evaluate the pain associated with DOMS following the exercise protocol, and 2) Evaluate the rate of recovery (pain relief) following each session of DOMS. The participant provided these ratings once a day at the same time, prior to bed. The following daily pain measures were collected electronically:

1. Pain Experience*:* Pain experience visual analog scale (PEVAS) is a series of seven 10cm lines. Each line was used to rate a different component DOMS pain experience including depression, anxiety, frustration, fear, anger, unpleasantness, and pain intensity. Each line is anchored at one end with 'None' or 'Not bad at all' and at the other with 'Worst imaginable.' The subject was asked to rate each component by placing a mark along the 10cm line [68].
2. Pain with Movement: The participants also rated pain during elbow extension and elbow flexion using the same scale VAS scale.

These ratings provided measures of both spontaneous pain and pain with movement. The peak value for each week post-DOMS on each rated variable was extracted and entered into subsequent analyses.

Statistical Analyses

Behavioral Ratings

To assess the effects of multiple bouts of DOMS on psychophysical variables, separate 2 x 2 ANOVAs were conducted for each pressure and thermal sensory measure to evaluate changes in pain sensitivity (Estimates were averaged for those collected at the right and left side of the body, e.g., right and left thermal pain threshold temperature were averaged). Session (Baseline vs. follow up) served as the within-subjects factor and Group (RD Group vs. Control Group) served as the between-subjects factor. For ramp and hold data, an additional within-subjects factor, temperature (45°C, 47°C, 49°C, and 51°C), was included for a 2 x 2 x 4 ANOVA.

Difference scores were calculated (Follow up minus baseline) for use in subsequent correlational analyses (See below). Measures assessed are listed in Table 2-1.

In the RD Group, paired samples t-tests were conducted to assess changes from baseline to follow up in peak post-DOMS daily ratings. Variables assessed included pain intensity, pain unpleasantness, pain with elbow extension, and pain with elbow flexion, anxiety, depression, anger, fear, and frustration. Difference scores were calculated for each measure (Follow up minus baseline) and entered subsequent correlational analyses (See below).

Image Processing and Analyses

fMRI data processing

SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) was used to preprocess fMRI data. Steps of preprocessing included slice-time correction, realignment, coregistration of the structural image to the mean functional image, normalization to the standard Montreal Neurological Institute ($2mm^3$) template, and spatial smoothing at $8mm^3$ full width at half maximum (FWHM). The Artifact Detection Tool (ART) toolbox (http://www.nitrc.org/projects/artifact_detect) was used to detect motion and signal artifacts. Time points in which the global signal exceeded +/-3 standard deviations from the mean of the previous image, or translation exceeded 0.5 mm, or rotation exceeded 0.02 radians from the previous image were identified as outliers. Outliers and rigid-body motion parameters calculated in the realignment step were included in denoising (See below).

Additional processing was completed with the CONN toolbox [103], which performs component-based noise correction for physiological and other noise source reduction. Temporal filtering is commonly used to remove effects of low and high

frequency oscillations (e.g. scanner drift, head motion, heart rate, respiration rate). Within pain neuroimaging, several studies explored infraslow oscillations, as low as 0.005 Hz [2,8], and identified unique aspects of pain processing. One such study identified regional signal variability and connectivity related to resilient pain modulatory system adaptation [74]. Therefore, a temporal (band-pass) filter was applied to the functional data, and set between 0.005 and 0.05 Hz. Removal of nonspecific variance was also performed with regression. Nuisance variables included: 1) The average signal over the lateral ventricles, 2) The average signal over the deep cerebral white matter, 3) The 6 parameters of translation and rotation and their first order derivative, and 4) the outlier data points identified with the ART toolbox.

Functional connectivity analyses

Connectivity analyses were performed using the CONN toolbox [103]. To further control for the effects of motion and signal confounds in resting-state data [63,64], second-level covariates of-no-interest were included to remove the effects of total number of outlier scans across visits, and the average value across all time points and dimensions of head motion and outlier parameters. Connectivity estimates were extracted controlling for these factors in correlational analyses.

ROI-ROI functional connectivity: For each subject, first-level ROI-to-ROI analyses were performed to assess BOLD signal correlation with respect to time among the NAc and mPFC at baseline and follow up. ROIs were generated as 10mm spheres around coordinates previously specified in studies of pain adaptation and modulation, NAc: 10, 12, -8; mPFC: 2, 52 [10,108]. The resulting correlation coefficients were converted to *Z*-scores using Fisher's r-to-*Z* transformation for subsequent second-level comparisons.

A second-level 2x2 mixed between-within-subjects ANOVA (Between-subjects factors: RD group and Control Group; within-subjects factors: baseline and follow up) was used to identify group differences in coherence changes from baseline to follow up. Analyses were performed to identify a group-by-time interaction: (Between-subjects contrast: RD Group, Control Group [1 -1]; within-subjects contrast: Follow Up, Baseline [1 -1]; between source contrast: mPFC [1]; Target: NAc). It was hypothesized that a significant group-by-time interaction would be discovered such the RD Group would display significantly greater reductions in NAc-mPFC connectivity than the Control Group.

Sensorimotor network group independent components analysis: Group-level independent component analysis (ICA) was performed to assess SMN connectivity at baseline and follow. ICA is a data-driven statistical analysis technique that yields components, or distinct sources of variance that are orthogonal in time course between components and correlated with spontaneous fluctuations in regions within each component. ICA involved the following steps in accordance with the method described by Calhoun, et al. (2001): 1) Temporal concatenation of functional volumes across subject and condition, 2) Group-level dimensionality reduction via principle components analysis 3) Identification of spatial-independent components via the fastICA algorithm, and 4) Backprojection of these components to individual subjects by dual regression (univariate spatial regression and multivariate temporal regression). This procedure results in maps of regression coefficients that represent functional connectivity between the IC network and every whole-brain voxel. 20 unique components were identified.

To assess SMN functional connectivity, the IC that best correlated with an SMN template across combined groups and sessions was identified. This IC was used in subsequent comparisons. The template of the SMN as documented by Riedl, et al. (2011) was used. A mask was defined using WFU PickAtlas [55], and it comprised of the SI, SII, and the supplementary motor area [24,88] from the AAL Atlas [96]. Subject-level SMN ICs were entered into a second-level general linear model (GLM) to compare the spatial extent and coherence of the SMN between baseline and follow up across groups (Between-subjects contrast: RD Group, Control Group [1 -1]; within-subjects contrast: Follow Up, Baseline [1 -1]; between source contrast: SMN IC [1]). Analyses were initially restricted to a mask of the vmPFC, defined as a 10mm sphere around MNI coordinates 0, 42, -18 ($p < 0.001$, uncorrected). This region was shown to display greater connectivity with the SMN following repeated exposure to painful stimuli [72]. Whole-brain analyses were then conducted to identify additional significant clusters ($p_{height} < 0.001$, uncorrected; $p_{cluster} < 0.05$, FDR; [107]. Mean values from significant clusters were then extracted for subsequent correlational analyses.

sgACC seed-to-voxel functional connectivity: First-level analyses were performed to assess connectivity among the sgACC and voxels of the whole brain. sgACC sub-regions identified in previous studies of habituation and pain modulation [12,15] were used, and specified as 10mm spheres around MNI coordinates 3, 36, -12, and -6, 30, -9. GLM was used to examine significant BOLD signal correlation with respect to time between ROIs and the whole brain. The resulting correlation coefficients were converted to *Z*-scores using Fisher's r-to-*Z* transformation. Subject-level maps then were entered into a second-level GLM to compare sgACC-whole brain connectivity

between groups and across sessions (Between-subjects contrast: RD Group, Control Group [1 -1]; within-subjects contrast: Follow Up, Baseline [1 -1]; between source contrast (for each ROI): sgACC ROI [1]). Analyses were initially restricted to areas in one of two masks. The first mask consisted of areas involved in ascending pain processing including the thalamus, insula, SI/SII, and the anterior cingulate cortex (ACC). Regions identified with the Harvard-Oxford Atlas [28,35,41,54,74]. The second mask consisted of areas involved in anti-nociception including the PAG (6mm sphere around 0, -32, -10) and rostroventral medulla (RVM; 2mm sphere around 0, -34, -50; Rogachov et al., 2016). Finally, whole-brain analyses conducted to identify additional significant clusters ($p_{height} < 0.001$, uncorrected; $p_{cluster} < 0.05$, FDR [107]). Mean values from significant clusters were then extracted for subsequent correlational analyses.

Association among Neural And Psychophysical Adaptation

Metrics of pain adaptation were calculated as the difference score of pressure and thermal QST metrics at baseline and follow up. For ramp and hold pain ratings, the difference in slope and intercept for each subject across stimuli temperatures (45°C, 47°C, 49°C, and 51°C) across sessions was calculated. Change from baseline to follow up in RD Group, peak post-DOMS VAS ratings (e.g. maximum rating in the week following each DOMS induction) was calculated. Differences scores in estimates of NAc-mPFC connectivity, and mean values from clusters displaying significant changes in SMN and sgACC connectivity were calculated. Bivariate correlations between change in psychophysical and neural adaptation were performed ($p = 0.05$). It was hypothesized that individuals who display greater neural adaptation would also display greater adaptation in QST metrics.

Influence of Psychosocial Factors on Neural Adaptability

Separate multiple linear regressions were conducted with BRS and PCS scores taken at Session 1 as predictors of each difference score from baseline to follow up for NAc-mPFC, and SMN and sgACC functional connectivity estimates. It was hypothesized that BRS scores would significantly predict change in NAc-mPFC and SMN connectivities, while PCS scores would significantly predict change in sgACC connectivity.

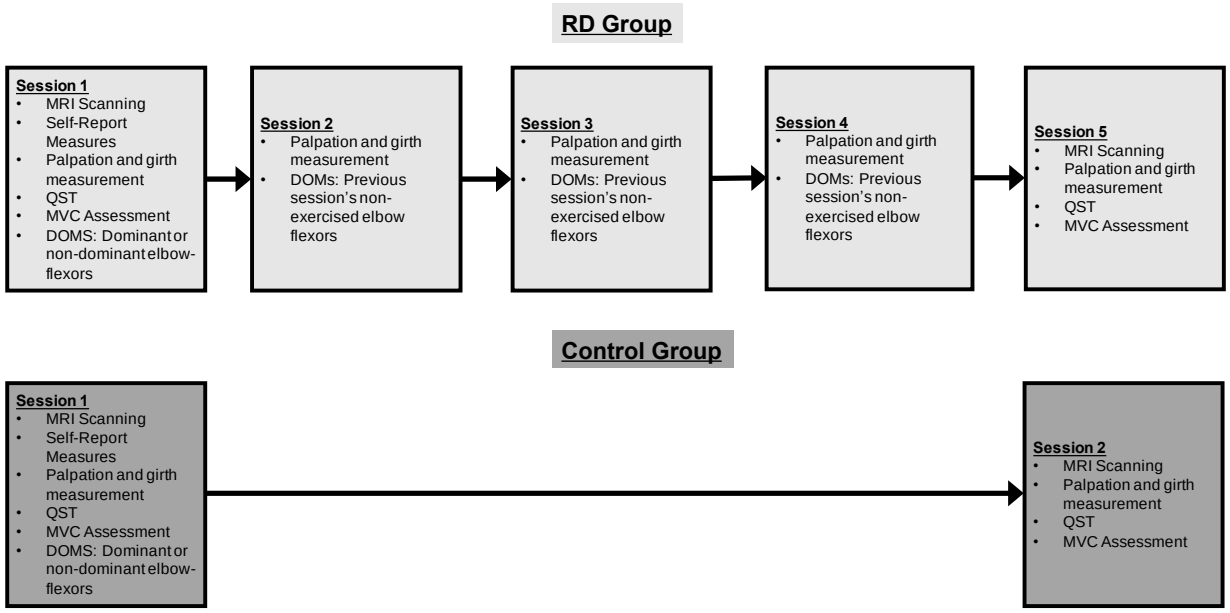

Figure 2-1. Study Design. Subjects were randomized into one of two groups (RD Group or Control Group) in which they completed a total of either five or two sessions.

Figure 2-2. Biodex setup for isometric strength and DOMS.

Table 2-1. QST Measures Assessed at Baseline and Follow Up

Modality	Measure	Site of Body
Thermal	Temperature at Threshold	Volar Forearm
	Rating at Threshold	Volar Forearm
	Temperature at Tolerance	Volar Forearm
	Rating at Tolerance	Volar Forearm
	Ramp and Hold	Dorsal Calf
	Temporal Summation of Second Pain	Foot
	After Sensations	Foot
Mechanical	Pressure at Threshold	Hand
	Rating at Threshold	Hand
	Pressure at Threshold	Foot
	Rating at Threshold	Foot

CHAPTER 3
RESULTS

Participant Characteristics

23 subjects (17 female) completed the study (RD Group N = 12). The mean age of the sample was 32.52 (SD = 17.11). There were no significant differences in age or sex between groups. 17 participants identified as White/Caucasian, four as Asian, one as Black/African American, and one as Other Race/Multiple Races. Two identified as Hispanic or Latino.

Quantitative Sensory Testing, Behavioral Ratings and Psychosocial Variables

Descriptive statistics for QST variables are listed by group and session in Table 3-1. Peak-post DOMS daily rating descriptive statistics are listed in Table 3-2. Separate 2-by-2 ANOVAs were performed for each QST measure to assess changes in pain processing across time and between groups.

QST Adaptation

For rating at thermal pain threshold, results revealed a significant group-by-time interaction ($F_{1,21} = 4.27$, $p = 0.05$, $\eta^2_p = 0.17$, Figure 3-1), in which the RD Group displayed a greater decrease in ratings at thermal pain threshold from baseline to follow up than that of the Control Group. For temperature at thermal pain threshold, results approached a significant group-by-time interaction ($F_{1,21} = 3.94$, $p = 0.06$, $\eta^2_p = 0.16$, Figure 3-2), suggesting that the RD Group displayed a greater increase in the temperature needed to achieve thermal pain threshold than that of the Control Group. Analyses performed for thermal pain temperature at tolerance displayed a significant

effect of time ($F_{1,21}$ = 5.91, p = 0.02, η^2_p = 0.22). In both groups, there was a significant increase in temperature needed to achieve thermal pain tolerance.

Ramp and hold data for one Control Group subject was lost to collection error. As a result, the following analyses were completed with data for the 22 remaining subjects. Analyses identified a significant main effect for time ($F_{1,20}$ = 18.95, p = 0.000, η^2_p = 0.49), which indicated a significant decrease in ratings from baseline to follow up. A significant main effect of temperature ($F_{3,18}$ = 79.71, p = 0.000, η^2_p = 0.80) was also identified, which showed an increase in ratings to higher temperatures . These main effects were modified by a temperature-by-time interaction ($F_{3,18}$ = 6.62, p = 0.001, η^2_p = 0.25), which indicated that greater decreases in pain ratings over time were observed for lower ramp and hold stimulus temperatures (Figure 3-3). The effects of group, group-by-time, group x temperature, and the three-way interaction did not reach statistical significance.

Among the additional QST measures collected, there were no significant effects or group, time, or group-by-time interactions.

Post-DOMS Daily Ratings

Within-subjects t-tests were performed to assess changes in peak, post-DOMS daily ratings following the first and final DOMS inductions. Across time points, there were significant decreases in ratings of pain intensity (mean difference = 7.33, T_{11} = 3.35, p = 0.006, d = 2.02), pain unpleasantness (mean difference = 7.50, T_{11} = 3.00, p = 0.012, d = 1.81), pain with elbow flexion (mean difference = 7.42, T_{11} = 2.59, p = 0.025), and pain with elbow extension (mean difference = 14.00, T_{11} = 3.68, p = 0.004, d = 1.56). No significant differences across time were found for the other daily ratings

collected; however, the mean differences for depression (mean difference = 5.98, T_{11} = 1.88, p = 0.086, d = 1.13), anxiety (mean difference = 11.42 T_{11} = 2.14, p = 0.056, d = 1.29), and fear (mean difference = 3.58 T_{11} = 2.07, p = 0.063, d = 1.25) approached statistical significance.

For all QST and behavioral ratings, differences scores from baseline to follow up were extracted and entered into subsequent correlational analyses to identify associations with neural adaptation.

Functional Connectivity Analyses

NAc-mPFC Connectivity

Region of interest (ROI)-to-ROI analyses were performed to identify differences in connectivity among the mPFC and NAc from baseline to follow up between groups (Figure 3-4). Regional time-series correlations were transformed to Z scores via the Fisher transformation prior to comparisons. Results revealed a significant group-by-time interaction ($F_{1,19}$ = 5.19, p = 0.03, η^2_p= 0.22), in which the RD group displayed a greater reduction than the Control Group in NAc-mPFC connectivity from baseline to follow up (Figure 3-5). Only the RD Group displayed significant adaptation among these regions.

Sensorimotor Network Independent Components Analysis

The component that provided the closest spatial match to the SMN template (Figure 3-6) was compared between time points and across groups. As discussed above, analyses were initially restricted to an *a priori* mask of the vmPFC identified by Riedl, et al. (2011), and then followed by whole-brain analyses to identify additional significant clusters. When restricted to the vmPFC mask, one voxel survived threshold. In subsequent, planned whole-brain analyses, this voxel was found to be part of a unique cluster within the vmPFC and was interpreted as part of that cluster.

Whole-brain results revealed significant group-by-time interactions in three prefrontal regions (Figure 3-7). The RD group displayed greater increases connectivity among the SMN and two clusters, the left dorsomedial prefrontal cortex (dmPFC; -22, 24, 46, k = 70, $F_{1,19}$ = 47.36, p = 0.000, η^2 = 0.714, Figure 3-8) and the right ventromedial prefrontal/medial orbitofrontal cortex (vmPFC; 6, 54, 26, k = 50, $F_{1,19}$ = 65.73, p = 0.000, η^2_p = 0.77, Figure 3-9). The RD group displayed a significantly greater decrease in connectivity than the Control group in one cluster of the rostromedial prefrontal cortex (rmPFC; 6, 58, 32; k = 39, $F_{1,19}$ = 39.28, p = 0.000, η^2_p = 0.67, Figure 3-10). Overall, participants who experienced repeated bouts of DOMS displayed greater connectivity among the SMN and the dmPFC and vmPFC, and lesser connectivity among the SMN and rmPFC, suggestive of novel, neural adaptation.

sgACC Seed-to-Voxel Connectivity

Functional connectivity was assessed among two sgACC regions of interest and the whole brain in both groups at baseline and follow up. Maps of sgACC connectivity were compared between time points and across groups to determine the effect of repeated bouts of DOMS. Analyses were initially restricted to two masks, one of regions involved in ascending pain processing [SI, SII, bilateral insula, thalamus, ACC and mid-cingulate cortex (MCC)] and another of regions involved in anti-nociception including (PAG and RVM). Whole-brain analyses were then performed to identify additional significant clusters. Across masked and whole-brain analyses no statistically significant clusters were identified.

Association among Neural Adaptation and Quantitative Sensory Testing

Bivariate correlations were performed to assess associations among neural and psychophysical adaptation. Given that some metrics displayed significant effect across groups (ramp and hold, and temperature at thermal pain tolerance) and others displayed significant group-x-time interactions (rating at thermal pain threshold, and connectivity estimates), correlational analyses were performed separately for each group (Tables 3-3 and 3-4). As literature suggests baseline NAc-mPFC connectivity may be predictive of adaptation to pain episodes [10], baseline NAc-mPFC connectivity was also included in these analyses along with differences scores for NAc-mPFC, dmPFC-SMN, vmPFC-SMN, and rmPFC-SMN connectivity.

Results revealed significant associations among baseline NAc-mPFC connectivity and change in rating at foot pressure pain threshold ($r = -0.62$, $p = 0.03$) in the RD Group, and change in thermal pain tolerance temperature ($r = -0.73$, $p = 0.01$), and ramp and hold slope ($r = -0.76$, $p = 0.01$) and intercept ($r = -0.78$, $p = 0.008$) in the Control Group. These findings indicate that individuals in the RD Group who displayed greater connectivity NAc-mPFC connectivity at baseline exhibited greater decreases in foot pressure pain threshold ratings, while individuals in the Control Group who had lower connectivity values at baseline exhibited greater increases in ramp and hold slope and intercept. In the Control Group, the only significant association among change in neural adaptation and QST metrics was observed among change in rmPFC-SMN connectivity and thermal pain tolerance temperature ($r = 0.60$, $p = 0.05$), suggesting that greater increases in rmPFC-SMN connectivity were associated with increases in temperature at thermal pain tolerance.

In the RD Group, a number of associations among neural and QST adaptation were observed. Individuals who displayed greater increases in dmPFC-SMN connectivity showed greater increases in temperature at thermal pain threshold (r = 0.58, *p* = 0.05). Across sessions, greater increases in vmPFC-SMN connectivity were also associated with increases in thermal pain threshold temperature (r = 0.61, *p* = 0.04) and rating (r = 0.70, *p* = 0.01). The association among change in NAc-mPFC connectivity and change in ramp and hold slope approached statistical significance (r = -0.57, *p* = 0.055), suggesting that individuals who displayed greater decreases in NAc-mPFC connectivity displayed greater increases in ramp and hold slope.

Association among Neural Adaptation and Post-DOMS Ratings

Associations among changes in functional connectivity and changes peak post-DOMS daily ratings were assessed. Bivariate correlations were performed among RD Group functional connectivity difference scores (i.e. NAc-mPFC, dmPFC-SMN, vmPFC-SMN, and rmPFC-SMN) and peak post-DOMS daily rating difference scores from baseline to follow up (Table 3-5). Results indicated that there were negative associations among changes in dmPFC-SMN connectivity and peak depression (r = -0.59, *p* = 0.05), frustration (r = -0.60, *p* = 0.04), and anger (r = -0.59, *p* = 0.04), suggesting that those who exhibited greater alterations in dmPFC-SMN connectivity exhibited greater reductions in peak depression, frustration, and anger. Change in vmPFC-SMN connectivity corresponded with change in peak anxiety (r = -0.64, *p* = 0.02), indicating that greater increases in vmPFC-SMN connectivity were associated with greater decreases in anxiety. Finally, there were positive associations among change in rmPFC-SMN connectivity and change in peak depression (r = 0.61, *p* = 0.03), frustration (r = 0.59, *p* = 0.04), and anger (r = 0.65 *p* = 0.02). Given the significant

decrease in RD Group rmPFC-SMN connectivity, these results likely indicate that individuals who displayed greater reductions in rmPFC-SMN connectivity also displayed greater reductions in depression, frustration, and anger. No significant associations among changes in functional connectivity and changes in peak post-DOMS pain ratings (intensity, unpleasantness, extension, and flexion) were observed.

Association between Psychosocial Factors and Neural Adaptation

To assess the influence of baseline psychosocial variables on subsequent neural adaptation in the RD Group, separate multiple regressions were performed with BRS, a measure of general resilience, and PCS, a measure of pain-related catastrophic thinking, scores as predictors of the change separately for NAc-mPFC, dmPFC-SMN, vmPFC-SMN, and rmPFC-SMN connectivity. BRS and PCS scores were predictive of a significant portion of variance of change in rmPFC-SMN connectivity ($R^2 = 0.50$, $R^2_{adjusted} = 0.39$, $F_{2,11} = 4.55$, $p = 0.04$). BRS scores were the only predictor with a regression coefficient significantly different from zero (BRS: $b = -0.79$, $\beta = -0.73$, $t_{11} = -2.60$, $p = 0.03$; PCS: $b = -0.05$, $\beta = -0.03$, $t_{11} = -0.12$, $p = 0.91$). No other statistically significant regression models were found.

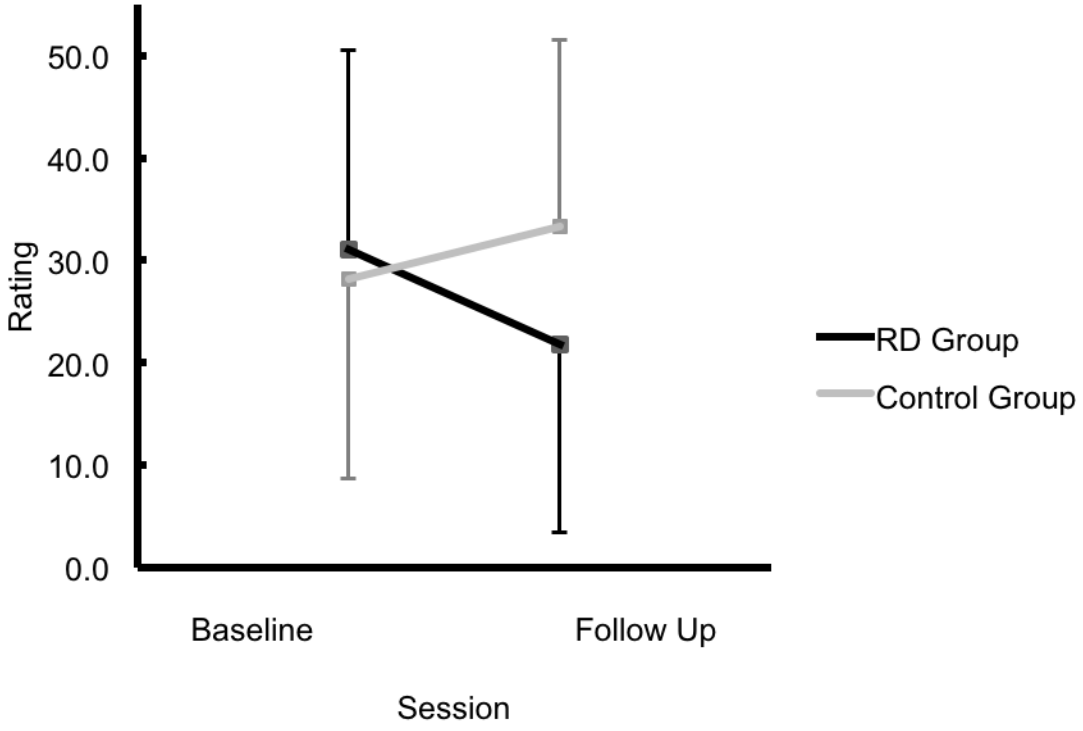

Figure 3-1. Means for rating at thermal pain threshold for each group and across sessions. Results displayed a group-by-time interaction ($F_{1,21} = 4.27$, $p = 0.05$, $\eta^2_{partial} = 0.17$), in which the RD Group displayed a greater decrease in ratings than did the Control Group. Error bars represent one standard deviation and, to improve clarity, are depicted uni-directionally when error bars from both lines intersect.

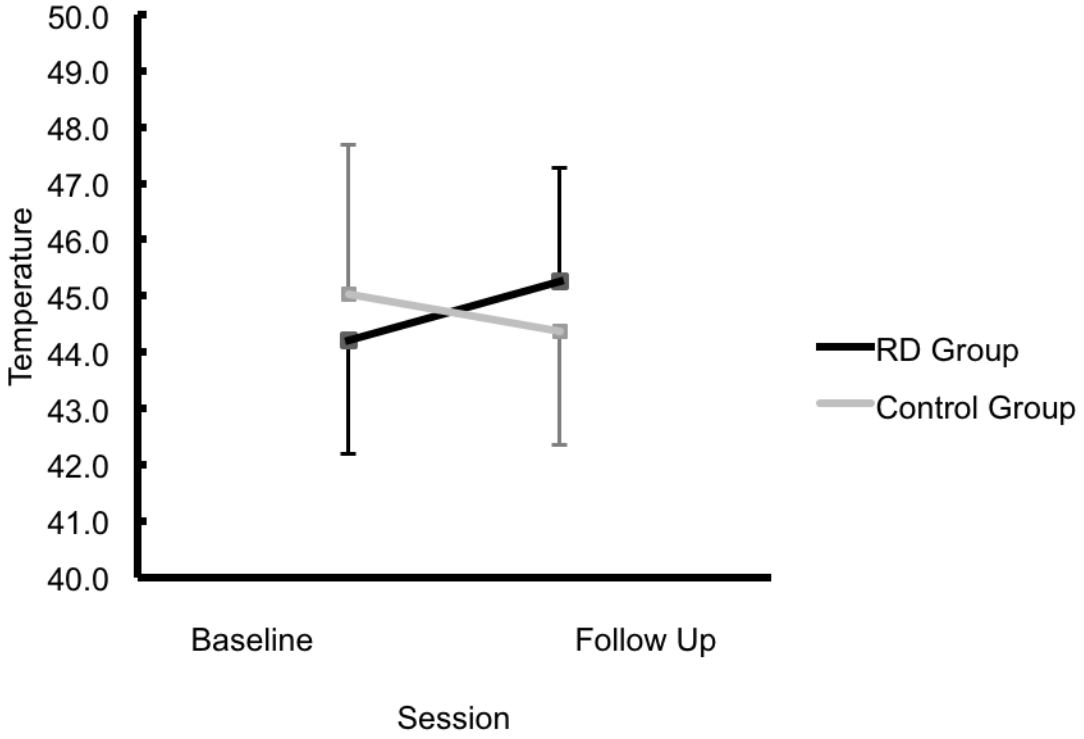

Figure 3-2. Means for temperature at thermal pain threshold for each group and across sessions. Results displayed a group-by-time interaction that approached statistical significance ($F_{1,21} = 3.94$, $p = 0.06$, $\eta^2_{partial} = 0.16$). Error bars represent one standard deviation and, to improve clarity, are depicted uni-directionally when error bars from both lines intersect.

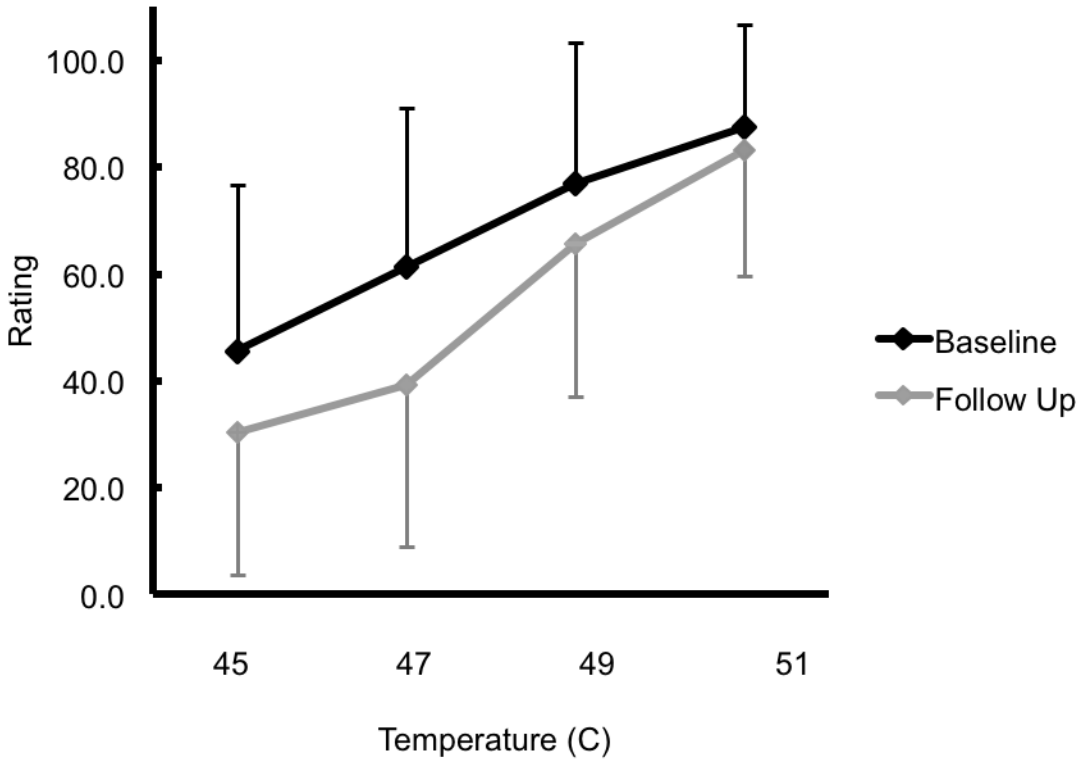

Figure 3-3. Means for ratings across ramp and hold temperatures at baseline and follow up. Results displayed a temperature x time interaction ($F_{3,18} = 6.62$, $p = 0.001$, $\eta^2_{partial} = 0.25$) in which there was a greater decrease in ratings at lower temperatures across sessions. Error bars represent one standard deviation and, to improve clarity, are depicted uni-directionally when error bars from both lines intersect.

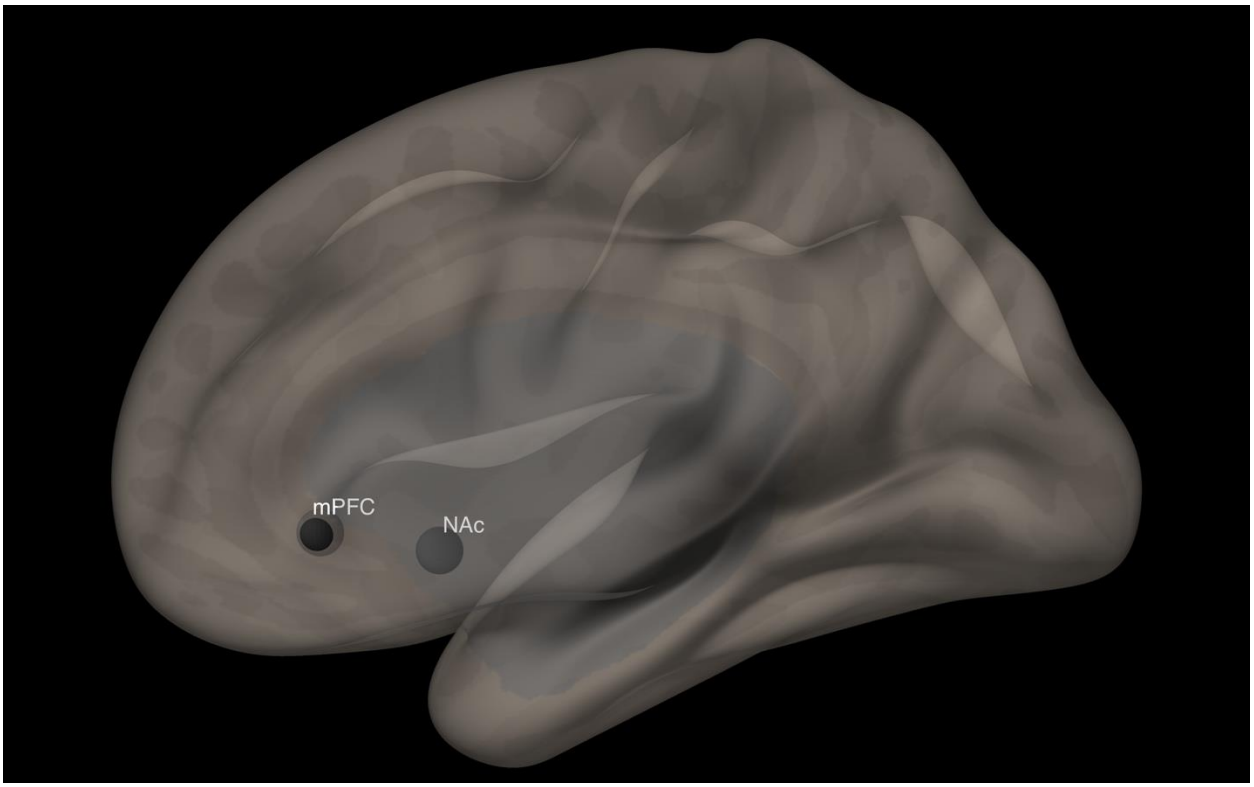

Figure 3-4. mPFC and NAc ROI locations are depicted in right medial view.

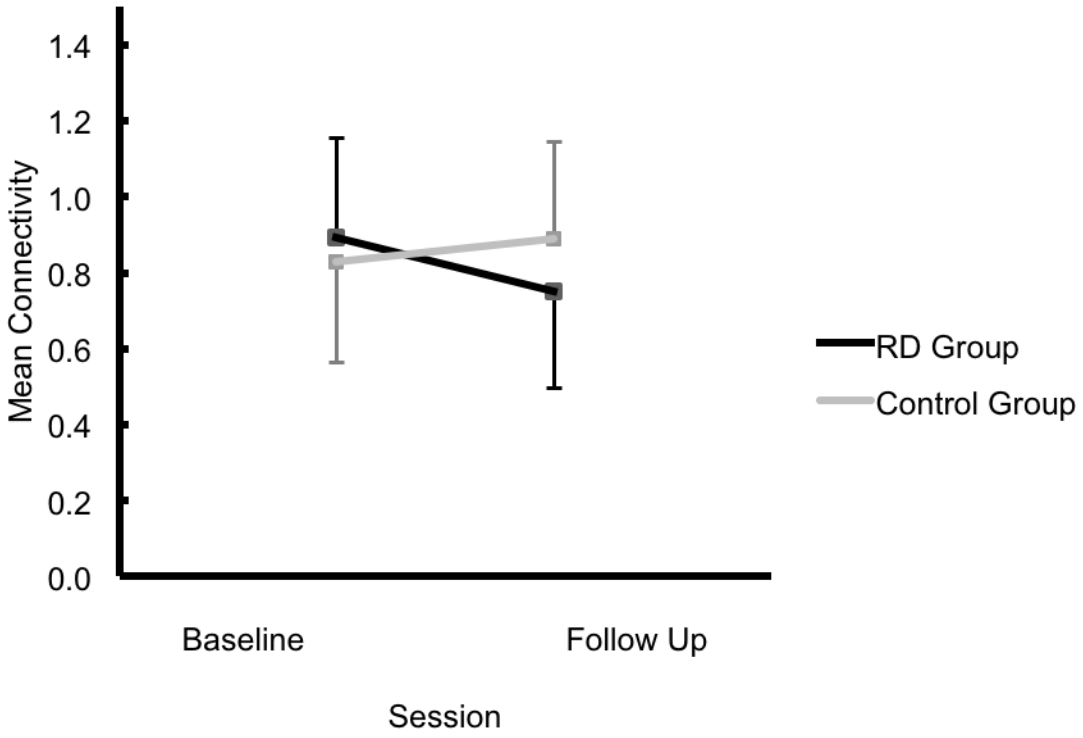

Figure 3-5. Mean NAc-mPFC connectivity values for each group and across sessions. Results displayed a group-by-time interaction in which the RD Group displayed a greater decrease in connectivity than the Control Group ($F_{1,19} = 5.19$, $p = 0.03$, $\eta^2_{partial} = 0.22$). Error bars represent one standard deviation and, to improve clarity, are depicted uni-directionally when error bars from both lines intersect.

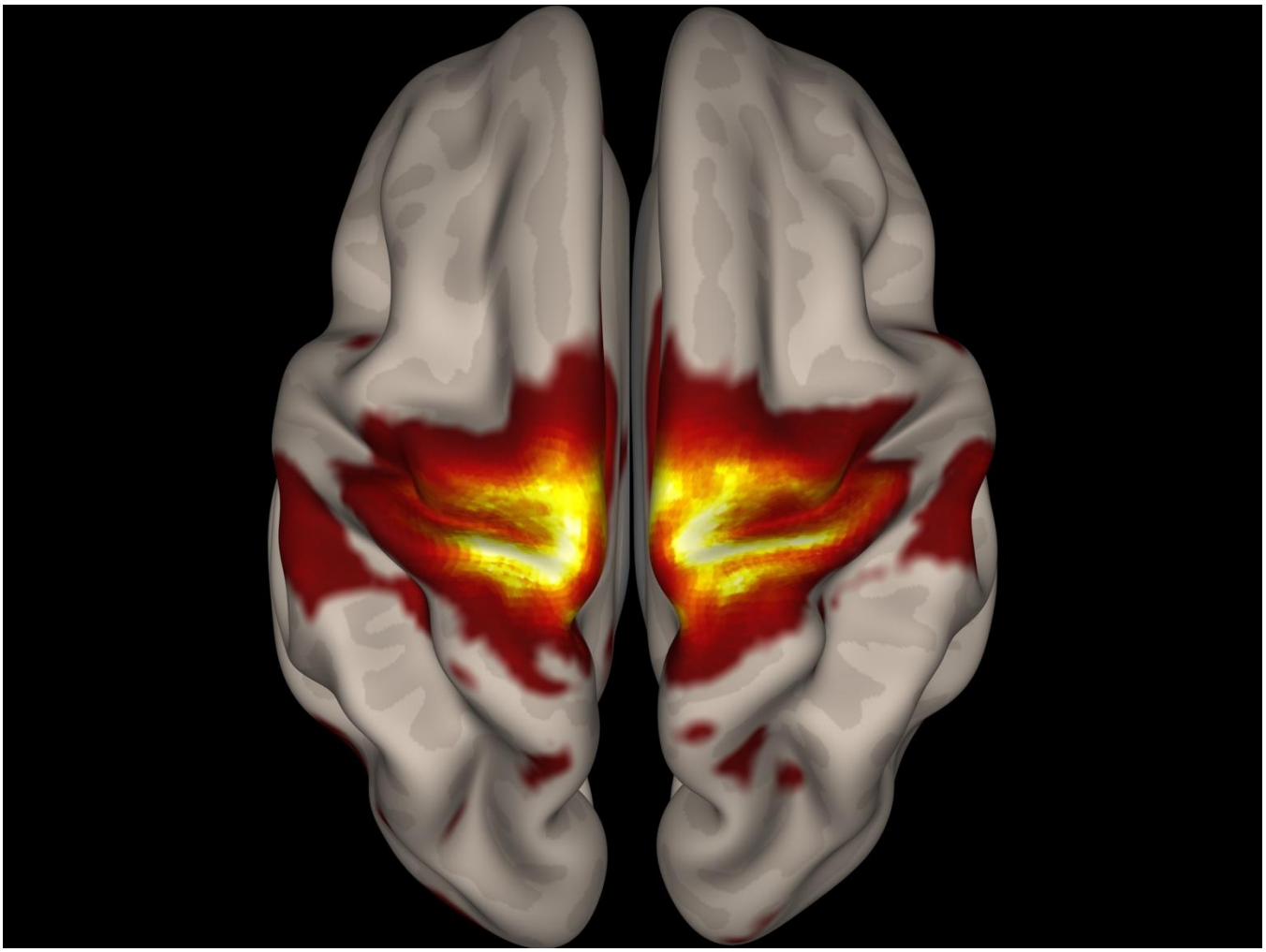

Figure 3-6. Superior view of the independent component that provided the highest spatial match to the sensorimotor network template.

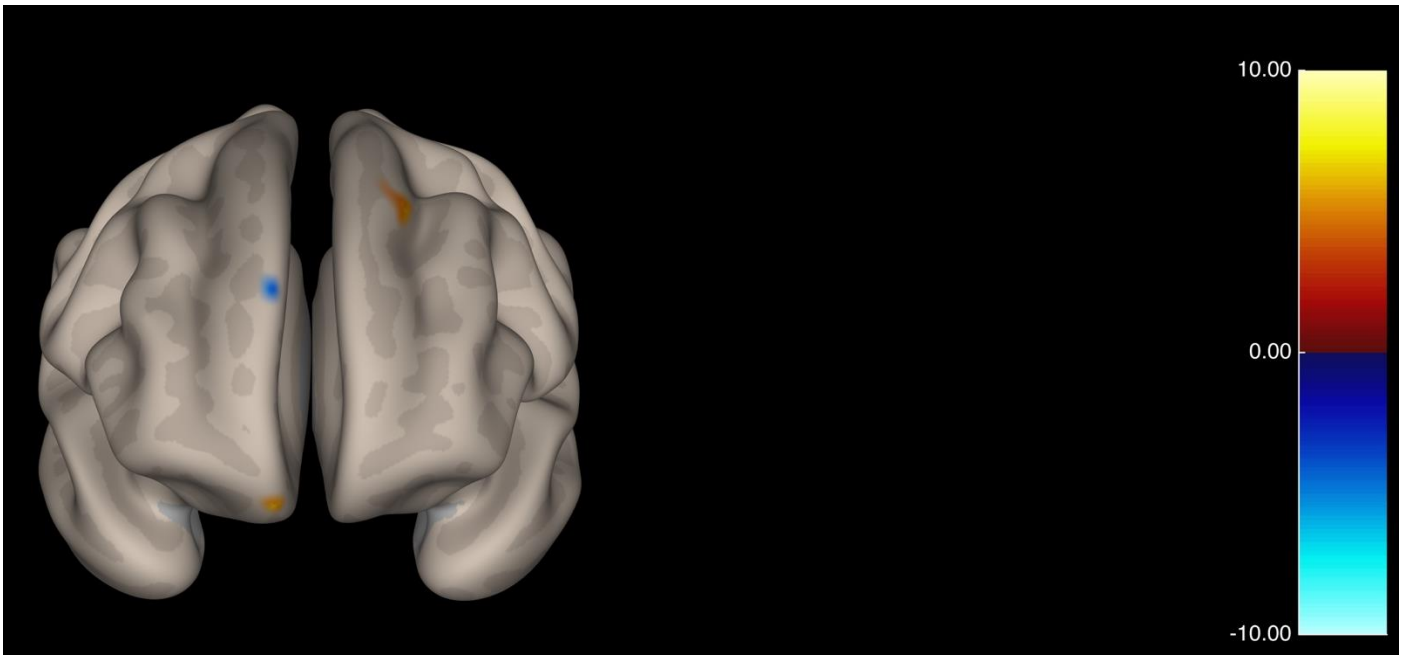

Figure 3-7. Anterior view clusters that are functionally connected to the SMN in which a significant group-by-time interaction was found. Results indicated that the RD Group displayed greater increases in functional connectivity with the SMN than the Control Group in the right dmPFC and left vmPFC, and displayed greater decreases than the Control Group among the left rmPFC and SMN.

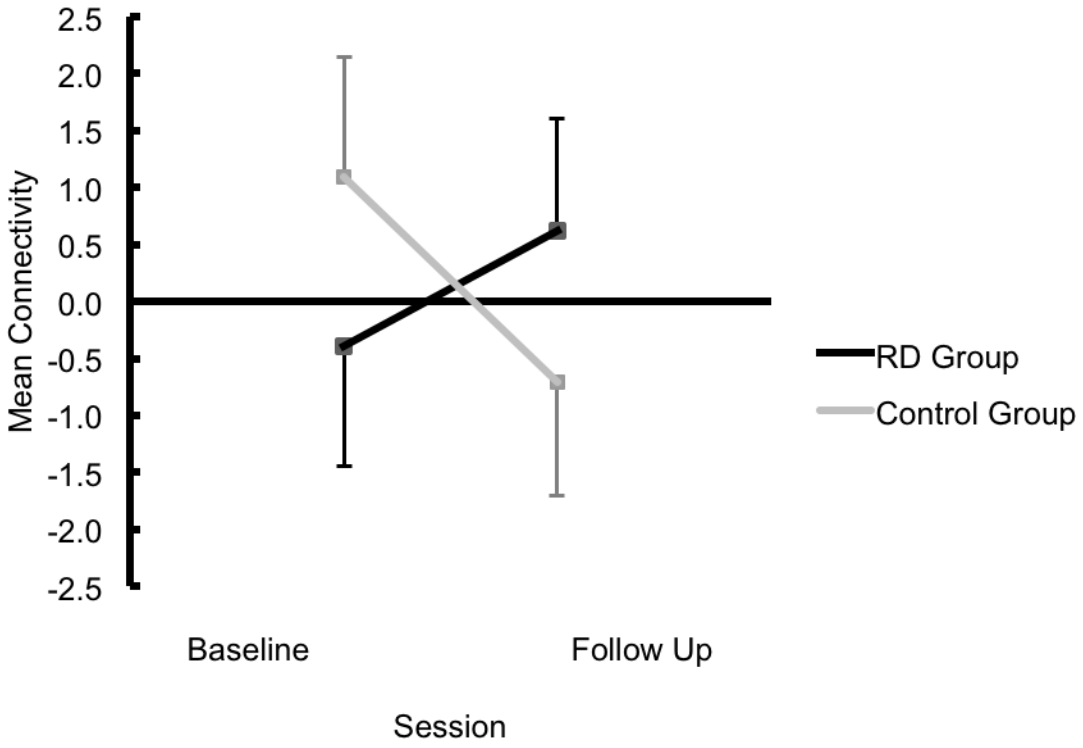

Figure 3-8. Mean dmPFC-SMN connectivity values for each group and across sessions. Results displayed a group-by-time interaction in which the RD Group displayed a greater increase in connectivity than did the Control Group ($F_{1,19} = 47.36$, $p = 0.000$, $\eta^2_{partial} = 0.714$). Error bars represent one standard deviation and, to improve clarity, are depicted uni-directionally when error bars from both lines intersect.

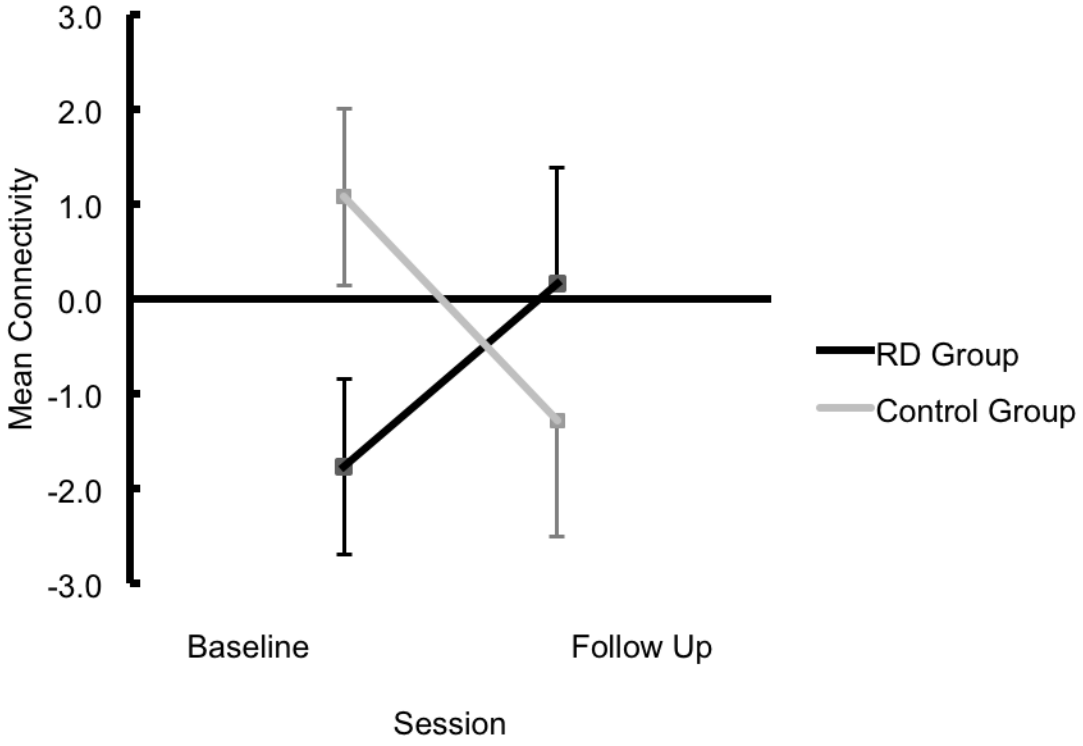

Figure 3-9. Mean vmPFC-SMN connectivity values for each group and across sessions. Results displayed a group-by-time interaction in which the RD Group displayed a greater increase in connectivity than did the Control Group ($F_{1,19}$ = 65.73, p = 0.000, $\eta^2_{partial}$ = 0.77). Error bars represent one standard deviation and, to improve clarity, are depicted uni-directionally when error bars from both lines intersect.

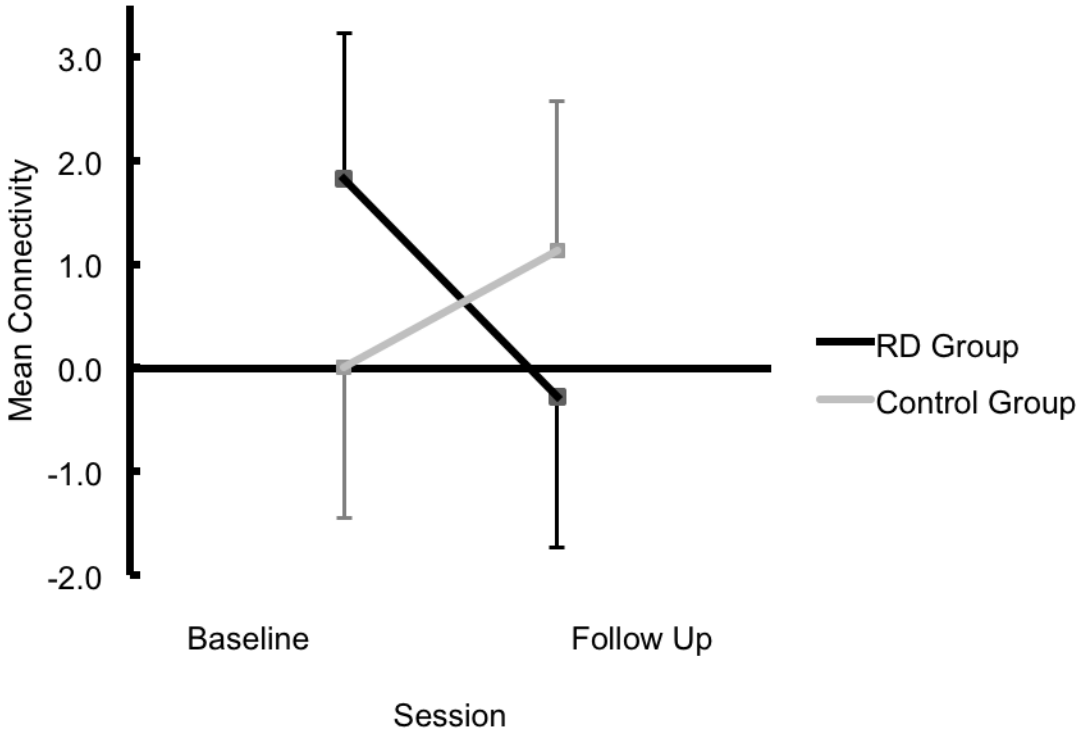

Figure 3-10. Mean rmPFC-SMN connectivity values for each group and across sessions. Results displayed a group-by-time interaction in which the RD Group displayed a greater decrease in connectivity than did the Control Group ($F_{1,19} = 39.28$, $p = 0.000$, $\eta^2_{partial} = 0.67$). Error bars represent one standard deviation and, to improve clarity are depicted uni-directionally when error bars from both lines intersect.

Table 3-1. Quantitative Sensory Testing Descriptive Statistics

				RD Group		Control Group	
Modality	Measure	Site	Session	Mean	SD	Mean	SD
Thermal	Threshold Temp.	Forearm	Baseline	44.21	2.64	45.03	2.70
			Follow Up	45.26	2.14	44.37	1.88
	Threshold Rating		Baseline	31.04	17.50	28.18	21.52
			Follow Up	21.83	16.19	33.27	20.39
	Tolerance Temp.		Baseline	47.67	1.70	47.73	2.10
			Follow Up	48.21	1.38	48.30	1.47
	Tolerance Rating		Baseline	76.54	15.86	64.05	23.58
			Follow Up	83.50	10.20	71.25	22.23
	R&H 45°C	Calf	Baseline	48.33	24.67	39.77	34.43
			Follow Up	25.00	19.77	35.85	32.50
	R&H 47°C		Baseline	64.50	26.39	53.55	33.58
			Follow Up	37.96	26.31	41.10	34.76
	R&H 49°C		Baseline	79.38	21.80	68.41	33.25
			Follow Up	61.75	25.19	69.65	30.06
	R&H 51°C		Baseline	89.58	16.47	79.55	27.01
			Follow Up	85.33	19.87	81.00	25.34
	TSSP	Foot	Baseline	5.92	19.71	-2.45	19.35
			Follow Up	12.00	22.55	-1.70	19.94
	After Sensation		Baseline	13.00	13.43	6.82	11.02
			Follow Up	6.50	7.78	7.40	11.11
Mechanical	Threshold Pressure	Hand	Baseline	3.43	1.37	3.49	1.38
			Follow Up	4.08	1.69	3.50	1.32
	Threshold Rating		Baseline	25.65	16.61	28.39	17.16
			Follow Up	23.02	16.33	33.59	21.22
	Threshold Pressure	Foot	Baseline	3.76	1.76	3.18	1.38
			Follow Up	3.92	1.21	3.14	1.15
	Threshold Rating		Baseline	24.67	18.64	28.32	17.84
			Follow Up	22.63	15.88	33.25	22.20

Abbreviations: TSSP, temporal summation of second pain; SD, standard deviation; R&H, ramp and hold; Temp. temperature.

Table 3-2. Peak Post-DOMS Daily Rating Descriptive Statistics

Rating	Post-DOMS Induction	Mean	SD
Depression	1	16.00	16.93
	4	6.42	7.22
Anxiety	1	20.00	17.85
	4	8.58	7.72
Frustration	1	18.25	18.67
	4	10.75	10.58
Fear	1	10.50	9.73
	4	6.92	8.58
Anger	1	15.17	19.64
	4	6.50	6.26
Pain Intensity	1	18.42	17.00
	4	11.00	11.32
Pain Unpleasantness	1	16.83	13.56
	4	9.42	10.94
Pain with Flexion	1	19.67	16.68
	4	12.25	18.99
Pain with Extension	1	26.83	19.21
	4	13.00	19.12

Note: Daily ratings were assessed in the week following each DOMS induction. Peak rating descriptive statistics for each measure following the first and final DOMS induction are displayed. Abbreviations: DOMS, delayed onset muscle soreness; SD, standard deviation.

Table 3-3. RD Group Correlations among Neural and QST Adaptation

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	NAc-mPFC															
2	dmPFC-SMN	0.05														
3	vmPFC-SMN	0.17	0.50													
4	rmPFC-SMN	-0.06	-0.25	-0.15												
5	Thermal Thresh. Temp.	0.01	0.58*	0.61*	-0.16											
6	Thermal Thresh. Rating	0.21	0.21	0.70*	-0.08	0.31										
7	Thermal Tol. Temp.	-0.23	0.43	0.10	0.16	0.43	0.18									
8	Thermal Tol. Rating	-0.04	-0.24	-0.25	-0.13	-0.16	0.29	0.17								
9	Mech. Thresh. Hand	0.13	0.06	0.21	0.01	-0.08	-0.18	-0.21	-0.45							
10	Mech. Thresh. Hand Rating	-0.13	0.10	0.21	0.52	0.00	-0.06	0.39	-0.37	0.00						
11	Mech. Thresh. Foot	-0.14	-0.03	0.30	0.35	0.15	-0.11	-0.19	-0.39	.74**	0.18					
12	Mech. Thresh. Foot Rating	0.11	-0.09	-0.04	0.49	0.22	-0.05	0.17	0.32	-0.23	0.26	0.04				
13	TSSP	0.39	0.24	-0.24	-0.15	-0.05	0.02	0.27	0.14	-0.30	0.05	-0.42	-0.14			
14	After Sensation	-0.20	-0.17	0.05	0.23	-0.37	0.06	-0.56	-0.21	0.18	-0.07	0.48	-0.39	-0.16		
15	R&H Slope	-0.57	-0.47	-0.41	0.17	-0.51	-0.15	0.18	0.29	0.17	-0.02	0.09	-0.24	-0.35	0.13	
16	R&H Intercept	0.34	0.52	0.23	-0.25	0.34	0.12	-0.22	-0.07	-0.37	-0.11	-0.27	0.19	0.38	0.03	-.88**

Notes: Bivariate correlations were performed to identify associations among change in functional connectivity and QST estimates across sessions.
*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: Thresh., threshold; Temp., temperature; Tol., tolerance; R&H, ramp and hold; TSSP, temporal summation of second pain; Mech., mechanical NAc, nucleus accumbens; mPFC, medial prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; rmPFC, rostromedial prefrontal cortex; SMN, sensorimotor network.

Table 3-4. Control Group Correlations among Neural and QST Adaptation

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	NAc-mPFC															
2	dmPFC-SMN	0.09														
3	vmPFC-SMN	-0.68*	0.10													
4	rmPFC-SMN	0.30	-0.04	-0.51												
5	Thermal Thresh. Temp.	0.29	0.19	-0.18	0.55											
6	Thermal Thresh. Rating	-0.09	-0.43	0.32	-0.39	-0.20										
7	Thermal Tol. Temp.	0.51	-0.24	-0.52	0.60*	0.56	0.04									
8	Thermal Tol. Rating	-0.14	-0.37	0.22	-0.38	-.65*	0.74**	-0.24								
9	Mech. Thresh. Hand	0.17	0.17	0.17	0.27	0.17	0.04	0.19	0.27							
10	Mech. Thresh. Hand Rating	-0.02	-0.41	0.33	-0.46	-0.38	0.96**	-0.07	0.82**	0.07						
11	Mech. Thresh. Foot	0.01	0.27	0.36	0.22	0.09	0.23	0.08	0.38	.89**	0.26					
12	Mech. Thresh. Foot Rating	-0.17	-0.35	0.50	-0.42	-0.37	0.84**	-0.36	0.77**	0.09	0.90**	0.30				
13	TSSP	0.52	0.06	-0.01	0.25	0.82**	0.76*	0.42	0.09	0.32	0.79**	0.41	0.73*			
14	After Sensation	-0.04	0.24	-0.35	-0.28	-0.85**	-0.51	-0.42	0.38	-0.24	-0.40	-0.30	-0.45	-0.72*		
15	R&H Slope	0.09	-0.51	0.08	0.48	-0.01	-0.07	0.44	-0.20	0.14	0.07	0.14	0.02	-0.02	-0.37	
16	R&H Intercept	-0.07	0.44	-0.08	-0.51	0.03	0.08	-0.43	0.19	-0.15	-0.05	-0.19	0.01	0.00	0.39	-0.99**

Notes: Bivariate correlations were performed to identify associations among change in functional connectivity and QST estimates across sessions.
*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: Thresh, threshold; Temp, temperature; Tol., tolerance; R&H, ramp and hold; TSSP, temporal summation of second pain; Mech, mechanical; NAc, Nucleus accumbens; mPFC, medial prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; rmPFC, rostromedial prefrontal cortex; SMN, sensorimotor network.

Table 3-5. Correlations among Neural and Peak Post-DOMS Daily Rating Adaptation

		1	2	3	4	5	6	7	8	9	10	11	12
1	NAc-mPFC												
2	dmPFC-SMN	0.05											
3	vmPFC-SMN	0.18	0.47										
4	rmPFC-SMN	-0.06	-0.25	-0.15									
5	Depression	-0.01	-0.59*	-0.48	0.61*								
6	Anxiety	0.03	-0.28	-0.64*	0.00	0.26							
7	Frustration	0.04	-0.60*	-0.24	0.59*	0.77**	-0.12						
8	Fear	0.38	-0.03	-0.33	0.30	0.12	0.62*	0.03					
9	Anger	0.05	-.059*	-0.31	0.65*	0.93**	0.14	0.79**	0.03				
10	Pain Intensity	-0.30	0.15	-0.29	-0.09	0.09	0.59*	-0.33	0.16	0.09			
11	Pain Unpleasantness	-0.11	-0.23	-0.28	0.12	0.34	0.68*	-0.05	0.29	0.40	0.85**		
12	Pain with Flexion	-0.10	0.08	0.31	0.15	0.02	-0.45	0.31	-0.18	0.26	0.16	0.15	
13	Pain with Extension	-0.43	0.28	0.07	-0.18	-0.33	-0.38	0.04	-0.29	-0.25	0.12	-0.24	0.63*

Notes: Bivariate correlations were performed to assess the association among change in functional connectivity and change in peak post-DOMS daily ratings from baseline to follow up. *. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed). Abbreviations: NAc, nucleus accumbens; mPFC, medial prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; rmPFC, rostromedial prefrontal cortex; SMN, sensorimotor network.

CHAPTER 4
DISCUSSION

Standard analgesic agents employed in the management of chronic pain often aim to achieve a pain state or one of minimal pain variability. Such treatments, however, displayed limited effectiveness in achieving long-term relief, and in the case of opioid analgesics, may induce maladaptive neurophysiological changes. Considerable evidence suggests that individuals who have previously successfully recovered from pain episodes are more resilient to future episodes and suggests that repeated exposure to experimental pain may induce pain modulatory neural adaptation. The present study sought to investigate whether repeated exposure to clinically-relevant pain results in pain modulatory neural and behavioral adaptations. Results suggest that, compared to individuals who experienced one bout of DOMS, individuals that experienced repeated bouts exhibited alterations in resting state functional connectivity and substantial decreases in DOMS-related pain. Notably, the RD Group displayed significant decreases in NAc-mPFC and rmPFC-SMN functional connectivity, and significant increases in dmPFC-SMN and vmPFC-SMN functional connectivity. Importantly, these changes were associated with greater decreases in negative, pain-related psychological symptoms such as depression, anxiety, frustration, and anger in the weeks following DOMS induction.

Behavioral Ratings and Quantitative Sensory Testing

Participants who experienced repeated bouts of DOMS displayed significant reductions in peak pain intensity and unpleasantness, and pain related to movement at the site of DOMS induction. Although statistical significance was not achieved, considerable reductions in peak DOMS-related fear, depression, and anxiety were

observed (*d* = 1.25, 1.13, and 1.29, respectively). Given that throughout the course of the study the DOMS-inducing stimulus remained stable, results are consistent with previous documentation of the effects of multiple bouts of DOMS [47] and are suggestive of increased PMC from baseline to follow up,.

QST was also used to assess changes in pain sensitivity at proximal and distal sites to assess generalization of repeated DOMS-related modulatory adaptation in aspects of the central and peripheral nervous system. Repeated DOMS, compared to single DOMS, inductions resulted in a decrease in ratings and an increases in temperature at thermal pain threshold (*d* = 0.84 and 0.76, respectively). Additionally, participants in both groups displayed significant decreases in temperature at thermal pain tolerance. Across groups, ratings in response to ramp and hold stimuli significantly decreased across the study, and lower temperature stimuli showed greater rating decreases than higher temperature stimuli. As ramp and hold stimuli were applied to the calf, these results suggest adaptation extended sites distal from the point of injury. Because both groups exhibited beneficial changes in QST, it is possible that exposure to and recovery from one bout of DOMS is sufficient to result in pain modulatory adaptation. Future investigations are necessary to clarify theses effects and to systematically vary DOMS parameters.

Similar C and Aδ nociceptive fibers are involved in both thermal and mechanical nociception [29]. As such, it was not predicted that participants would only display adaptation in response to thermal stimuli. However, different nociceptive fiber populations may be activated depending on specific stimulus properties. For example, DOMS exposure may have resulted in adaptation in Aδ receptors that respond to lower

temperature ramp and hold stimuli, potentially A-mechanoheat receptors II (A-MH II), but not those that respond to other stimulus properties including certain aspects of mechanical pain (e.g. A-MH I or A-M [29]). Further investigation is necessary to clarify this dissociation.

Functional Connectivity Adaptation

Data suggest that following repeated exposure to DOMS, subjects exhibited a number of functional neural adaptations among regions related to pain modulation and resilience.

NAc-mPFC Regional Coherence

Subjects in the RD Group displayed significantly greater decreases in connectivity among the NAc and mPFC than did the Control Group. Individuals with lower baseline connectivity among these regions displayed greater adaptations in ramp and hold stimulus response. This pathway's role in pain chronicity has received significant attention. For example, chronic pain patients displayed higher coupling among these regions than healthy controls [9], and individuals with lower connectivity values among these structures were less likely to transition to chronicity following subacute back pain [4,10]. In light of these investigations, it appears that following repeated exposure to clinically-relevant pain, subjects displayed greater resemblance to individuals who successfully recovery from subacute back pain and lesser resemblance to individuals who transition to chronicity, suggesting a potentially protective effect of repeated DOMS inductions.

Additionally, there is considerable evidence documenting the role of these regions in pain modulation. Following noxious stimulus termination NAc dopamine release occurs, and nucleotide-gated channels in the mPFC and dorsal root ganglia are

actively involved in nociceptive transmission. D2 binding in basal ganglia structures is associated with pain modulation [44,45], and following noxious stimulus termination NAc dopamine release occurs [57]. These effects may be due to direct supraspinal mechanisms or indirect spinal mechanisms via NAc pathways to brainstem structures [44,45]. Furthermore, application of dopamine blockade to the NAc limits the effectiveness of exogenous opioids [3]. Additional neuroimaging studies have highlighted the role of this circuitry in cognitive self-regulation of pain [108] via numerous opioid, dopamine, and neurokinin pathways [39,58]. Nucleotide-gated channels common to the mPFC and dorsal root ganglia may also be involved [57]. Processes that subsume this involvement include: encoding prediction errors for aversive stimuli, hedonic valuation, regulation of learning and motivated behavior, assigning meaning to nociceptive stimuli, and inhibition of limbic responsive to nociceptive stimuli (Apkarian et al., 2011; Vachon-Presseau et al., 2016).

Although significant correlations among changes in this pathway and changes in ramp and hold slope were found, it is somewhat inconsistent with previous literature [108] that RD Group changes in NAc-mPFC connectivity were not associated with additional changes in QST or post-DOMS peak daily ratings. However, the processes this pathway is most involved in were not measured directly in the present study. For example, Baliki et al. (2010) found that NAc activation was associated with stimulus salience and predicted reward. Additionally, previous associations between NAc-mPFC connectivity and perceived stimulus ratings were not assessed at rest [108]. It is novel that the present study identified connectivity changes in this pathway at rest, which potentially signals greater generalization of these functional changes. Future studies are

recommended to assess aspects of pain processing more closely linked to NAc-mPFC functions (e.g. predicted pain relief) or to assess the connectivity among these regions during painful stimuli in order to more accurately identify associations among this pathway and increased PMC.

Sensorimotor Intrinsic Network Connectivity

ICA was also used to assess changes across sessions and between groups in the spatial extent and magnitude of SMN functional connectivity. Results show that the RD Group displayed significant changes in SMN connectivity with three subregions of the PFC including positive connectivity among the right vmPFC and left dmPFC, and negative connectivity among the right rmPFC. Interestingly, the Control Group, following one induction of DOMS, appeared to display an opposite pattern of change among these clusters, and also displayed reductions in pain ratings to certain thermal stimuli. Additionally, in the RD Group individuals who displayed greater increases in dmPFC-SMN connectivity and those who displayed greater decreases in rmPFC-SMN connectivity displayed greater reductions in post-DOMS peak depression, frustration, and anger. Greater increases in vmPFC-SMN connectivity were also associated with greater decreases in peak anxiety. Changes in connectivity among these regions and the SMN were also associated with changes in thermal pain threshold temperature (dm- and vmPFC) and rating (vmPFC) in the RD Group. These three PFC subregions display anatomical connectivity with the PAG, a region vital in mediating anti- and pro-nociception [43,46], which suggests that they may directly influence pain modulation.

The dmPFC was previously linked to processes of theory of mind, empathy, and moral judgment [32], which require evaluation of self-referential and emotional stimuli [59]. The dmPFC displays functional connection with the amygdala and insula, and is

likely also involved in threat appraisal, and in facilitating or inhibiting maladaptive processes such as catastrophizing via connections to additional limbic system regions [48]. In the present study, recruitment of the dmPFC into the SMN may have functioned to inhibit pain-related psychological distress given that individuals who displayed greater recruitment of the dmPFC into the SMN exhibited greater decreases depression, anger, and frustration.

The vmPFC appears to be involved in pain modulation by mediating affective appraisals and valuation of pain stimuli. vmPFC functional neuroplasticity was associated with adaptive coping and resilience in response to stress stress [83]. Riedl, et al (2011) additionally found that, following habituation, pre-stimulus vmPFC connectivity anticipated pain perception. This region has also been linked to valuation of pain stimuli and reward-related pain inhibition [11], and in assessing the value of pain avoidance [105]. The connectivity between the vmPFC and PAG was demonstrated to be sensitivity to changes in the contextual, hedonic value of pain stimuli such that greater vmPFC-PAG connectivity was related to decreased pain intensity ratings [53]. Pain inhibition through these processes may be achieved by either supraspinal mechanisms [11] or descending inhibitory mechanisms [34]. These theories are congruent with the present finding of correlation between greater vmPFC-SMN recruitment and decreased peak post-DOMS anxiety. Following repeated exposure to DOMS the individual may learn that anticipated the pain is less threatening, and pain-related anxiety decreases as affective valuation of pain is inhibited.

The rmPFC has received relatively little attention in with regard to pain modulation and it is rarely identified in neuroimaging studies of pain processing.

However, its role in the regulation, monitoring and evaluation of emotion is well documented. Ochsner and colleagues (2004) found increased rmPFC activation, potentially related to its role in retrieval of emotional knowledge, when subjects attempted to up-regulate (increased) their experience of negative emotion. In line with these findings, the region is thought to be involved in the making and the elaboration of emotional meaning [75,101,102]. The decreased connectivity among this region and the SMN found in the present study, along with the association of greater decreases in connectivity with greater decreases in depression, anger, and frustration may be suggestive of decreased assignment of emotional meaning to painful stimuli or down-regulation of DOMS pain-evoked negative emotions following repeated inductions. Individuals who self-reported greater levels of average resilience also displayed greater rmPFC-SMN adaptation. Given the role of the rmPFC in emotion regulation and the associations between rmPFC-SMN adaptation and decreases in negative pain-related affect, it is possible that resilience to pain may be achieved through greater regulation of negative emotional valuation of pain perceptions rather than directly through greater anti-nociception. It is notable that this was the only neural adaptation associated with self-reported resilience or pain catastrophizing. Although previous studies found associations between resilience, catastrophizing, and pain modulation, it appears that regardless of one's baseline levels of pain catastrophizing or resilience, significant neural adaptation following repeated exposure to pain stimuli is still possible.

Vachon-Presseau, et al (2016) proposed that healthy pain modulatory system function depends on cortical inhibition of baseline nociceptive signals and also cortical inhibition of limbic system-mediated emotional learning in response to acute pain

episodes. Thus, chronicity occurs when pain sensations are overly represented in emotional, motivational regions of the brain. Given the association with the observed SMN-PFC connectivity changes and changes in depression, anxiety, anger, and frustration, it appears that adaptation following repeated exposure to DOMS may be linked to cortical inhibition of limbic circuits responsible for attaching emotional meaning to painful stimuli. Greater recruitment of these regions into the SMN, which is primarily responsible for sensory processing, is suggestive of greater cortical and perhaps inhibitory control in the processing of noxious, sensory information. This postulate is also consistent with data suggestive of the functioning of these individual prefrontal regions as described above.

Post-hoc tests also revealed that significant baseline differences existed in these three clusters between groups. Given that these groups were presumably of the same population, displayed no significant differences on demographic or QST variables at baseline, it is difficult to predict the cause of these differences. However, when controlling for baseline differences in SMN functional connectivity, both the dmPFC and rmPFC clusters displayed significant between-groups differences at follow up, providing further support for the effect of repeated DOMS exposure on neural adaptation. Furthermore, whole-brain, corrected SMN ICA comparisons between groups did not reveal significant differences among these clusters at baseline.

sgACC Adaptation

The present study did not identify significant changes in sgACC connectivity across sessions and between groups. This finding is not consistent with the existing literature that documents the sgACC's role in pain modulation [13,66,82,104] and previous evidence of sgACC adaptation underlying habituation [15]. An important factor

in this finding may be methodological differences. Although Wang, et al. (2014) suggested differences in pain modulatory capacity may be observed in sgACC resting-state connectivity, previous investigations of sgACC and rostral ACC (rACC) involvement in pain modulation [14,62,98,99] were identified in task-based studies. As such, this region may respond specifically during active pain processing, and adaptation following repeated DOMS may not have been identifiable by the present study, which only assessed connectivity at rest. Future studies are encouraged to investigate changes in pain processing during experimental pain tasks to further clarify present findings.

Limitations and Future Directions

The present study represents an important step in identifying a method to increase endogenous PMC and is a vital step in identifying neural correlates of increased PMC in healthy individuals. In addition to these innovations, the present study exhibited some limitations that could be addressed in future research. Although significant and large effects were identified in neural and behavioral measures, the study's relatively small sample size may have prevented the identification of nuanced effects. This also signals the necessity of replication of the present results. Likewise, although the RD Group and Control Group did not significantly differ in sex, the study's sample was predominantly female and future studies are encouraged to assess larger, more balanced samples to determine the generalizability of these results and investigate potential sex or gender differences in adaptation. The present included two groups, one that experienced a single bout of DOMS and another that experienced repeated bouts of DOMS. Results suggested that significant adaptations occurred in both groups. Without an additional control group that did not experience exercise-

induced pain, it is unclear whether these effects were achieved following a single bout of DOMS and it is difficult to disambiguate the contribution of regression to the mean. Future research is needed to address a number of different factors including the stability of these effects over time, the effectiveness of these adaptations in preventing pain persistence, the translation of these processes in chronic pain patient populations, and the optimization of the pain induction for maximal benefit.

Conclusion

Significant advances have been made in understanding vulnerability factors in chronic pain. However, a paradigm shift is necessary to develop effective and safe interventions aimed at decreasing chronic pain severity and reducing risk of chronicity. Innovative approaches and conceptualizations of pain modulation aimed at increasing resilience may achieve this goal, and may result in novel and potentially preventative interventions. Results of the present study indicate that repeated exposure to and recovery from pre-clinical pain results in significant pain modulatory neural adaptation and significant reductions in pain reports. Importantly, this neural adaptation was such that, following multiple pain inductions, functional connectivity more closely resembled that of individuals who successfully recovered from subacute pain than that of individuals who transitioned to pain persistence [10]. Further investigations of interventions aimed at increasing PMC rather than eliminating pain may pave the way to vital innovations in pain management.

LIST OF REFERENCES

[1] Alschuler KN, Kratz AL, Ehde DM. Resilience and vulnerability in individuals with chronic pain and physical disability. Rehabil. Psychol. 2016;61:7–18. doi:10.1037/rep0000055.

[2] Alshelh Z, Di Pietro F, Youssef AM, Reeves JM, Macey PM, Vickers ER, Peck CC, Murray GM, Henderson LA. Chronic Neuropathic Pain: It's about the Rhythm. J. Neurosci. 2016;36:1008–18. doi:10.1523/JNEUROSCI.2768-15.2016.

[3] Altier N, Stewart J. The role of dopamine in the nucleus accumbens in analgesia. - PubMed - NCBI. Life Sci 1999;65:2269–2287. Available: http://www.ncbi.nlm.nih.gov.besta.clas.cineca.it/pubmed/10597883.

[4] Apkarian A V, Baliki MN, Farmer MA. Predicting transition to chronic pain. Curr Opin Neurol 2013;26:360–367. doi:10.1097/WCO.0b013e32836336ad.

[5] Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain. Pain 2011;152:S49-64. doi:10.1016/j.pain.2010.11.010.

[6] Babenko V V, Graven-Nielsen T, Svensson P, Drewes AM, Jensen TS, Arendt-Nielsen L. Experimental human muscle pain induced by intramuscular injections of bradykinin, serotonin, and substance P. Eur. J. Pain 1999;3:93–102. doi:10.1053/eujp.1998.0103.

[7] Badley EM, Rasooly I, Webster GK. Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization: findings from the 1990 Ontario Health Survey. J. Rheumatol. 1994;21:505–14. Available: http://www.ncbi.nlm.nih.gov/pubmed/8006895. Accessed 1 Apr 2017.

[8] Baliki MN, Baria AT, Apkarian AV. The Cortical Rhythms of Chronic Back Pain. J. Neurosci. 2011;31:13981–13990. doi:10.1523/JNEUROSCI.1984-11.2011.

[9] Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting Value of Pain and Analgesia: Nucleus Accumbens Response to Noxious Stimuli Changes in the Presence of Chronic Pain. Neuron 2010;66:149–160. doi:10.1016/j.neuron.2010.03.002.

[10] Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Supplementary Infromation. Nat. Neurosci. 2012;15:1117–9. doi:10.1038/nn.3153.

[11] Becker S, Gandhi W, Pomares F, Schweinhardt P. Orbitofrontal cortex mediates pain modulation by monetary reward. Progr. No 26818/WW12013 Neurosci. Meet. Plan. San Diego, CA Soc. Neurosci. 2013 Online 2013:nsw173. doi:10.1093/scan/nsw173.

[12] Bingel U, Herken W, Teutsch S, May A. Habituation to painful stimulation involves the antinociceptive system - a 1-year follow-up of 10 participants. Pain 2008;140:393–394. doi:10.1016/j.pain.2008.09.030.

[13] Bingel U, Lorenz J, Schoell E, Weiller C, Büchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;120:8–15. doi:10.1016/j.pain.2005.08.027.

[14] Bingel U, Lorenz J, Schoell E, Weiller C, Büchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;120:8–15. doi:10.1016/j.pain.2005.08.027.

[15] Bingel U, Schoell E, Herken W, Büchel C, May A. Habituation to painful stimulation involves the antinociceptive system. Pain 2007;131:21–30. doi:10.1016/j.pain.2006.12.005.

[16] Bingel U, Schoell E, Herken W, Büchel C, May A. Habituation to painful stimulation involves the antinociceptive system. Pain 2007;131:21–30. doi:10.1016/j.pain.2006.12.005.

[17] Bishop MD, Horn ME, George SZ. Exercise-induced pain intensity predicted by pre-exercise fear of pain and pain sensitivity. Clin. J. Pain 2011;27:398–404. doi:10.1097/AJP.0b013e31820d9bbf.

[18] Bishop MD, Horn ME, George SZ, Robinson ME. Self-reported pain and disability outcomes from an endogenous model of muscular back pain. BMC Musculoskelet. Disord. 2011;12:35. doi:10.1186/1471-2474-12-35.

[19] Borsook D, Becerra L, Hargreaves R. Biomarkers for chronic pain and analgesia. Part 1: the need, reality, challenges, and solutions. Discov. Med. 2011;11:197–207. doi:ISSN: 1539-6509.

[20] Calhoun V, Adali T. A method for making group inferences from functional MRI data using independent component analysis. Hum. Brain Mapp. 2001;14:140–151. doi:10.1002/hbm.1048.

[21] Charney DS. Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptations to extreme stress. Am. J. Psychiatry 2004;161:195–216. doi:10.1176/foc.2.3.368.

[22] Chou YH, Panych LP, Dickey CC, Petrella JR, Chen NK. Investigation of long-term reproducibility of intrinsic connectivity network mapping: A resting-state fMRI study. Am. J. Neuroradiol. 2012;33:833–838. doi:10.3174/ajnr.A2894.

[23] Clarkson PM, Tremblay I. Exercise-induced muscle damage, repair, and adaptation in humans. J. Appl. Physiol. 1988;65:1–6. Available: http://articles.sirc.ca/search.cfm?id=225616%5Cnhttp://ezproxy.library.yorku.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=sph&AN=SPH225616&site=ehost-live%5Cnhttp://www.jap.org. Accessed 1 Apr 2017.

[24] Damoiseaux JS, Beckmann CF, Arigita EJS, Barkhof F, Scheltens P, Stam CJ, Smith SM, Rombouts SARB. Reduced resting-state brain activity in the “default network” in normal aging. Cereb. Cortex 2008;18:1856–1864. doi:10.1093/cercor/bhm207.

[25] Dannecker EA, Koltyn KF, Riley JL, Robinson ME. Sex differences in delayed onset muscle soreness. J Sport. Med Phys Fit. 2003;43:78–84. Available: http://www.ncbi.nlm.nih.gov/pubmed/12629467.

[26] Dannecker EA, Koltyn KF, Riley JL, Robinson ME. The influence of endurance exercise on delayed onset muscle soreness. J Sport. Med Phys Fit. 2002;42:458–465. Available: http://www.ncbi.nlm.nih.gov/pubmed/12391441.

[27] Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat. Neurosci. 2014;17:192–200. doi:10.1038/nn.3628.

[28] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968–980. doi:10.1016/j.neuroimage.2006.01.021.

[29] Dubin AE, Patapoutian A. Nociceptors: The sensors of the pain pathway. J. Clin. Invest. 2010;120:3760–3772. doi:10.1172/JCI42843.

[30] Ebbeling CB, Clarkson PM. Muscle adaptation prior to recovery following eccentric exercise. Eur. J. Appl. Physiol. Occup. Physiol. 1990;60:26–31. doi:10.1007/BF00572181.

[31] Edwards RR, Campbell C, Jamison RN, Wiech K. The neurobiological underpinnings of coping with pain. Curr. Dir. Psychol. Sci. 2009;18:237–241. doi:10.1111/j.1467-8721.2009.01643.x.

[32] Eickhoff SB, Laird AR, Fox PT, Bzdok D, Hensel L. Functional Segregation of the Human Dorsomedial Prefrontal Cortex. Cereb. Cortex 2016;26:304–321. doi:10.1093/cercor/bhu250.

[33] Feder A, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. Nat. Rev. Neurosci. 2009;10:446–57. doi:10.1038/nrn2649.

[34] Fields HL. Understanding How Opioids Contribute to Reward and Analgesia. Reg. Anesth. Pain Med. 2007;32:242–246. doi:10.1016/j.rapm.2007.01.001.

[35] Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR, Bent EK, Koneru VK, Dieterich ME, Hodge SM, Rauch SL, Grant PE, Cohen BM, Seidman LJ, Caviness VS, Biederman J. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am. J. Psychiatry 2005;162:1256–1265. doi:10.1176/appi.ajp.162.7.1256.

[36] Friborg O, Hjemdal O, Rosenvinge JH, Martinussen M, Aslaksen PM, Flaten MA. Resilience as a moderator of pain and stress. J. Psychosom. Res. 2006;61:213–219. doi:10.1016/j.jpsychores.2005.12.007.

[37] Fridén J, Sjöström M, Ekblom B. Myofibrillar damage following intense eccentric exercise in man. Int. J. Sports Med. 1983;4:170–6. doi:10.1055/s-2008-1026030.

[38] Gaskin DJ, Richard P. The economic costs of pain in the United States. J. Pain 2012;13:715–724. doi:10.1016/j.jpain.2012.03.009.

[39] Gear RW, Levine JD. Nucleus accumbens facilitates nociception. Exp. Neurol. 2011;229:502–506. doi:10.1016/j.expneurol.2011.03.021.

[40] George SZ, Dover GC, Fillingim RB. Fear of pain influences outcomes after exercise-induced delayed onset muscle soreness at the shoulder. Clin. J. Pain 2007;23:76–84. doi:10.1097/01.ajp.0000210949.19429.34.

[41] Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS, Kennedy DN, Faraone S V., Tsuang MT. Hypothalamic Abnormalities in Schizophrenia: Sex Effects and Genetic Vulnerability. Biol. Psychiatry 2007;61:935–945. doi:10.1016/j.biopsych.2006.06.027.

[42] Graven-Nielsen T, Mense S. The peripheral apparatus of muscle pain: evidence from animal and human studies. Clin. J. Pain 2001;17:2–10. doi:10.1097/00002508-200103000-00002.

[43] Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: A diffusion tensor imaging study in healthy controls. Pain 2006;123:169–178. doi:10.1016/j.pain.2006.02.027.

[44] Hagelberg N, Jääskeläinen SK, Martikainen IK, Mansikka H, Forssell H, Scheinin H, Hietala J, Pertovaara A. Striatal dopamine D2 receptors in modulation of pain in humans: A review. Eur. J. Pharmacol. 2004;500:187–192. doi:10.1016/j.ejphar.2004.07.024.

[45] Hagelberg N, Martikainen IK, Mansikka H, Hinkka S, Någren K, Hietala J, Scheinin H, Pertovaara A. Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. Pain 2002;99:273–279. doi:10.1016/S0304-3959(02)00121-5.

[46] Hardy SGP, Leichnetz GR. Frontal cortical projections to the periaqueductal gray in the rat: A retrograde and orthograde horseradish peroxidase study. Neurosci. Lett. 1981;23:13–17. doi:10.1016/0304-3940(81)90183-X.

[47] Hyldahl RD, Hubal MJ. Lengthening our perspective: Morphological, cellular, and molecular responses to eccentric exercise. Muscle and Nerve 2014;49:155–170. doi:10.1002/mus.24077.

[48] Kalisch R, Gerlicher AM V. Making a mountain out of a molehill: On the role of the rostral dorsal anterior cingulate and dorsomedial prefrontal cortex in conscious threat appraisal, catastrophizing, and worrying. Neurosci. Biobehav. Rev. 2014;42:1–8. doi:10.1016/j.neubiorev.2014.02.002.

[49] Karatoreos IN, McEwen BS. Annual research review: The neurobiology and physiology of resilience and adaptation across the life course. J. Child Psychol. Psychiatry Allied Discip. 2013;54:337–347. doi:10.1111/jcpp.12054.

[50] Karatsoreos IN, McEwen BS. Resilience and vulnerability: a neurobiological perspective. F1000Prime Rep. 2013;5:13. doi:10.12703/P5-13.

[51] King T, Ossipov MH, Vanderah TW, Porreca F, Lai J. Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? NeuroSignals 2005;14:194–205. doi:10.1159/000087658.

[52] Lee M, Manders TR, Eberle SE, Su C, D'amour J, Yang R, Lin HY, Deisseroth K, Froemke RC, Wang J. Activation of Corticostriatal Circuitry Relieves Chronic Neuropathic Pain. J. Neurosci. 2015;35:5247–5259. doi:10.1523/JNEUROSCI.3494-14.2015.

[53] Leknes S, Berna C, Lee MC, Snyder GD, Biele G, Tracey I. The importance of context: When relative relief renders pain pleasant. Pain 2013;154:402–410. doi:10.1016/j.pain.2012.11.018.

[54] Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone S V., Tsuang MT, Seidman LJ. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr. Res. 2006;83:155–171. doi:10.1016/j.schres.2005.11.020.

[55] Maldjian JA, Laurienti PJ, Kraft RA, Burdettea JH. An automated method for neuroanatomic and cytoarchitectonic\ratlas-based interrogation of fMRI data sets. Neuroimage 2003;19:1233–1239. doi:Doi 10.1016/S1053-8119(03)00169-1.

[56] Mäntyselkä P, Kumpusalo E, Ahonen R, Kumpusalo A, Kauhanen J, Viinamäki H, Halonen P, Takala J. Pain as a reason to visit the doctor: A study in Finnish primary health care. Pain 2001;89:175–180. doi:10.1016/S0304-3959(00)00361-4.

[57] Mitsi V, Zachariou V. Modulation of pain, nociception, and analgesia by the brain reward center. Neuroscience 2016;338:81–92. doi:10.1016/j.neuroscience.2016.05.017.

[58] Navratilova E, Xie JY, Okun A, Qu C, Eyde N, Ci S, Ossipov MH, King T, Fields HL, Porreca F. Pain relief produces negative reinforcement through activation of mesolimbic reward-valuation circuitry. Proc. Natl. Acad. Sci. U. S. A. 2012;109:20709–13. doi:10.1073/pnas.1214605109.

[59] Northoff G, Bermpohl F. Cortical midline structures and the self. Trends Cogn. Sci. 2004;8:102–107. doi:10.1016/j.tics.2004.01.004.

[60] Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ. For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 2004;23:483–499. doi:10.1016/j.neuroimage.2004.06.030.

[61] Ong AD, Zautra AJ, Reid MC. Psychological resilience predicts decreases in pain catastrophizing through positive emotions. Psychol. Aging 2010;25:516. doi:10.1037/a0019384.

[62] Peciña M, Stohler CS, Zubieta JK. Neurobiology of placebo effects: Expectations or learning? Soc. Cogn. Affect. Neurosci. 2014;9:1013–1021. doi:10.1093/scan/nst079.

[63] Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 2014;84:320–341. doi:10.1016/j.neuroimage.2013.08.048.

[64] Power JD, Schlaggar BL, Petersen SE. Recent progress and outstanding issues in motion correction in resting state fMRI. Neuroimage 2015;105:536–551. doi:10.1016/j.neuroimage.2014.10.044.

[65] Price DD, Dubner R. Mechanisms of First and Second Pain in the Peripheral and Central Nervous Systems. J. Invest. Dermatol. 1977;69:167–171. doi:10.1111/1523-1747.ep12497942.

[66] Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu. Rev. Psychol. 2008;59:565–590. doi:10.1146/annurev.psych.59.113006.095941.

[67] Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain 1977;3:57–68. doi:10.1016/0304-3959(77)90035-5.

[68] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45–56. doi:10.1016/0304-3959(83)90126-4.

[69] Ramírez-Maestre C, Esteve R. Disposition and adjustment to chronic pain. Curr. Pain Headache Rep. 2013;17:312. doi:10.1007/s11916-012-0312-9.

[70] Rennefeld C, Wiech K, Schoell ED, Lorenz J, Bingel U. Habituation to pain: Further support for a central component. Pain 2010;148:503–508. doi:10.1016/j.pain.2009.12.014.

[71] Richardson GE. The Metatheory of Risk and Resiliency. J. Clin. Psychol. 2002;58:307–321. doi:10.1002/jclp.10020.

[72] Riedl V, Valet M, Wöller A, Sorg C, Vogel D, Sprenger T, Boecker H, Wohlschläger AM, Tölle TR. Repeated pain induces adaptations of intrinsic brain activity to reflect past and predict future pain. Neuroimage 2011;57:206–213. doi:10.1016/j.neuroimage.2011.04.011.

[73] Rivata C, Ballantyne J. The dark side of opioids in pain management: basic science explains clinical observation. Pain Reports 2016;1:e570. doi:10.1097/PR9.0000000000000570.

[74] Rogachov A, Cheng JC, Erpelding N, Hemington KS, Crawley AP, Davis KD. Regional brain signal variability: a novel indicator of pain sensitivity and coping. Pain 2016;2:1. doi:10.1097/j.pain.0000000000000665.

[75] Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends Cogn. Sci. 2012;16:147–156. doi:10.1016/j.tics.2012.01.005.

[76] Russo SJ, Murrough JW, Han M-H, Charney DS, Nestler EJ. Neurobiology of resilience. Nat. Neurosci. 2012;15:1475–1484. doi:10.1038/nn.3234.

[77] Seery MD. Challenge or threat? Cardiovascular indexes of resilience and vulnerability to potential stress in humans. Neurosci. Biobehav. Rev. 2011;35:1603–1610. doi:10.1016/j.neubiorev.2011.03.003.

[78] Seery MD. Resilience: A Silver Lining to Experiencing Adverse Life Events? Curr. Dir. Psychol. Sci. 2011;20:390–394. doi:10.1177/0963721411424740.

[79] Seery MD, Leo RJ, Holman EA, Silver RC. Lifetime exposure to adversity predicts functional impairment and healthcare utilization among individuals with chronic back pain. Pain 2010;150:507–515. doi:10.1016/j.pain.2010.06.007.

[80] Seery MD, Leo RJ, Lupien SP, Kondrak CL, Almonte JL. An upside to adversity?: moderate cumulative lifetime adversity is associated with resilient responses in the face of controlled stressors. Psychol. Sci. 2013;24:1181–9. doi:10.1177/0956797612469210.

[81] Seminowicz DA, Davis KD. Cortical responses to pain in healthy individuals depends on pain catastrophizing. Pain 2006;120:297–306. doi:10.1016/j.pain.2005.11.008.

[82] Shackman AJ, Salomons T V, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 2011;12:154–167. doi:10.1038/nrn2994.

[83] Sinha R, Lacadie CM, Constable RT, Seo D. Dynamic neural activity during stress signals resilient coping. Proc. Natl. Acad. Sci. 2016;113:8837–8842. doi:10.1073/pnas.1600965113.

[84] Slepian PM, Ankawi B, Himawan LK, France CR. Development and initial validation of the pain resilience scale. J. Pain 2016;17:462–472. doi:10.1016/j.jpain.2015.12.010.

[85] Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int. J. Behav. Med. 2008;15:194–200. doi:10.1080/10705500802222972.

[86] Smith BW, Tooley EM, Montague EQ, Robinson AE, Cosper CJ, Mullins PG. The Role of Resilience and Purpose in Life in Habituation to Heat and Cold Pain. J. Pain 2009;10:493–500. doi:10.1016/j.jpain.2008.11.007.

[87] Smith BW, Tooley EM, Montague EQ, Robinson AE, Cosper CJ, Mullins PG. The Role of Resilience and Purpose in Life in Habituation to Heat and Cold Pain. J. Pain 2009;10:493–500. doi:10.1016/j.jpain.2008.11.007.

[88] Sorg C, Riedl V, Mühlau M, Calhoun VD, Eichele T, Läer L, Drzezga A, Förstl H, Kurz A, Zimmer C, Wohlschläger AM. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 2007;104:18760–18765. doi:10.1073/pnas.0708803104.

[89] Sternbach RA. Pain and "hassles" in the united states: findings of the nuprin pain report. Pain 1986;27:69–80. doi:10.1016/0304-3959(86)90224-1.

[90] Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: Perspectives on comprehensive modeling of individual pain adaptation topical collection on psychiatric management of pain. Curr. Pain Headache Rep. 2013;17:317. doi:10.1007/s11916-012-0317-4.

[91] Sturgeon JA, Zautra AJ. Resilience: A new paradigm for adaptation to chronic pain. Curr. Pain Headache Rep. 2010;14:105–112. doi:10.1007/s11916-010-0095-9.

[92] Sturgeon JA, Zautra AJ, Arewasikporn A. A multilevel structural equation modeling analysis of vulnerabilities and resilience resources influencing affective adaptation to chronic pain. Pain 2014;155:292–298. doi:10.1016/j.pain.2013.10.007.

[93] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol. Assess. 1995;7:524–532.

[94] Teutsch S, Herken W, Bingel U, Schoell E, May A. Changes in brain gray matter due to repetitive painful stimulation. Neuroimage 2008;42:845–849. doi:10.1016/j.neuroimage.2008.05.044.

[95] Treede R, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Kosek E, Lavand P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang S. A classification of chronic pain for ICD-11. Pain 2015;156:1003–1007. doi:10.1097/j.pain.0000000000000160.

[96] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–289. doi:10.1006/nimg.2001.0978.

[97] Vachon-Presseau E, Centeno M V, Ren W, Berger SE, Tetreault P, Ghantous M, Baria A, Farmer M, Baliki MN, Schnitzer TJ, Apkarian A V. The Emotional Brain as a Predictor and Amplifier of Chronic Pain. J Dent Res 2016;95:605–612. doi:10.1177/0022034516638027.

[98] Wager TD. Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. Science (80-.). 2004;54:155–161. doi:10.1126/science.1093065.

[99] Wager TD, Atlas LY, Leotti LA, Rilling JK. Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. J. Neurosci. 2011;31:439–452. doi:10.1523/JNEUROSCI.3420-10.2011.

[100] Wang G, Erpelding N, Davis KD. Sex differences in connectivity of the subgenual ACC. Pain 2014;155:755–763. doi:10.1016/j.pain.2014.01.005.

[101] Waugh CE, Zarolia P, Mauss IB, Lumian D, Ford B, Davis T, Ciesielski BG, Sams K V, Mcrae K. Emotion regulation changes the duration of the BOLD response to emotional stimuli. 2016. Available: http://scan.oxfordjournals.org/. Accessed 2 Apr 2017.

[102] Waugh CEC, Lemus MG, Gotlib IH. The role of the medial frontal cortex in the maintenance of emotional states. Soc. Cogn. Affect. Neurosci. 2014;9:2001–2009. doi:10.1093/scan/nsu011.

[103] Whitfield-Gabrieli S, Nieto-Castanon A. Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. Brain Connect. 2012;2:125–141. doi:10.1089/brain.2012.0073.

[104] Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. Trends Cogn. Sci. 2008;12:306–313. doi:10.1016/j.tics.2008.05.005.

[105] Wiech K, Tracey I. Pain, decisions, and actions: A motivational perspective. Front. Neurosci. 2013;7:46. doi:10.3389/fnins.2013.00046.

[106] Windle G, Bennett KM, Noyes J. A methodological review of resilience measurement scales. Health Qual. Life Outcomes 2011;9:8. doi:10.1186/1477-7525-9-8.

[107] Woo CW, Krishnan A, Wager TD. Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. Neuroimage 2014;91:412–419. doi:10.1016/j.neuroimage.2013.12.058.

[108] Woo CW, Roy M, Buhle JT, Wager TD. Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-Regulation on Pain. PLoS Biol. 2015;13:e1002036. doi:10.1371/journal.pbio.1002036.

[109] Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: Test-retest evaluation using ICA and dual regression approach. Neuroimage 2010;49:2163–2177. doi:10.1016/j.neuroimage.2009.10.080.

BIOGRAPHICAL SKETCH

Landrew Sevel was born and raised in Columbus, Ohio. Before pursuing graduate studies in clinical and health psychology at the University of Florida (UF), he obtained degrees in music performance and psychology at Bowling Green State University. Currently he studies adaptive and modulatory aspects of pain processing with human neuroimaging techniques. After the completion of his Ph.D., Landrew plans to pursue post-doctoral training at the Osher Center for Integrative Medicine at Vanderbilt University. Outside the laboratory, Landrew devotes his time to multi-sport athletics, practicing yoga and mindfulness, cooking, music, and spending time with friends and family.