CHARACTERIZATION OF PSYCHOPHYSIOLOGICAL RESPONSES TO PRESSURE PAIN

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A thesis submitted to the

School of Graduate Studies

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Master of Science

Graduate Program in Psychology

Written under the direction of

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New Brunswick, New Jersey

October 2021
Pain stands at the intersection of multiple health crises and is a leading contributor to disability. Current pain assessments rely on self-reports (which assume a capacity to understand and verbalize mental and emotional states) and behavioral observation which can be subject to limitations and misinterpretation. Subjective methods to evaluate pain can be substantially enhanced with objective biometrics that incorporate the sensory, motor, and psychophysiological aspects of the full pain experience. This thesis questions how experimentally induced pressure pain influences motor and cardiac activity (biophysical signals) elicited via the peripheral somatic and autonomic nervous systems, respectively. This work uncovers signatures in the biophysical responses to pain as subjects perform motor-cognitive tasks such as resting, drawing, and pointing to a target, under control and pain conditions.
During the pain condition, sustained pressure is induced on the nonperforming arm via a standardized pain induction procedure that mimics pathological pain. Each of the tasks used in this study require different levels of cognitive effort and motor skill, helping reveal unique aspects of how the nervous systems respond to pain. Motion sensors are used to record the kinematics of various limbs of the body while electrocardiographic sensors are utilized to measure the electrical activity of the heart. These biophysical responses are also assessed in consideration of subjective pain ratings. This multi-method design allows us to evaluate the relationships among physiological, motor, and cognitive processes associated with pain via a unified statistical framework, along with traditional measures such as heart rate variability (HRV). The biophysical responses of the nervous systems are assessed via personalized analysis of the moment-by-moment fluctuations in the time series signals. These include variations in the amplitude of the body’s kinematics and in the timings of the heart’s inter-beat-interval. Movements elicited during experimental tasks have varying levels of spontaneity (which occur largely beneath awareness), and deliberateness (goal-directedness) that is under conscious control. These kinesthetic processes are susceptible to environmental and bodily changes and thus can help reveal how pain influences the body’s proprioceptive system. Autonomic responses such as cardiac activity serve as inevitable processes which cannot be volitionally controlled. They exhibit a narrower range of dynamics, helping provide robust signatures of the body’s responses to pain. We find that the pain’s influence on the body’s motor system depends on the motor and cognitive demands of the experimental task at hand.
Pressure pain also elicits shifts in the stochastic signatures and HRV of the cardiac signal, regardless of the sensory-motor and cognitive demands of the task. Unique relationships are also observed between the objective metrics obtained from the biophysical data and self-reported pain ratings. Such methods are novel to the study of pain as they evaluate, in tandem, the continuous physiological signals harnessed from the peripheral (somatic and autonomic) nervous systems. The implications of this work are discussed in the context of precision medicine with possible applications in clinical populations.
Acknowledgements

I would like to thank my advisor Dr. Elizabeth Torres, my committee members, Dr. Pernille Hemmer and Dr. Jessica Hamilton, and all the members of the Sensory-Motor Integration Lab for their help and support with my thesis.

This work was funded by the New Jersey Governor’s Council for Medical Research and Treatment of Autism. It was also supported by the Nancy Lurie Marks Family Foundation Career Development Award to E.B. Torres.
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INTRODUCTION

1.1 Pain as a multifaceted problem

Pain is an intrinsically undesirable experience that is implicated in a variety of physical and mental illnesses. Pain also stands at the intersection of multiple health crises, contributing to the opioid epidemic, health disparities, disability, and chronic pain [1,2]. At least 125 million Americans suffer from acute or chronic pain, and this epidemic has been the root cause of the opioid crisis that arose in the late 1990s [2]. The increased use and misuse of opioids has led to over 47,000 deaths in the United States between 2013-2017 alone [3]. Gaining a complete understanding of the neurobiological underpinnings of pain can lead to the most effective solutions to this epidemic [2]. The human somatic sense of pain is yet to be explored and digitally characterized in terms of its effects on both somatic and autonomic nervous system (NS) activity. Aside from potential tissue damage, pain is associated with sensory, cognitive, and social components [1]. Investigating pain thus requires multidisciplinary approaches that can integrate insights from psychology (cognition, sensation, perception), neuroscience (nervous system physiology), and psychiatry (social/clinical).

An objective and noninvasive assessment of pain is also yet to be discovered and utilized in the clinical realm. Current pain assessments rely on surveys and questionnaires such as numerical rating scales, illustrative visual analog scales, and verbal rating scales which rely on semantic descriptors such as ‘moderate’ and ‘severe’ [4-5]. Such assessments often assume a capacity to understand and verbalize mental/emotional states, making
them disadvantageous for minimally verbal individuals or those with neurodevelopmental disorders/disabilities. While traditional self-report techniques are useful and convenient in the clinical realm, they should be complemented with more objective approaches. Thus, this thesis will focus on gaining a better understanding and building a more wholistic characterization of how pain influences multiple layers of the peripheral nervous system by exploring heart (autonomic) and movement (somatic) activity during various motor-cognitive tasks. This work is part of a larger effort to distinguish, within the motor stream, contributions from afferent pain and afferent temperature channels. In other words, we will use kinesthetic reaference – the continuous motor streams from naturalistic motions under induced pain and without it – as a proxy of pain afference. Since pressure, movement, temperature, and pain afferents are interrelated but separable [6], here we will focus on pressure-induced pain to evaluate its effects via the kinesthetic-reafferent motor stream continuously flowing between the peripheral and central nervous systems. In addition, we will simultaneously evaluate the effect of pressure pain on autonomic cardiac regulation, an inevitable process that cannot be consciously controlled during experimental tasks. The current study ultimately aims to develop digital biomarkers that can be used to detect pain from motor and cardiac signals flowing in tandem across the central and peripheral nervous systems.

1.2 Sensory-Motor signals as a proxy for Peripheral Nervous System (PNS) activity

Movement at will would not be possible without the action of efferent signals eliciting muscle activity via the peripheral nervous system (PNS) and kinesthetic re-afferent
signals providing sensory feedback to the central nervous system (CNS). This continuous communication between the brain and the body, a concept termed ‘kinesthetic re-afference’ [7], helps maintain awareness of our body’s position and movement in space (proprioception) and helps inform us about the external world (Figure A1). Internal models for sensorimotor integration suggest that the CNS plans, continuously updates, and specifies efferent signals for motor planning, control, and learning, based on the re-afferent somatosensory information and their consequences [8]. However, such kinesthetic/proprionceptive abilities remain physiologically distinct from our ability to sense pain, pressure, and temperature. Afferent nerves that conduct pressure and proprioceptive information via the (often forgotten) sense of touch, remain biologically distinct from afferent nerves that conduct pain and temperature information [9]. Thus, it is important to disentangle the differences between these afferent signals flowing in tandem via the somatic PNS. Part of this effort entails understanding and characterizing the different spatio-temporal and frequency scales of these signals, and the personalized ranges of activity of randomized samples within the population.

Assessments of behavior have mostly relied on observation and discretized categorization without considering the continuous flow of motor activity associated with the behavior along with the micro-motions that remain undetected by the naked eye [10-12]. Not all physical movements are performed with the same level of awareness and intent – a large portion occur spontaneously or beneath full awareness [13]. Such actions have spontaneous behavioral variability (SBV) that is often disregarded as gross data in motor control research, which typically takes grand
averages of data epochs under a priori assumed theoretical probability distributions [14]. Furthermore, traditional approaches in motor control typically focus on instructed, goal-directed, and imitated actions [12,13], leaving out spontaneous (goal-less) aspects of behavior. Prior work in our lab has shown that SBV, in the form of moment-to-moment fluctuations of the motor signal, is quite informative in characterizing various disorders and neurological conditions [14-18].

While there have been significant advances in understanding kinesthetic mechanisms for bodily awareness and the neuro-cognitive mechanisms for motor action and learning [10-13], far less is known about how somatosensory inputs from the pain modality influence this process. Previous studies have shown that such patterns of variability (coined ‘micro-movement spikes’ or MMS) inherent to our natural movements can be informative of the stochastic quality of the sensory feedback the CNS/brain receives from the peripheral NS to help coordinate future motor output [12]. Deficits in this kinesthetic feedback loop (communication between the brain and the body – the CNS and PNS) are thought to underly neurological disorders such as Parkinson’s Disease and autism [17,18]. Such deficits may be due to noisier and more random sensory feedback that in turn decreases the brain’s predictive control over its bodily/motor outputs, circularly leading to greater motor output variability [12]. Proper kinesthetic re-afferent sensory input from the PNS allows the individual to gain predictive control and build expectations for their future actions [10]. Our lab has discovered and studied these features of the continuous motor stream in schizophrenia [15], Parkinson’s disease [19], autism [10], and in a deafferented patient.
who lacks kinesthetic reafference, owing to a viral infection that killed the proprioceptive nerves but spared the pain-temperature afferent nerves [20]. Disruption of the maturation of proprioception thus interferes with the regulation of motor outputs, anticipatory planning, bodily autonomy/volitional control, and the ability to turn movement into a stable percep [10-13].

1.3 Cardiac signals as a proxy for Autonomic NS (ANS) regulation

Heart activity is under the dynamic control of the sympathetic cardiac nerves and the parasympathetic vagus nerve via the autonomic nervous system (ANS). The ANS is largely responsible for maintaining the body's overall homeostasis [21]. The sympathetic NS works to increase heart rate while the parasympathetic NS serves as the breaks that turn the cardiac activity back to normal functioning. Exposure to painful stimuli and/or discomfort and distress is known to activate the sympathetic NS which elicits the excitatory fight-or-flight response [22]. Fluctuations in sympathetic and parasympathetic activity can also allude to unique physiological responses related to stress and anxiety.

Previous studies on stress and autonomic responses such as heart rate can provide insight into the assessment of NS responses to pain sensation [23]. Heart rate variability (HRV) has been a useful and advantageous measure of such autonomic reactivity [24]. HRV is widely used to evaluate sympathetic and parasympathetic NS activity via various time & frequency-domain parameters. Improper balance between these two nervous systems is associated with many cardiac pathologies [24]. HRV represents the various statistics of the inter-beat-interval (IBI), the timing between
beats in a cardiac signal. Previous work on HRV and stress have shown that when humans experience mental/physical strain, the parasympathetic NS’s control over the heart decreases while sympathetic NS activity increases [25-27]. In such studies, physical strain was induced by having subjects perform intensive exercises [26] or mental strain was induced by asking subjects to solve difficult puzzles or arithmetic problems [27]. Thus, there is a clear interaction between the ANS and the nociceptive system as pain may induce both mental and/or physical strain [21, 22].

1.4 Statistical framework and Precision Medicine perspective

To digitally model how pain affects motor and cardiac responses, biophysical sensor outputs (time series) are analyzed using the Statistical Platform for Individualized Behavioral Analysis (SPIBA) [12, 28]. SPIBA allows us to characterize the variability present in various biorhythms via a unifying scale by tracking minute fluctuations in the timing and amplitude of the waveforms produced by biophysical sensor output. By adapting well-known statistical methodologies to analyze human NS activity, we can obtain a glimpse of how pain influences the afferent feedback the brain receives during motor-cognitive tasks in a personalized manner. Under the SPIBA framework, the probability density functions (PDFs) that represent the returning afferent signals the motions themselves caused can be empirically estimated by assessing the kinematics of the body’s movements to characterize the re-afferent pain signals (via the closed feedback loop between the CNS and PNS). SPIBA also allows us to assess the autonomic variability of cardiac activity as modulated by the ANS. The benefits and efficacy of using such analytics is demonstrated through condition-dependent signature clustering which self-emerge based on the
intrinsic stochastic properties of the original time series data [10-12].

The personalized data analysis techniques offered by SPIBA work in line with approaches in precision medicine. Precision medicine is a modern approach that integrates knowledge across physical, engineering, biological, and health sciences via data-driven approaches [29]. It looks beyond the traditional ‘one-size-fits-all’ model and aims to create personalized healthcare and targeted treatments based on the individual’s unique biosignatures. As such, the goals of precision medicine fall hand in hand with analytical approaches used in the present study, which aim to track the dynamics of the individual’s biorhythmic activity in a personalized manner.

1.5 An Integrated Approach: Sensory-motor and psychophysiological reactivities

With the advent of wearable sensing technology, it is possible to use physical motion tracking in combination with other physiologically relevant signals (electrocardiography/ECG) to help assess an individual’s biophysical states as they are experiencing pain. This study will utilize a multifaceted approach that investigates the role of pain in sensory-motor integration and cardiac reactivity in relation to self-reports of pain, all while utilizing a precision medicine perspective. Using motions sensors, we record the kinematics of various limbs of the body to understand how pain influences the feedback patterns that contribute to the coordination and autonomous regulation of motor output. With ECG sensors, we track the dynamics of cardiac activity and characterize how pain influences autonomic regulation. Pain-related biosignatures obtained via wearable sensor outputs as the person experiences pain are also compared to the results
of subjective pain assessments self-reported by the individual. This integrative approach (Figure 1) can help in developing a clearer psychophysiological understanding of pain to ultimately help create robust techniques to assess pain in those who have difficulty expressing it and in the general population.

Figure 1. Integration of subjective and objective metrics to assess pain. (A) Self-reports of pain and pain sensitivity levels are assessed by numeric rating scales traditionally used in the clinical realm to assess pain. Wearable sensors that can track heart activity (B) and the kinematics (speed, acceleration, orientation) of various limbs across the body (C) serve as a proxy for ANS and somatic PNS-related activity, respectively.
METHODS AND MATERIALS

2.1 Participants

Thirteen neurotypical individuals (6 males and 7 females) between the ages of 18 and 64 were recruited via study advertisement or from the Rutgers human subject pool system. Participants provided informed consent, which was approved by the Rutgers University Institutional Review Board. Subjects received research credits or monetary compensation for their time.

Two subjects were left-handed, and all had normal or corrected-to-normal vision. Post-experiment, one subject reported experiencing chronic back pain and acute shoulder pain due to a weight-lifting injury. No subjects reported a history of and/or current documented neurological conditions, sleep deprivation, clinical anxiety/depression, bleeding disorders, circulation problems, or heart disease.

2.2 Biophysical Sensor Equipment

During this study, kinematic, heart, and video data were collected via motion capture systems, physiological wearable sensors, and camcorders, respectively. Assessment of video data from this study is outside the scope of this thesis and will be reserved for future work. Due to the COVID-19 pandemic (where some data was collected remotely), dynamic changes within the experimental design as the study progressed, and instrumentation failure/malfunctions, not all data types were collected from all participants. Motion capture data was collected for only ten subjects while heart data was only collected from twelve subjects. For about four of these subjects, the heart data
was corrupted by instrumentation noise or incomplete, and thus excluded from analysis. A summary of which data types were collected for each subject is included in Table A1.

2.2.1 Motion Capture System

Wireless motion tracking sensors (XSENS MVN Awinda, Enschede, Netherlands) with a sampling rate of 60 Hz were used to capture the subject’s continuous motion. The sensors were strapped to 17 different locations on the body including: center of the forehead, chest/thorax, pelvis, as well as the left & right shoulders, upper arms, forearms, hands, upper legs/thighs, lower legs, and feet. Sensors were secured with athletic tape to avoid unwanted sensor movement/dislocation. The motion sensors gathered real-time 3D kinematics (angular velocity, center of mass, orientation, acceleration) of the participant’s body throughout the entirety of the experiment.

2.2.2 Physiological Biosensors

Electrocardiographic (ECG) activity was captured via wearable biosensors (MC10 BioStamp-nPoint, Lexington, MA) at a sampling rate of 250 Hz. These sensors contain 4 electrodes which are placed on the chest at the standardized lead II position via gel adhesives. An additional biosensor was placed on the dominant arm of the participant to capture electromyographic (EMG) activity of the bicep muscle. Analysis of the EMG signal will be reserved for future work.

2.3 Experimental procedure, tasks, and apparatus

At the beginning of the experiment, participants are asked to rate their perceived pain sensitivity (relative to other people) on a scale of 0-10, where zero represents complete
insensitivity and 10 represents extreme sensitivity [30]. Sensors are then placed on the participant and each system is calibrated via manufacture-provided software technology. A manual blood pressure cuff (standard sphygmomanometer/tourniquet) is placed around the non-dominant arm of the subject for the entirety of the session. Participants are then seated at a table where they perform 4 different experimental tasks (resting, drawing, pointing, and peg) under different conditions (Figure 2).

**Figure 2. Experimental conditions and tasks.**

(A) A total of five tasks are used in the study. The first is the resting task to assess baseline NS activity. The participants then perform three motor-cognitive tasks: drawing, pointing, and peg, each requiring varying levels of motor and cognitive control. The last task is natural walking to assess individualized gait patterns. (B) Chronological sequence of conditions the subjects performed the three motor-cognitive tasks. The resting task was performed under only the first control and the pain condition. The walking task was only performed during the control condition. Image for pointing task extracted from [12] with permission of author.

In the first and second condition of the experiment (controls), the participant performs each task under normal conditions. The first condition serves as the first baseline where the subject learns how to perform each task. The second condition serves as a second baseline where the subject has learned how to perform the tasks. The third serves as the pain condition where sustained pressure pain is introduced.
via the blood pressure cuff. This pain induction method serves as a modified version of submaximal effort tourniquet test [31], which is found to mimic pathological pain [32]. In this procedure, a cuff is gradually inflated to a pressure level of about 200 mmHg on the non-performing (non-dominant) arm (above the elbow) of the subject [33]. The cuff stays inflated at this level for the entirety of the task and is deflated right after task completion. Right before the cuff is deflated, subjects verbally report their pain level using a Numeric Rating Scale (NRS) ranging from 0-10, where 0 indicates no pain, 4-6 indicates moderate pain, and a 10 indicates extreme pain [34]. Longer breaks between the tasks during the pain condition were used to ensure that the pressure pain subsided and to mitigate the effects of adaptation to the pressure sensation. Before the start of the next task during the pain condition, the pressure cuff is inflated again and deflated at task completion. The fourth condition serves as a post-pain condition where the subject performs each task again without inflation of the pressure cuff. This is done to assess any aftereffects of the pain stimulation. Near the end of the study, the subject performs a final task consisting of walking naturally for five minutes under only the control condition. This task allows us to examine each subject’s baseline gait patterns.

2.3.1 Resting Task

The participant first performs a resting task where they sit in a relaxed position for three minutes and avoid excess movement. This task is used to establish baseline autonomic and somatic NS activity as no movement or cognitive effort is required. This task is only performed under the first control and the pain condition.

2.3.2 Drawing Task
With their dominant hand, the subject then performs a drawing task that consists of trail making tests where they connect circles containing letters and/or numbers in a specified order. These tests are a component of the Montreal Cognitive Assessment (MoCA) which helps assess processing speed and visuomotor skills [35]. The subject’s performance on this task is judged in terms of the time, in seconds, required to complete all trails. An ‘error’ score is recorded based on the number of times the subject connects the circles in the wrong sequence. Of all the tasks used in this study, the drawing task requires the greatest amount of cognitive effort as participants must maintain a sequence of 26 letters in memory as they individually connect them to numbers in ascending order. However, with this task (unlike with the pointing task described below), participants receive continuous pressure-based haptic feedback from the pen used to make the drawings, as well as from the surface of the table (via the pen-pressing).

2.3.3 Pointing Task

Next, the participant performs a pointing task which consists of bringing the index finger of the dominant hand to a visual target in front of them (intentional/goal-directed segment) and then bringing the arm back to rest (consequential segment) repeatedly in a self-paced manner, fifty times. This task has been used widely in motor control research and is implicated in characterizing sensorimotor integration and kinesthetic abilities [10,12,36]. Pointing to a target serves as a ballistic mechanical motion that is learned early in life and thus does not require much cognitive effort. During this task, participants receive tactile/haptic feedback for only a short period of time (when their index finger reaches the target) as they move their hand back and forth against gravity.
2.3.4 Peg Task

With their dominant hand, the participant then performs a manipulative dexterity test using a Perdue Grooved Pegboard (Lafayette, IN) which consists of 25 holes with randomly oriented slots. Pegs, which have a key along one side, must be (mentally and physically) rotated to match the grooved slots in order to be inserted. This test is routinely given in lab and clinical settings to assess fine-motor skills and touch/haptic sensitivity. It requires intricate visuo-motor coordination as it demands complex coordinate transformations – from the visual orientation of the groove to the physically sensed orientation of the peg by the fingers – to correctly insert the peg in the grooved slot. The controlled hand rotation to insert pegs (goal-directed) into & remove pegs (consequential) from grooved slots follows from the successful realization of this complex coordinate transformation from visual to physical spaces. Solving this requires fine control by the brain of the abundant degrees of freedom in the trunk-arm-hand-fingers complex linkage [37]. This task also serves as an informative proxy of embodied cognition as it assesses the subject’s mental space and the sensory-motor transformations the brain needs to perform to bring the head, arm, and hand into proper synergistic configurations to smoothly complete the task. To assess performance, the length of time to finish inserting and removing all pegs from the grooved slots, was recorded in seconds. An ‘error’ score was counted based on the number of times the subject unintentionally dropped a peg during transfer. Compared to the other tasks in this study, the peg task requires a moderate amount of motor-cognitive effort related to the problem of appropriately referencing the body and visual spaces, coordinating synergies of muscles
to attain successful configurations, and generating smooth motor trajectories that fundamentally depend on haptic feedback during the transport and insertion portion of the task. During the peg task, participants receive a moderate level of tactile/pressure-based haptic feedback when holding the pegs and when placing them into the grooved slots of the pegboard.

2.4 Data Analysis

2.4.1 Unified statistical framework for biophysical signals

To analyze the biosignals harnessed from the autonomic and somatic PNS activity in a unified manner, the current study adopts the SPIBA framework [28]. This framework differs from traditional analytical approaches which assume a priori a ‘one-size-fits-all’ model where groups fall under a Gaussian distribution with additive statistics and homogenous variance. The SPIBA platform looks at the micro-movement spikes (explained in detail in the following section) of biophysical signals and is designed to assess the stochastic changes elicited by various nervous systems across the body. It has also been used to characterize different NS pathologies as they emerge, dynamically change, stabilize, and degenerate over the lifespan of human development [10,12,18]. The SPIBA framework allows for personalized assessments as inspired by approaches in Precision Medicine [29]. Characterizing each participants’ biorhythmic responses in a personalized manner eventually allows us to formulate and compare groups based on similarity in trends and statistical patterns [12].

2.4.2 Micro-Movement Spikes (MMS) explained

Biorhythmic signals obtained from motion and physiological sensors such as the
kinematics of body movements, EMG activity, brain waves/electroencephalographic (EEG) activity, and cardiac activity (ECG), give rise to time series data with fluctuations represented by peaks and valleys. Changes in the timing (inter-peak intervals) and amplitude (peak height) of these peaks and valleys serve as the ‘micro-movements’ of biophysical signals. For example, the micro-movement spikes (MMS) associated with the peak amplitudes of the signal can be calculated by dividing each local peak amplitude by the sum of the average data points between two local valleys/minima and the peak amplitude. This forms a continuous spike train in between the range of 0 and 1 that captures variations in the peak amplitudes of the signal while conserving the timing of the original peaks. This ultimately allows us to treat the signal as a random Poisson process commonly utilized for analysis in computational neuroscience [19]. This micro-movement normalization process also helps us avoid allometric effects due to anatomical differences across subjects [12].

2.4.3 Micro-Movements Analysis Pipeline

To digitally characterize how pain influences somatic and autonomic NS responses, motion and cardiac sensor outputs were analyzed under the SPIBA framework, respectively (Figure 3). For the heart data, inter-beat-interval (IBI) timings were computed by extracting the time elapsed between consecutive R-peaks in the ECG signal (explained in more detail in the following section). For the movement data, we focused on the 3D center of mass (COM) speed kinematic, which serves as a summary of the 17 sensors across the entire body. The COM data was chosen because it was reliably collected across most subjects. The Euclidean norm of the 3D COM data was used to obtain a single time series for each task under each condition of the experiment. In
analyzing the COM speed norm, fluctuations in peak amplitudes were normalized to obtain amplitude micro-movements. The MMS data was then accumulated across entire trials to obtain a frequency histogram via optimal binning [38]. The histogram of MM spikes was then fitted using maximum likelihood estimation (MLE), to determine the best continuous family of probability distributions that fit the data. Based on previous studies in the lab assessing a variety of NS signals (kinematics, ECG, EEG) across thousands of subjects [10,12,19,28,39], we find that biophysical data widely range from the exponential to the normal distribution and thus are best characterized by the Gamma family of distributions (as determined by Kolmogorov-Smirnov tests for empirically derived distributions as well as MLE tests). The Gamma probability distribution function (PDF) reflects the additive random processes in continuous biophysical data during natural behaviors. The Gamma family encompasses a wide range of distributions (symmetrical, skewed, and exponential) allowing us to utilize a unifying family of distributions to characterize different biophysical signals and different populations.

From the Gamma PDF, two parameters – the shape and scale – were empirically estimated with 95% confidence intervals (CI) for each histogram of the MMS data (Figure 4A). Within a Gamma plane, the shape parameter (horizontal axis) ranges from the memory-less exponential distribution (where the shape parameter is 1) to the symmetric Gaussian-like distribution (where the shape parameter is high), with skewed distributions in between. The scale parameter (vertical axis) represents the level of variability of the distribution, from low to high dispersion values. The scale value is mathematically equivalent to the noise-to-signal ratio (NSR) of the distribution. Additionally, the
estimated Gamma moments were visualized by computing the PDF’s mean, variance, skewness, and kurtosis, and plotting them in a four-dimensional graph. These graphs allow us to stratify the statistical features and understand how the stochastic signatures of the motion and heart data shift across different tasks, experimental conditions, and individuals. Under the SPIBA framework, the stochastic signatures reflecting the body’s biophysical responses were thus used to characterize changes in autonomic and sensory-motor feedback elicited by pressure pain.

Figure 3. Unified statistical pipeline for motor and cardiac (biophysical) signals. 
(A) The IBI signal is first extracted from the filtered ECG data to obtain timing micro-movements. 
(B) The 3D COM speed data is converted to a 1D vector via Euclidean normalization. The normalized peaks of the COM norm are then used to obtain amplitude micro-movement spikes (MMS). (A-B) The peaks of the MMS are fit to the best continuous family of probability distributions in an MLE sense. This is the continuous Gamma family whereby the Gamma distribution has shape and scale parameters and an estimated Gamma PDF, along with Gamma moments (mean, variance, skewness, and kurtosis).

2.4.4 Heart Rate Variability Analyses

ECG data typically includes consecutive QRS complexes representing each heartbeat in the cardiac signal. The R-peaks (sharp peaks) within QRS complexes are traditionally used to
assess the timing between consecutive heartbeats (known as the R-R or inter-beat-interval/IBI). Accurately detecting R-peaks is essential for assessing the fluctuations in the IBI signal and in computing various heart rate variability (HRV) parameters. ECG signals may easily be corrupted by various artifacts such as baseline wandering and electrode motion [40]. To pre-process the ECG data, an 8th order Butterworth IIR bandpass filter in the 5-30Hz range was utilized based on the frequency ranges associated with the QRS complex and improvements in signal to noise ratios [41]. A 2nd order Butterworth IIR band-stop filter in the 40-125Hz range was also used to eliminate excess noise/frequencies outside the range of a typical ECG recording. Butterworth filters were used because they minimize corruption of biosignals and effectively suppress signal disturbances beyond the passband [42]. Once the ECG data was preprocessed, R-peaks were detected via a simple peak detection algorithm in MATLAB (MathWorks) software, and the IBI signal was obtained by computing the time between consecutive R-peaks.

Changes in heart rate are the result of autonomic control via the sympathetic (excitatory) and parasympathetic (inhibitory) NSs, which are informative in assessing how pain influences the autonomic NS [21]. The activities of the parasympathetic NS and sympathetic NS can be inferred from the Power Spectral Density (PSD) and Poincaré plots of the IBI signal (Figure 4B-C). The high frequency (HF) component of the PSD (in the 0.15-0.4 Hz range) is associated with parasympathetic activity and a general decrease in heart rate [43]. The low frequency (LF) component of the PSD (in the 0.04-0.15 Hz range) is associated with sympathetic NS activity and blood pressure control [43, 44]. Increases in the ratio between the LF and HF components (LF/HF ratio) have been previously
associated with stress and intense exercise [26,27]. The LF/HF ratio reflects the sympathovagal balance—the contribution of the sympathetic NS in controlling the heart compared to the parasympathetic NS [24]. Since consecutive IBIs are not uniformly spaced, the Lomb-Scargle PSD was utilized because it can handle signals that have been unevenly sampled without introducing resampling problems [45]. The HF, LF, and LF/HF ratio, were computed by integrating the PSD over the associated frequency range.

To better visualize which frequencies (in the HF and LF ranges) dominate the cardiac signal across time, continuous wavelet transforms (CWT) were used to obtain magnitude scalograms of the IBI data using the generalized ‘morse’ wavelet (via the MATLAB signal processing toolbox). The generalized morse wavelets were chosen because they are more versatile in analyzing signals with time varying amplitude and frequency characteristics [46]. CWTs were used to visualize and evaluate temporal changes in frequency power because they can effectively decompose nonstationary (where mean and variance of the time series data can shift over time) signals and provide a personalized assessment of the cardiac activity for each individual.

Poincaré plots were also used to assess sympathetic and parasympathetic activation via time-domain metrics. Poincaré plots serve as a geometrical and nonlinear method to assess the dynamics of HRV and are formed via a scatter of the IBI interval against the preceding IBI interval [47]. The width of the scatter is used to determine the SD1 parameter, which reflects parasympathetic NS activity and is correlated with HF power [48,49]. The length of the scatter is used to determine the SD2 parameter,
which reflects sympathetic NS activity and is correlated with LF power [48].

The PhysioNet Cardiovascular Signal Toolbox was also used to assess the ECG time series. This open-source toolbox is implemented via MATLAB and is designed to assess HRV via standardized algorithms [50]. The raw ECG data was assessed via 30-second windows with 10-second overlap and was preprocessed via the toolbox to obtain a fine grain set of HRV parameters for the full recording. For subjects with relatively clean ECG signals, we obtained a distribution of LF, HF, LF/HF, SD1, SD2, and SD2/SD1 parameters for each task and condition recorded in the study. These distributions were accumulated and assessed across all subjects using boxplots and violin plots created via MATLAB’s kernel density estimation function [51].

The Gamma shape and scale parameters of the IBI signal were also plotted against the frequency and time-domain HRV analytics for the purposes of parameter identification. Because the IBI signals are relatively short for the motor-cognitive tasks (~60-180 samples depending on the task and the participant’s heart rate), the baseline walking task (longest of all the tasks) was used for this evaluation. To obtain a larger sample, cardiac signals obtained from general gait profiling conducted in the lab were also used and analyzed in the same manner. Trend lines were fitted to assess the strength of the linear relationship between parameters from the different forms of analysis (HRV vs. micro-movements approach). The corresponding residuals were checked for any distinct patterns/trends. Stem plots were also used to assess changes in the Gamma MMS and HRV parameters across conditions.
2.4.5 Task Performance and self-report data

To assess how pain influences performance on motor-cognitive tasks, the time elapsed between the start of the task and task completion was computed. This was done for the drawing, pointing, and peg tasks for each subject across all four conditions. Task performance was also compared to changes in the Gamma MMS parameters obtained from the motion data across control and pain conditions. Trend lines were fitted to assess the relationship between the digital biometrics and task performance. The corresponding residuals were checked for any distinct patterns/trends.

To explore the relationship between subjective NRS pain ratings and the digital biometric data, scatter plots were made comparing each subject’s ratings against the absolute difference between the metrics (motor and cardiac) obtained from the pain and control conditions. Pain ratings were also compared to each subject’s perceived pain sensitivity (PPS) rating. Scatterplots were used to assess possible relationships between PPS ratings and changes in the biometrics obtained from both the cardiac and motor signals. Such methods allow us to evaluate the correspondence between physiological metrics and common psychological assessments of pain.
Figure 4. Interpretability of the stochastic signatures and HRV metrics.

(A) Gamma parameter plane spanned by the shape and scale dimensions. The scale parameter corresponds to the noise-to-signal ratio (NSR) of a signal and is inversely proportional to the shape parameter. The shape parameter can span exponential, skewed, and Gaussian distributions. Signatures that fall in the upper left (red point) quadrant demonstrate high randomness (towards 1, the shape represents the memoryless exponential distribution) and a high NSR. Signatures that fall in the lower right quadrant (blue point) demonstrate lower randomness (tending to the Gaussian distribution) and a low NSR. Bars indicate 95% confidence intervals.

(B) Power spectral density of an IBI signal where the red area under the curve represents the LF power and the green area under the PSD represents the HF power.

(C) Poincaré plot of the IBI signal where the width of the scatter represents the SD1 parameter and the length corresponds to the SD2 parameter.

(B-C) The LF, SD2, LF/HF ratio, and SD2/SD1 ratio all correspond to sympathetic NS activity whereas the HF and SD1 correspond to parasympathetic NS activity.
RESULTS

3.1 SPIBA of Motor Activity

The Gamma parameters of the movement signals’ (COM speed) amplitude MMS data were compared across all conditions for each subject individually. Both control conditions often exhibited similar results so only the first control condition is included for clarity and conciseness. The post-pain condition was also not included because it did not demonstrate clear patterns/trends across subjects (Figure A2). This indicated that there were no distinct aftereffects of the pressure pain on the peripheral NS responses or that the aftereffects were too minute to be accurately detected for all participants. For these reasons, we only focus on the control and pain conditions of the experiment for the motor responses. The scale and shape parameters were plotted on the Gamma parameter plane with 95% confidence intervals for the entirety of the resting, drawing, pointing, and peg tasks.

The resting task exhibited a distinct trend across subjects where the control condition showed a consistently higher scale and lower shape parameter compared to the pain condition, with 95% confidence across all subjects (Figure 5).

![Figure 5. Motor signatures during the resting task.](image)

All subjects demonstrated a distinct trend where the motor signal during the control condition fell in the upper left quadrant while the motor signal for the pain condition fell in the lower right quadrant.
The drawing task exhibited a similar trend across subjects where the pain condition showed a lower scale and higher shape parameter compared to the control condition, for seven out of ten of the subjects. For one of these seven subjects (P01), this pattern did not lead to distinct separation at the 95% confidence level. The remaining three subjects exhibited the opposite trend where the pain condition demonstrated a higher scale and lower shape parameter (Figure 6). For one of these three subjects (P10), the control and pain condition had overlapping 95% confidence intervals.

Figure 6. Motor signatures during the drawing task.
Subjects P02, P03, P06, P07, P08, and P09 demonstrated a distinct trend where the motor signal during the control condition fell in the upper left quadrant while the motor signal for the pain condition fell in the lower right quadrant. Subjects P04 and P05 showed the opposite trend. For subjects P01 and P10, the distinction between the control and pain condition was not as clear.

The drawing task exhibited a similar trend to the resting task across subjects, where the pain condition showed a lower scale and higher shape parameter compared to the control condition, with 95% confidence for six out of ten of the subjects. For these subjects, the motor signal tends to a more Gaussian distribution during the pain
condition, indicating that the pain sensation reduces the noise present in the motor stream. Two subjects (P04 and P05) exhibited the opposite trend where the pain condition demonstrated a higher scale and lower shape parameter. For these subjects, the pain signature exhibits a higher NSR and is close to the memory-less exponential distribution (where shape parameter is 1), indicating that the pain introduces more randomness/variability to the motor signal. The remaining two subjects demonstrated motor signatures that overlap at the 95% confidence level, indicating that the motor activity may be impervious to the pain sensation during the drawing task.

The pointing task exhibited a distinct trend that was opposite from that observed from the resting and drawing tasks. Across all subjects, the pain condition showed a higher scale and lower shape parameter compared to the control condition, with 95% confidence for six out of ten subjects (Figure 7). This may indicate that the pain sensation introduces noise/variability to the kinesthetic-reafferent motor signal.

![Figure 7. Motor signatures during the pointing task.](image)

All subjects demonstrated a distinct trend where the motor signal during the pain condition fell in the upper left quadrant while the motor signal for the control condition fell in the lower right quadrant. For subjects P02, P08, and P10, the separation between conditions is not as distinct.
The peg task demonstrated a similar trend to the resting and drawing task. For eight out of ten participants, the pain condition showed a lower scale and higher shape parameter compared to the control condition (for one of these participants, there was not distinct separation at the 95% confidence level). For these eight subjects, the motor signal during baseline tends to a more skewed/exponential distribution while the pain condition elicits movement that is more Gaussian. This indicates that the pain may enhance the kinesthetic signal and increase bodily awareness, both of which may add cognitive load and/or interfere with task performance. The remaining two subjects (P06 and P08) exhibited an opposite trend where the pain condition demonstrated a higher scale and lower shape parameter compared to the control (Figure 8).

![Figure 8. Motor signatures during the peg task.](image)

Subjects P01-P04, P07, P09, and P10 demonstrated a distinct trend where the motor signal during the control condition fell in the upper left quadrant while the motor signal for the pain condition fell in the lower right quadrant. For subject P05, the same trend is observed but the separation is not as distinct. Subjects P06 and P08 show the opposite trend.

The estimated Gamma moments (mean, variance, skewness, and kurtosis) of the COM speed MMS were assessed for each subject via four-dimensional plots (Figure 9).
This was done for both the pain and control conditions and across each of the motor-cognitive tasks (drawing, pointing, and peg task). Lines connect the tasks in the order they were performed, forming triangles that demonstrate the transition in the motion statistics across the 3D gamma space. For each subject we see a unique statistical transition across all moments for most of the motor-cognitive tasks. For most subjects, this triangle seems narrower in the pain condition compared to the control. For some subjects (P04, P08, and P10), the shifts in stochastic signatures differ from the rest — the statistics of the motor signal during the pointing task does not shift drastically across conditions compared to that of the other tasks. For the most subjects, the most drastic shifts in the gamma moments across the control and pain condition appears to occur for the peg and drawing tasks.

**Figure 9. Gamma moments of COM speed across motor-cognitive tasks.**
The 4D plots show the estimated Gamma mean, variance, skewness, and kurtosis (size of marker) across the pain and control condition. Each subject’s motor signals demonstrate unique statistics that shift across the 3D space when pressure pain is introduced. When viewing these points as the vertices of a triangle with the pointing task as a pivotal point, participants P04, P08, and P10 show a rotation of the triangle about this pivotal point, whereas the rest of the participants both translate this point and rotate the triangle about it.
3.2 Analysis of Cardiac (ANS) Responses

3.2.1 SPIBA Approach

The Gamma parameters of the IBI data were compared across all conditions for each subject individually. Heart data from a few subjects and experimental tasks exhibited excess instrumental error to be included for analysis. The first two conditions of the experiment often exhibited similar results so only one control condition was assessed further for clarity and conciseness. The post-pain condition was also not extensively analyzed because it did not demonstrate a clear pattern/trend across all subjects and/or it often resembled the control condition findings (Figure A3). For these reasons we mostly focus on the first control and pain conditions of the experiment. The estimated scale and shape parameters from the Gamma PDF of the IBI signal were plotted with 95% confidence intervals for the entirety of the resting, drawing, pointing, and peg tasks. Across all tasks, it appeared that the pain condition exhibited a higher scale and lower shape parameter compared to the control condition (Figure A4). However, in some cases there is not distinct separation between the control and pain condition at the 95% confidence interval, and for some subjects the opposite trend is observed.

The estimated Gamma moments (mean, variance, skewness, and kurtosis) of the IBI signal were assessed for each subject via four-dimensional plots (Figure 10). This was done for the pain and control condition and across each of the motor-cognitive tasks (drawing, pointing, and peg task). Lines connect the tasks in the order they were performed, forming triangles that demonstrate the transition in the IBI statistics across the 3D Gamma space. For each subject we see a unique statistical transition across all
moments for most of the motor-cognitive tasks. For most subjects, the triangle connecting each motor-cognitive task seems narrower in the pain condition compared to the control.

**Figure 10. Gamma moments of the IBI signal across motor-cognitive tasks.**  
4D plots of the estimated Gamma mean, variance, skewness, and kurtosis (size of marker) of the cardiac signal across the control and pain conditions. Each subject’s cardiac signals demonstrate unique statistics that shift across the 3D plane when pain is introduced.

### 3.2.2 Heart Rate Variability (Frequency + Time-Domain Metrics)

HRV results were compared across all conditions and subjects. Heart data from a few subjects and experimental tasks exhibited excess instrumental error to be included for analysis. As with the SPIBA assessments, the first two conditions often exhibited similar results so only one control condition was assessed further for clarity and conciseness. The post-pain condition was also not extensively analyzed because it did not demonstrate a clear pattern/trend across all subjects and/or it often resembled the control condition findings ([Figure A5](#)). Frequency-domain analysis of the IBI data demonstrated that the pain condition often elicited an increase in LF power (corresponding to sympathetic NS activation) and/or a decrease in HF power (corresponding to parasympathetic NS activity)
for most subjects. Such frequency changes can be visualized qualitatively across the entirety of each task via CWT plots (Figure A6). The LF/HF and SD2/SD1 ratios (where an increase represents sympathetic NS activation) were also computed across the control and pain conditions for each task. Violin plots demonstrate changes in the shape of the probability density of these parameters across participants (Figure 11). For the resting (Figure 11A and 11E) and drawing tasks (Figure 11B and 11F), there is a general increase in both ratios based on data accumulated across subjects. Nonparametric Kruskal-Wallis tests indicate that the ratios across the control and pain conditions come from significantly different distributions for these two tasks (Table A2). However, for the peg and pointing tasks, the changes in both the SD2/SD1 and LF/HF ratios are not explicitly clear.

Figure 11. Combining HRV parameters across participants and domains of analysis for each task. (A-D) Time-domain analysis of the IBI demonstrates changes in the probability densities of the SD2/SD1 ratios across the control and pain conditions. These differences are significant (based on Kruskal-Wallis tests) for the resting, drawing, and pointing tasks. (E-H) Frequency-domain analysis of the IBI demonstrates changes in the probability densities of the LF/HF ratios across the control and pain conditions. These differences are significant (based on Kruskal-Wallis tests) for the resting and drawing tasks. *p<0.05, **p<0.01
3.3 Combining SPIBA and HRV Approaches

To gain a better understanding of how pain influences cardiac responses, results from HRV analyses were assessed considering those obtained via the SPIBA approach. By looking at the results of subjects individually (Figure A4), we noticed specific patterns across both the Gamma statistics and the HRV results. In cases where there was a clear increase in LF power during the pain condition based on the signal’s CWT plot, there was often a clear increase in the scale (as well as a decrease in the shape) of the Gamma parameter plane (Figure 12). This indicated that the pain condition elicited a cardiac signal that was less statistically predictable.

Figure 12. Common trends observed across Gamma and HRV parameters. (A) Gamma PDF of the IBI series during the pain condition. (B) Gamma PDF of the IBI series during the control condition. (C) Gamma parameters tend to fall in the upper left quadrant with higher scale/NSR and lower shape (compared to the other conditions). This corresponds to high magnitude in the LF range of the CWT plot (D). The control condition with high shape and low NSR parameters does not exhibit high magnitude in the LF range (E). Note: These schematic results are obtained from one subject performing the peg task.
3.3.1 The Unique Case of a Subject with Chronic Pain

Heart data analyses for a subject known to experience chronic and acute pain led to unique and consistent findings compared to the remaining subjects. The CWT plots of this subject consistently exhibited high LF power specifically in the 100-150 mHz range. This pattern was observed across all tasks and conditions for this particular participant. It is important to note that while this subject did experience the experimentally induced pressure sensation, they were accustomed to experiencing a consistent level of pain throughout their daily life. The Gamma parameters of the IBI signals from this participant did not show clear separation across all conditions (Figure 13). These results emphasize the importance of looking at the biophysical data in a personalized manner before looking at summary statistics or assessing trends based on the entire sample.

Figure 13. Gamma signatures of cardiac activity and HRV parameters of chronic pain subject. (A) Gamma parameters across conditions do not distinctly separate from one another, alluding to the commonality in the IBI signal across conditions. (B-E) CWT plots consistently show high power in the 100- 150mHz range (corresponding to LF power) regardless of whether pressure pain was or was not introduced.
3.3.2 Relationship between Gamma and HRV parameters

To further assess the relationship between the Gamma PDF and HRV parameters, the Gamma shape and scale obtained from the walking task were plotted against the LF, HF, SD2, and SD1 parameters (Figure A7). Because the IBI signals are relatively short for the motor-cognitive tasks, the control (5 minute) walking task was used for this evaluation. To obtain a larger sample size for this analysis (N=20 subjects), cardiac signals obtained from general gait profiling conducted in the lab were also used and analyzed in the same manner. The strongest linear relationship was observed between the Gamma scale (NSR) and SD2 parameter, and a moderately strong correlation was observed between the Gamma NSR and the LF power (Figure 14). Residual plots from these trend line fittings did not exhibit any distinct trends/appeared randomly distributed. Such exploratory analyses helped us narrow down which parameters/features would be most useful to explore in further assessments.

![Figure 14. Relationship between Gamma NSR and HRV parameters based on the cardiac signal. (A) Strong positive correlation was observed between the log of the Gamma scale (NSR) and the log of the SD2 parameter. (B) Moderately strong correlation was observed between the log of the Gamma scale (NSR) and the log of the LF power from two different modes of analysis.](image)
3.4 Self-Reports in Comparison with Motor, Cognitive, and Physiological Components

Subjective pain ratings were compared across tasks to assess how participant’s perception of their own pain sensitivity (Perceived Pain Sensitivity – PPS) corresponds with the pain ratings reported during experimentally induced pain (Figure 15a).

Subjective pain ratings appeared to positively correlate with perceived pain sensitivity, indicating that participants have a good understanding of their personal pain sensitivity level relative to other people. Interestingly, the deviation between the pain and control condition’s scale parameter (NSR difference/Diff) of the motor signal seems to positively correlate with PPS ratings for the resting and drawing tasks and with the pain ratings for the drawing and pegs tasks (Figure 15B-D).

![Figure 15. Relationship between Gamma NSR of the motor signal and self-reports of pain.](image)

(A) Pain ratings appear to positively correlate with PPS ratings across experimental tasks. (B) For the resting task, the deviation between the pain and control condition’s scale parameter (NSR diff) seems to positively correlate with PPS, but its relationship with the pain ratings is not as clear. (C) For the drawing task, NSR difference seems to positively correlate with both the PPS and pain ratings. (D) For the peg task, the NSR difference seems to negatively correlate with the PPS rating but positively correlate with the pain ratings. Note: Each colored data point in (B-D) represents an individual subject.
3.4.1 Pain Ratings vs. Gamma and HRV Parameters

To assess the relationship between subjective and objective measures, we compare the HRV and Gamma NSR parameter of the cardiac signal with each subject’s pain ratings during the resting task. We focus on the SD2 and NSR parameters as they were identified to be the most informative based on the above findings (Figure 14). During the pain condition, each subject (except the chronic pain subject) exhibits a higher SD2 and scale (NSR) parameter in the pain condition compared to the control (Figure 16A). The absolute difference (Diff) in these parameters was computed to assess how much each subjects’ cardiac signatures during pain deviate from those of the baseline/control condition. This deviation in both the SD2 and NSR parameters seems to positively correlate with subjective pain ratings and perceived pain sensitivity (Figure 16B and 16C, respectively). This indicates that it is possible to elucidate relationships between objective and subjective measures of pain sensation.

Figure 16. Comparing SD2 and Gamma NSR parameters of the cardiac signal to subjective reports for the resting task. (A) SD2 and Gamma scale (NSR) are generally higher during the pain condition for all subjects except the one experiencing chronic pain (starred). (B, C) The deviation between the pain and control NSR and SD2 parameters appears to correlate positively with self-reported pain ratings and perceived pain sensitivity (PPS) ratings.
3.5 Task Performance and Motor Signatures

To evaluate how each subject’s performance on motor-cognitive tasks changes when pain is introduced, the time to complete each motor-cognitive task (drawing, pointing, peg) was compared across each of the four conditions in this study (Figure 17). Errors made in both the drawing and peg tasks were not observed in this sample of neurotypical individuals, thus they were not evaluated here. For the drawing task, there is not a clear change in performance between the pain and the control conditions. However, for most subjects, the time to complete the drawing task was highest for the first condition, and then it gradually decreased for the remaining three conditions, indicating a strong learning component. For the pointing task, there is not a clear change in performance timings between pain and the other conditions. However, it appears that subjects who generally take a longer amount of time to complete the pointing task (subjects #8-13), tend to take more time to finish during the pain condition compared to the control (Figure 17B). For the peg task, there is a clear decrease in performance during the pain condition compared to the remaining conditions for most subjects.

To evaluate the relationship between performance and the Gamma parameters of the motion signal, we fit first-degree polynomials to the data from the pain condition. For the drawing and pointing tasks, the Gamma scale (NSR) appears to positively correlate with the time taken to complete the tasks (Figure 17D-E). However, this correlation is not as clear for the peg task. Residual plots from these linear fittings appeared randomly distributed.
Figure 17. Task performance in relation to the Gamma NSR of the motor signal.
(A) Time to finish the drawing task generally declines from control 1 to the post-pain condition, with a generally higher time to finish the task when pain is induced. (B) Time to finish the pointing task generally changes in a random fashion across conditions. (C) Time to finish the peg task is generally higher during the pain condition compared to the rest of the conditions. (D-F) Correspondence between the log of the Gamma scale (NSR) and the time to finish each motor-cognitive task across conditions. Red lines demonstrate the trends within the scatter for the pain condition. A positive correlation between task performance and the log of the Gamma NSR during the pain condition is observed for the drawing and pointing tasks (D-E), but for the peg task this association is not distinct (F). It is important to note here that the changes in NSR across conditions is shown for the entire sample at once (from these scatter plots we cannot determine how each subject’s pain signature shifts from baseline); combining data across subjects makes the personalized patterns less discernable.
DISCUSSION

The goal of this study was to assess changes in the peripheral nervous systems responses (autonomic and somatic/kinesthetic-afferent information) when the body experiences pressure pain. We aimed to determine whether pain could be objectively characterized via heart rate and motor output variability metrics, and to see how these metrics would compare to self-reported measures of pain. This work ultimately aims to develop a wholistic biometric of pain by characterizing shifts in physical and physiological responses. Such biometrics can help objectively determine if and when the body is experiencing pain and identify how pain influences our kinesthetic abilities. Analyzing motor (kinematic speed) and physiological (ECG) signals in tandem and across fundamentally different motor-cognitive tasks can help elucidate the effects of pain on multiple layers of the nervous systems, helping us develop a multi-faceted biological understanding of pain.

4.1 Pressure pain is reflected differently in motor signals across experimental tasks with different levels of cognitive load

The stochastic patterns (micro-movements/motor output variability) of motions elicited by the peripheral somatic NS – proxied via the Gamma parameters of the center of mass speed signal – shifted during the pain condition compared to the baseline condition. The stochastic shifts differed as a function of the task, depending on the amount of haptic/touch feedback that the task provided and the cognitive demands of the task (memory in drawing and spatio-temporal transformations in the peg).

During the Resting task, the pain signature becomes more Gaussian and maintains
a lower noise-to-signal ratio (scale parameter) compared to baseline. During this task, participants are instructed to sit in a relaxed position and to avoid excess movement. The motor signal during this task may thus represent bodily unsteadiness or jitter not visible to the naked eye. When pain is introduced to the system, it steadily enters awareness, leading to a more predictable stream of motion – the afferent pain signal enhances the predictability of the kinesthetic signal from the proprioceptive system. This is captured by the shifts of the scale and shape Gamma parameters towards lower regimes of noise and more Gaussian distributions. Since the resting task requires no cognitive effort, it is possible that the mind is allowed to form a sustained memory of the lingering pain sensation, which further enhances bodily awareness. This increased bodily awareness then enhances the kinesthetic system’s predictive code, masking external random noise and increasing motion steadiness/reducing excess jitter. Indeed, prior work assessing EEG responses during resting state has shown that thermal pain elicits high statistical certainty that alludes to a more reliable predictive code [6]. This enhanced predictability allows impending variations in the brain signals to be anticipated systematically, building a sustained memory of the lingering pain sensation [6]. The present results are congruent with this inference, and extend the findings from the temperature-pain to the pressure-pain domains.

For the motor-cognitive tasks, we see differences in how the pressure pain influences movement based on the level of cognitive load and touch/haptic (pressure) feedback associated with each task. When movement is involved, it adds a kinesthetic reaference signal that competes with the incoming pain sensation/afference signal.
When assessing the pointing task, we see a flip in the pain signature, where the statistics of the COM speed becomes noisier (higher NSR) and less predictable compared to baseline. This may be due to the nature of the mechanical motion – during this task, subjects must balance the weight of their arm against gravity as they receive little to no pressure-based haptic feedback. Such findings may indicate that the pain sensation easily interferes with the kinesthetic signal, diminishing the sensory feedback the CNS/brain receives to help guide future motor output (predictive code).

On the other hand, for the drawing and peg tasks, we see distinct pain signatures depending on the subject. The drawing task requires the highest level of cognitive effort as subjects must maintain a memory of a sequence of letters and numbers. This introduces a level of distraction as participants are motivated to complete the task quickly and accurately. During the drawing task, participants also receive the highest pressure-based haptic feedback from holding the pen and moving it against the paper surface. This haptic feedback may interfere with the afferent pain signal induced by the pressure pain and enhance bodily awareness as well as the predictive code.

The peg task however requires a moderate level of cognitive effort consisting of visuo-motor geometric transformations and relies more on fine-motor skills. During the peg task, participants receive a moderate level of pressure-based haptic feedback from holding the pegs and inserting them into the grooved pegboard. Both of these may serve to interfere with and/or distract them from the incoming pain sensation.

For both the drawing and peg tasks, the pain signature for most participants appears to exhibit lower noise and higher predictability, however for some subjects the
opposite trend is observed. This result may allude to how the pain differentially influences each subject. For most subjects, the haptic pressure feedback appears to enhance the stability of movement, with the pain sensation inducing higher bodily awareness – both of which can work to enhance the predictive code, allowing for less variable movement patterns. For some subjects, the pain sensation may compete with or overwhelm the kinesthetic signal, leading to a less stable motor output (more variable and less predictable motion). For other subjects, the cognitive component of the task may distract them from the pain sensation, or the pressure-based haptic feedback may interfere with the afferent pressure pain signal, leading to an unclear separation between the pain and baseline condition.

When assessing task performance, we generally observe that it takes longer for subjects to complete the motor-cognitive tasks during the pain condition compared to baseline. This pattern is most clearly observed for the peg task. This may indicate that the pain adds cognitive load (as the body becomes more aware), thus interfering with the time it takes to complete the task. When evaluating the relationship between performance and the Gamma parameters of the motion signal, we observe positive correlations based on the task performed. For the drawing and pointing tasks, we see that a high NSR (in the motor signal) is generally associated with a longer time to complete the tasks. This may indicate that increased noise in the kinesthetic-reafference stream leads to less predictable/stable movements, which in turn interferes with task performance.

For the motor-cognitive tasks, it is possible that there is competition between the kinesthetic and pain signals, and it becomes a matter of which signal is more reliable. If
the pain signal is more reliable (pain awareness is high), it will interfere with the predictive code of the kinesthetic signal and ultimately impede task completion/performance. If the pain signal is less reliable (noisier pain awareness), it will not compete with the kinesthetic signal and will not significantly impact task performance. This contrasts with the resting task where no movement or cognitive effort is required. During the resting task, the motor signal linked to the pain sensation becomes more predictable, offering the possibility of a buffering memory to sustain the lingering sensation of pain, thus bringing it from bodily to full mental awareness.

4.2 Pain’s influence on cardiac activity is apparent across both HRV and SPIBA metrics

Across experimental tasks, we see that the pressure pain sensation influences cardiac activity in a consistent manner. With SPIBA metrics, we typically observe an increase in the NSR and a decrease in the shape parameter during the pain condition compared to baseline. Shifts towards the exponential regimes of the Gamma family (toward the shape value of 1) and towards higher noise levels (scale/NSR) are evident during the pain condition for the drawing, peg, and pointing tasks. This suggests the interpretation that the heart signal becomes noisier and uncertain, and therefore, less predictable during pressure pain stimulation [12]. Concurrently, we observed frequencies in the LF range dominating the heart signal during the pain condition.

For most subjects, we also see a corresponding decrease in HF power, which ultimately leads to an increased LF/HF ratio. Such changes in the frequency-domain metrics indicate that the pain leads to sympathetic activation and/or a general increase in heart rate [24]. Interestingly, when assessing the cardiac activity of a participant who experiences both
chronic and acute pain, we detected a consistent band of high LF power across all tasks and conditions. The Gamma parameters of the IBI signal for this subject also did not show a consistent trend. This may indicate that the subject’s chronic pain elicits a cardiac response that is impervious to the experimentally induced pressure pain.

However, the finding that this subject’s cardiac activity resembles that of typical subjects under the pain condition helps provide some external validity to the pain induction procedure and provides further evidence for how pain leads to increases in LF power.

When looking at HRV metrics in the time-domain via Poincaré plots, we generally observe an increase in the SD2, a decrease in the SD1, and an increase in the SD2/SD1 ratio, each of which are associated with sympathetic NS activation [47]. When comparing metrics from the SPIBA approach with those obtained from HRV analyses, we uncover for the first time a strong correlation between the Gamma scale (NSR) and the SD2 parameter. This new result indicates that the NSR of the IBI signal may also serve as a good indicator of sympathetic activity. Such an agreement in results obtained from different analytical pipelines offers the SPIBA approach as a new unifying statistical platform to analyze, interpret, and make inferences about motor and cardiac signals.

4.3 Personalized and objective biometrics complement subjective reports

Self-reports of pain and pain sensitivity are a quick and efficient way to assess pain in the clinical realm. In general, we see that people have an accurate perception of their pain sensitivity, as their PPS seems to positively correlate with their self-reported pain ratings. Such subjective reports are deemed very useful but could be complemented with more objective approaches. When assessing the relationship between personalized biometrics
such as the individual’s NSR of the motor and cardiac signals, we see that higher deviations in the NSR between the baseline and pain condition correspond to higher PPS and higher pain ratings. A similar pattern is observed when looking at the SD2 parameter of the cardiac signal – the more the SD2 changed across the control and pain conditions, the higher the corresponding PPS and pain ratings. Such findings indicate that objective measures such as the NSR and SD2 parameters can be informative in understanding a person’s pain levels and their general pain sensitivity.

4.4 Multi-faceted approach to understanding pain

With the combination of these findings, we can infer that pain influences motor and cardiac activity in unique ways (Figure 18). Pain signals travel along re-afferent pathways where they can enhance or interfere with kinesthetic reafference. During the resting task, pain provides higher bodily awareness (BA), enhancing the predictive code (PC), and adding stability to the motor stream. For the peg task, this bodily awareness may lead to increased cognitive load, interfering with task performance. For tasks with low pressure-based haptic feedback (such as the pointing task), we see that pain may overpower the kinesthetic signal, interfering with bodily awareness and adding noise to the predictive code. For tasks that provide high tactile feedback but require high cognitive load (such as the drawing task), the cognitive effort needed to accurately complete the task may divert attention from the pain sensation, and the pressure-based haptic feedback may enhance bodily awareness and the predictive code. Regardless of the nature of the motor-cognitive tasks, pain generally influences autonomic regulation, leading to sympathetic overdrive.

Statistically characterizing how pain influences signals extracted from different layers
of the peripheral nervous system (somatic and autonomic) provides a glimpse of the
dynamics between the body’s sensory, motor, cognitive, and autonomic systems. This
embodied approach helps provide a more wholistic perspective to study the facets of
pain sensation and perception. While we offer a summary schematic of how pain
appears to influence motor and cardiac signals, we have observed participants who do
not demonstrate distinct trends and some of which show the opposite trend compared
to the majority. This indicates that the pressure pain may not influence everyone’s PNS
signals of autonomic and somatic NSs in the same manner. These results highlight the
importance of a personalized approach to assessing the data.

**Figure 18. Schematic of pain’s influence across multiple layers of the NSs & experimental tasks.**
During the resting task, pain appears to increase bodily awareness (BA) and the predictive code (PC)
of the proprioceptive system. In this case, pain awareness is the highest. A similar pattern is observed
for the peg and drawing tasks but with variations across subjects depending on the amount of
distraction elicited by the task and how much the subject relies on pressure-based haptic feedback.
During the pointing task, the opposite trend is observed where the pain decreases bodily awareness
and the reliability of the proprioceptive system, leading to greater variability in the movement
trajectory. Pain influences cardiac activity via sympathetic overdrive (SO) for all tasks, but this
phenomenon is most apparent for the resting task.
Such methodologies lend themselves to the Precision Medicine platform which informs the development of personalized treatments [29]. In cases where the pain introduces excess noise to the motor and heart signals, it will be important to find therapies that can reduce bodily awareness, thus canceling out the lingering sensation of pain. Based on the person’s motor and cardiac responses, we can also individually tailor the noise cancellation to favor cognitive performance. While some subjects may rely on internal sources of guidance (such as the predictive code and kinesthetic/bodily awareness) others may rely on external sources (such as physical haptic feedback). The statistical approaches used in this study allow us to probe which feedback (internal vs. external) is most informative in reducing the interference introduced by pain. Ultimately, the biometrics obtained from the motor and cardiac signals can help in identifying the best therapies/treatments to improve motor-cognitive performance.

4.5 Study Implications, Limitations, and Future Work

Pain is a multi-faceted construct, associated with multiple biological, sensory, cognitive, and social components [1]. Thus, it must be explored via a multi-dimensional psychophysiological approach. This study demonstrated that the influence of pain on the body can be characterized via the micro-movement spikes’ statistics obtained from both cardiac and motor signals. With these findings we can begin to differentiate pain re-afference from the kinesthetic stream and understand the relationship between pain, movement, cognition, psychological responses, and physiological activity. Future work aims to incorporate the results of video-based
motion capture to assess facial expression changes during the pain condition. Such analyses will be useful in connecting the internal experience with the social aspects of the pain experience [52]. Facial features undergo subtle changes that sometimes go undetected by the naked eye [19]. Video-based motion capture technologies have been useful in detecting such changes, in objectively characterizing facial expressions, and in providing insight into the motor control processes involved in regulating pain expression [52-53].

The findings of this study also have several clinical implications. Characterizing the effects of sustained pressure on motor and cognitive functioning of healthy individuals can help in the development of accurate and objective digital biomarkers of pain sensation. Such objective assessments are vital to understanding whether and how individuals who may have difficulty communicating their pain – such as those with Autism Spectrum Disorder (1 of 59 in the US), Intellectual Disability, or impaired communication skills – experience pain under normal conditions [54-56]. Autistic individuals often exhibit higher sensitivity to painful stimuli and generally have trouble communicating their emotional or mental states to others [54, 55]. Individuals with Intellectual Disability experience chronic pain that often goes unnoticed and untreated [56]. As such, there is an urgent need to develop objective methods to characterize and understand pain in such individuals. Such assessments can ultimately contribute to early diagnoses, mitigated distress, and can significantly improve quality of life. Moreover, an understanding of the neurophysiological characteristics of our somatic senses is essential for developing long-term and effective solutions to the opioid epidemic [2].
This study has several limitations that can be improved upon:

(1) The results of this work are obtained from limited data from thirteen participants. In multiple cases, some data was missing, not collected, or corrupted. For more generalizable conclusions to be made, data should be collected from more participants. Assessing the pain signatures of various age groups can help develop more precise biometrics that can stratify subjects based on estimates of the population at large. Collecting baseline data from subjects who already experience acute or chronic pain can also provide us with more insight into how pain naturally influences cardiac and motor activity.

(2) It is possible that the experimentally induced pressure pain used in this study does not mimic the physical pain that humans would naturally experience. It is also possible that the pressure pain stimulation on the arm elicits a pain sensation/experience that varies across subjects. Thus, it would be important to test other forms of pain stimulation (such as temperature-induced pain) and see how it compares (via objective measures and pain ratings) to the physical pain subjects regularly experience. It would also be important to assess the time-dependent changes in motor and cardiac activity as pain (via sustained pressure as used in this study along with other pain induction methods) gradually increases and declines. More extensive analyses of pain sensitivity such as the use of the Pain Sensitivity Questionnaire (PSQ) could also help provide more insight into how subjects perceive pain in the context of real-world scenarios [53].

(3) The current study merely focused on specific components of the motor and cardiac signals. Here we only assessed the COM speed as a proxy of the peripheral somatic
NS but it is also possible to study additional kinematics such as the orientation and angular acceleration of various body parts (such as the arm and hand) as the pointing, drawing, and peg tasks are performed. These can help provide further insight into the limb posture, orientation, and curvature needed to complete the tasks. The muscle activity (EMG signal) underlying the arm movements as well as other signals from the ANS such as respiration rate and pupil dilation could also be assessed to provide a more holistic characterization of how pain influences physiological signals.

(4) The assessment of mental distress is an important aspect of the pain experience based on known comorbidities between the two [58]. The cardiac responses observed here may be confounded by a subject’s depressive symptoms, sleep deprivation, or baseline levels of stress/anxiety. Although the participants in this study did not report such symptoms, it would be important to include assessments such as the Depression, Anxiety, and Stress Scale (DASS) that can specifically help measure and control for negative emotional states [59].

4.6 Conclusions

This thesis provides an innovative approach to better understand the mechanisms by which experimentally induced pain – that mimics pathological pain [31] – influences multiple layers of the nervous systems by characterizing both motor and cardiac responses to pain. From this work, we learn that kinesthetic and pain reafference are differentiable and that the kinematic signal can give us a sense of how pain influences
bodily awareness and motor-cognitive task performance. In addition, we learn that pain can interfere with autonomic regulation, eliciting sympathetic overdrive. The observed patterns across the motor and cardiac reactivities also appear to correspond with self-reports of pain and pain sensitivity. This integrative psychophysiological approach can ultimately help create robust techniques to detect pain and aid in the development of personalized interventions. The added convenience of using wearable sensors makes this technique flexible and translatable for use in the clinical realm. The digital biomarkers explored in this thesis open a new realm of research that can help us scientifically understand and characterize pain in a variety of neurodevelopmental disorders and in those with communication disabilities. Ultimately, such research can lead to new methods of identifying and alleviating pain, improving the quality of life of individuals across the globe.
Figure A1. Kinesthetic-reafference: continuous feedback loop between the brain (CNS) and the body (PNS).

The efferent (blue) signals travel from the brain, eliciting motor output while afferent signals (red) travel to the CNS, providing sensory (kinesthetic, pressure, tactile/haptic) feedback from the body. Re-afferent signals continuously flow in closed loops between the central and the peripheral nervous systems with the underlying presence of the ANS. Figure extracted from [12,15] with author permissions.
Figure A2. Sample of Gamma scale and shape parameters for the COM speed across motor-cognitive tasks and participants for all conditions.

In some cases, the signatures of the post-pain condition fall close to the post-pain condition, and the signatures of the control 1 condition fall close to those of the control 2 condition. However, these patterns are not as distinct for all subjects.
Figure A3. Sample of Gamma scale and shape parameters for the IBI signal across motor-cognitive tasks and different participants for all conditions.
In some cases, the signatures of the post-pain condition fall close to the post-pain condition. However, in most cases the signatures of the control 1, control 2, and post-pain conditions cluster together.
Figure A4. Sample of Gamma scale and shape parameters for the IBI signal across experimental tasks and different participants for control and pain conditions. The signatures of cardiac activity during the pain condition tend to fall in regions of higher scale and lower shape compared to those of the control condition. However, in some cases this pattern is not as distinct.
Figure A5. HRV parameters across participants and domains of analysis for each motor-cognitive task.

The ranges of the LF/HF (top) and SD2/SD1 (bottom) ratios appear to increase during the pain condition for both the drawing and peg tasks. The ratios for the control 1, control 2, and post-pain conditions often resemble each other.
Figure A6. Sample continuous wavelet transform (CWT) plots across tasks and conditions. These magnitude scalograms demonstrate which frequencies dominate the IBI signal across time during the control (left) and pain (right) conditions, from different participants across experimental tasks. During the pain condition we see an increase in the magnitude of frequencies in the LF range and/or a decrease in the magnitude of frequencies in the HF range.
Figure A7. Relationship between HRV and Gamma parameters of the cardiac signal.
The strongest linear relationship is observed between the Gamma scale (NSR) and SD2 parameter. The Gamma scale has a moderately strong positive correlation with the LF power. Weaker correlations are observed between the Gamma parameters and the SD1 and HF power. All correlations are negative when looking at the Gamma shape parameter, alluding to the inverse relationship between the Gamma shape and scale. Color bars indicate the range (maximum – minimum) of the original IBI signal for each participant. Note: The results demonstrated here are obtained from the full IBI signal obtained from the walking task for subjects from this study and the same walking task performed during general participant profiling conducted in our lab.
Table A1. Data types collected and the corresponding experimental tasks completed for each participant.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Data Collected</th>
<th>Tasks Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>Motor + Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P02</td>
<td>Motor + Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P03</td>
<td>Motor + Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P04</td>
<td>Motor + Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P05</td>
<td>Motor + Cardiac</td>
<td>Resting, Drawing, Pointing, Peg</td>
</tr>
<tr>
<td>P06</td>
<td>Motor + Cardiac</td>
<td>Drawing, Pointing, Peg</td>
</tr>
<tr>
<td>P07</td>
<td>Motor</td>
<td>Drawing, Pointing, Peg</td>
</tr>
<tr>
<td>P08</td>
<td>Motor + Cardiac</td>
<td>Drawing, Pointing, Peg</td>
</tr>
<tr>
<td>P09</td>
<td>Motor + Cardiac</td>
<td>Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P10</td>
<td>Motor + Cardiac</td>
<td>Drawing, Pointing, Peg</td>
</tr>
<tr>
<td>P11</td>
<td>Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P12</td>
<td>Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
</tr>
<tr>
<td>P13</td>
<td>Cardiac</td>
<td>Resting, Drawing, Pointing, Peg, Gait</td>
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Table A2. Comparison of HRV parameters of the cardiac signal between the control and pain condition via nonparametric Kruskal-Wallis tests.

<table>
<thead>
<tr>
<th>Task</th>
<th>SD2/SD1</th>
<th></th>
<th></th>
<th>LF/HF Ratio</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>χ²</td>
<td>df</td>
<td>p-value</td>
<td>χ²</td>
<td>df</td>
<td>p-value</td>
</tr>
<tr>
<td>Resting</td>
<td>12.44</td>
<td>(1,179)</td>
<td>&lt;0.01**</td>
<td>14.37</td>
<td>(1,175)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Drawing</td>
<td>7.93</td>
<td>(1,157)</td>
<td>&lt;0.01**</td>
<td>6.88</td>
<td>(1,157)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Pointing</td>
<td>4.86</td>
<td>(1,103)</td>
<td>&lt;0.05*</td>
<td>1.39</td>
<td>(1,103)</td>
<td>0.24</td>
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<tr>
<td>Peg</td>
<td>5.48e-04</td>
<td>(1,91)</td>
<td>0.98</td>
<td>1.42</td>
<td>(1,93)</td>
<td>0.23</td>
</tr>
</tbody>
</table>
References


41. Das N, Chakraborty M. Performance analysis of FIR and IIR filters for ECG signal denoising based on SNR. In 2017 Third International Conference on Research in Computational Intelligence and Communication Networks (ICRCICN) 2017 Nov 3 (pp. 90-97). IEEE.


