scientific reports

Check for updates

OPEN

# Somatosensory and prefrontal cortex activity relates to emotional outcomes and hair cortisol concentration in chronic postsurgical pain

Margaret Moreland[1], Caitlin Curry[1], Anthony Wang[1], Madison Vansickel[1,3], Ziyan Wu[1,2] & Christine B. Sieberg[1,2,4]✉

**Chronic post-surgical pain (CPSP) poses significant socioeconomic and humanitarian challenges. This study investigated relationships between resting-state neural activation in the somatosensory cortex (SMC) and emotional functioning outcomes (depression, anxiety, perceived stress), and between prefrontal cortex (PFC) activation and chronic stress, measured by hair cortisol concentration (HCC); and whether pain intensity moderates these relationships in females with CPSP. Twenty-nine females with CPSP reported baseline pain, completed emotional functioning questionnaires, underwent functional Near-Infrared Spectroscopy, and provided hair samples for HCC analysis. Pearson's correlation examined associations between emotional functioning and SMC activation, and between HCC and PFC activation. Benjamini–Hochberg correction adjusted for multiple comparisons. Significant correlations were further tested using moderation analyses to assess whether pain intensity influenced these associations. Left SMC activation was positively correlated with depressive symptoms (r = 0.505, pFDR = 0.036) and anxiety(r = 0.705, pFDR = 0.039). Right lateral PFC activation showed a negative correlation with HCC (r = -0.475, pFDR = 0.048). Pain intensity did not significantly moderate these relationships. Findings suggest associations between brain activity and emotional functioning in females with CPSP, highlighting potential neural targets for future interventions. This study supports the utility of multimodal approaches to further phenotype CPSP and inform precision medicine strategies.**

**Keywords** Chronic post-surgical pain, Functional near-infrared spectroscopy, Chronic stress, Hair cortisol, Tissue saturation index, Somatosensory cortex

Chronic post-surgical pain (CPSP), defined as pain that persists at least three months following the "normal" recovery time of a surgery, is a major concern estimated to impact 20%—40% of surgical patients globally[1,2], making it a significant humanitarian and socioeconomic burden. CPSP severely impacts daily functioning, mental health, and overall quality of life[3]. Complicating this crisis is the number of opioids prescribed after surgery in the United States. An estimated 80% of patients are prescribed opioids after low risk surgeries, 80% of which involve oxycodone or hydrocodone[4], two drugs most commonly involved in drug overdose deaths[5]. Factors contributing to CPSP have been studied and include risks such as pre-surgical pain[6], the surgery itself (*e.g.*, surgery duration, intraoperative nerve injury[7,8]), psychosocial (*e.g.*, pre- and post-operative depression, anxiety, functional disability[9]), and biological (*e.g.*, psychophysical pain sensitivity, poor diffuse noxious inhibitory control efficiency[10–12]) factors. However, there are substantial gaps that warrant investigation in order to discover patient characteristic and disease subtype- specific algorithms to establish personalized, precision medicine for patients presenting for surgery and subsequent treatment selection. The current investigation aims

[1]Department of Psychiatry, Center for Health Outcomes and Interdisciplinary Research, Massachusetts General Hospital, One Bowdoin Square, Boston, MA 02114, USA. [2]Department of Psychiatry, Harvard Medical School, Boston, MA, USA. [3]Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA. [4]Division of Adolescent and Young Adult Medicine, Boston Children's Hospital, Boston, MA, USA. ✉email: CSIEBERG@mgh.harvard.edu

to broaden our mechanistic understanding of factors associated with chronic pain and their impact on outcomes in females with CPSP.

## Why study females?

Chronic pain is highly prevalent in females, with a large body of research dedicated to the biological and psychological sex differences (e.g. postoperative pain, pain intensity, pain tolerance, physical functioning) that contribute to this phenomenon[13–15]. While there are chronic pain conditions that overwhelmingly occur in females (endometriosis, vulvodynia, etc.), chronic pain conditions in general, such as fibromyalgia, migraines, and low-back pain, are overrepresented in females[16]. Regarding post-surgical outcomes, which are the focus of the current investigation, some studies have found females to have higher incidences of chronic pain after surgery, endorsing higher pain intensity and lower thresholds of perceived pain[16,17], findings that align with psychophysical and neuroimaging studies elucidating the mechanisms contributing to sex differences in chronic pain[18–20]. Notably, a recent review concluded that there are robust genetic, molecular, and cellular differences, as well as systems-level mechanisms of acute and chronic pain processing between male and female rodents and humans[21]. While the scope of this study focuses on females due to their heightened risk for CPSP, any proposed pain-stress interactions and outcomes are not proposed to be exclusive to this group.

## Somatosensory cortex activity and emotional regulation in CPSP patients

The biopsychosocial model, as first proposed by Engel[22], highlights the interplay between biological, psychological, and social factors shaping chronic pain experiences[23]. For instance, individuals who have chronic pain conditions are likely to endorse high rates of depression, anxiety, and perceived stress, which could precede pain, be a consequence of pain, or co-occur with pain[24–27]. Past research has been inconsistent regarding the role of factors such as pain intensity on influencing outcomes like depressive symptoms, anxiety, and quality of life among individuals with chronic pain. Some research suggests a multidirectional relationship between emotional functioning (e.g., anxiety and depression) and chronic pain, indicating that worse emotional functioning can exacerbate symptoms of chronic pain and pain intensity and while chronic pain and its symptoms can also contribute to worse emotional functioning[26,29,30]. Emerging research suggests that pain intensity may moderate the relationship between biological outcomes like neural activation patterns, and psychological outcomes, including health status and pain catastrophizing[31,32]. These findings offer a conceptual framework for investigating whether pain intensity similarly modulates associations between brain activity and broader emotional distress outcomes, such as anxiety and depression, particularly in chronic pain populations. Other evidence suggests that perceived pain intensity has a much weaker impact on emotional health and functioning outcomes like quality of life, anxiety, and depression, implicating other factors like pain beliefs, pain interference, and pain disability in predicting mental health outcomes[28,33]. Previous research has been limited by a lack of studies exploring the neurobiological mechanisms underlying the proposed role of pain intensity on emotional functioning outcomes in individuals with chronic postsurgical pain (CPSP). This gap in the literature highlights the need for targeted investigations examining pain intensity as a potential moderating factor in the relationship between neurobiological processes and emotional health outcomes in chronic pain populations.

From a neurobiological standpoint, the somatosensory cortex (SMC) is a major region of interest for understanding chronic pain, as it is known to be involved in pain perception and behavioral outcomes[34]. Neuroimaging studies suggest that maladaptive plasticity in the "pain matrix" brain regions, specifically the SMC, has a causal relationship in the maintenance of pain[35,36]. This proposed explanation suggests that prolonged pain is thought to trigger distinctive plasticity in the SMC associated with structural remodelling/cortical reorganization with direct or indirect involvement in the maintenance of chronic pain[35]. In humans, the SMC has also been found to have a major role in how one views their body, the incorporation of sensorimotor information, and the generation of appropriate affective emotional states[37]. The SMC has been implicated in depressive symptoms and anxiety in animal models, and further linked to emotional regulation in PET, fMRI and other neuroimaging studies. The neurobiological reorganization in the SMC brought on by chronic pain further suggests there may be an altered link to emotional functioning such as perceived stress, depressive symptoms, and anxiety in people with CPSP. This previous research suggests a mechanistic framework for SMC activity in CPSP patients in which distinctive SMC plasticity associated with chronic pain may impact emotional functioning related to depressive, stress and anxiety symptoms. With perceived pain intensity as a variable of interest in terms of its impact on emotional functioning in CPSP patients, this project suggests pain intensity as a potential moderator of the relationship between hemodynamic activity as it regulates emotional functioning in the SMC.

## Prefrontal cortex activity and chronic stress in CPSP patients

Chronic stress as an outcome of CPSP is particularly nuanced given its regulation by a distinct biological system and characterization by a complex endocrine response. Chronic stress can be quantified many ways, including through self-report measures or stress hormone biomarkers, like cortisol, which is a hormonal output of the hypothalamic-pituitary adrenal (HPA) axis. The HPA axis is a network of interactions between the hypothalamus, pituitary gland, adrenal gland and prefrontal cortex (PFC) that responds to stress and controls the secretion of glucocorticoids such as cortisol[38]. The PFC, especially the medial and lateral subregions, plays a critical regulatory role in modulating HPA axis reactivity, with neuroimaging and animal studies demonstrating its capacity to exert top-down inhibition over stress-related physiological responses[39]. Dysregulation or altered activity in the PFC has been linked to excessive cortisol secretion and impaired stress regulation, particularly in chronic pain states[38–40]. Hair cortisol concentration (HCC) analysis from a hair sample allows for researchers to extract chronic cortisol levels up to 9 months preceding collection[41,42]. While research has demonstrated that chronic stress correlates with negative psychological outcomes such as anxiety, perceived stress, and depressive

symptoms[43,44], the evidence has been mixed in female chronic pain populations, with little consensus about the relationship between these variables. For example, one study examining endometriosis found a positive correlation between HCC and quality of life, a pattern that did not exist in healthy controls[41]. This finding suggests a potential adaptive role of HPA axis activity in females with chronic pain, and that high cortisol could be an indication of continued functioning of the HPA axis as an adaptive stress response, including lower pain intensity (hypoalgesia). This may also reflect effective PFC-mediated inhibition of HPA axis overactivation in this subgroup. This finding aligns with the Pain-Stress Model proposed by Lunde & Sieberg (2020)[45] that posits a curvilinear relationship between chronic stress and chronic pain. However, other studies suggest that chronic stress might result in increased sensitivity to pain (hyperalgesia) in females[15]. Such variability in outcomes may reflect differential engagement or impairment of prefrontal regulatory mechanisms across individuals. Chronic stress is an important outcome of CPSP and has broad implications on quality of life and overall health. The impact of pain intensity on this outcome is of specific interest to further phenotyping this population. Given the complex interplay between PFC function, cortisol output, and pain perception in CPSP, this study investigates the extent to which pain intensity moderates the relationship between prefrontal hemodynamic activity and chronic cortisol levels (HCC).

### CPSP, stress, and the brain

Neuroimaging techniques offer a promising avenue for unravelling the neurobiological underpinnings of CPSP and its relationship with chronic stress. The PFC, with its high concentration of glucocorticoid receptors, plays a role in the regulation of the HPA axis—initiating and regulating stress responses[46,47]. Some rodent models have shown the PFC to play an inhibitory role in HPA axis activation thereby elucidating a negative correlation between PFC activation and cortisol levels[38,48,49]. Unique reactivity in the PFC has been implicated in chronic stress conditions, with treatments for psychiatric conditions suggesting improving the regulatory function of the PFC using tools like non-invasive brain stimulation. This research suggests PFC activity and cortisol levels to be associated, and changes in their activity to be implicated in behavioral and cognitive challenges[47,49]. These observations prompt investigation into whether the association between prefrontal cortical activity and cortisol levels in patients with CPSP is influenced by pain intensity, a critical determinant of CPSP pathophysiology. Thus, this exploratory study posits that there may be associations between hemodynamic activity in the PFC and HCC to be modulated by pain intensity in female patients with CPSP.

### Bringing it all together

To our knowledge, no studies have employed neuroimaging techniques to investigate the role of pain intensity on the stress and emotional functioning in females with CPSP. The use of Functional Near-Infrared Spectroscopy (fNIRS) is employed on the brain at rest to provide insights into hemodynamic activity in specific regions of interest (ROIs) thought to be implicated in chronic pain, chronic stress, and emotional regulation. fNIRS is a non-invasive, mobile neuroimaging technique that uses harmless near-infrared light and provides a high level of clinical flexibility and increased ability to study participants in a more naturalistic environment[50].

Considering the central role of the PFC and SMC in pain perception and emotional regulation, the functionality of these brain regions in chronic pain conditions, and the intricate relationship between pain intensity, chronic stress, and emotional functioning, the present investigation aims to further phenotype CPSP. In the current study, we look to 1) investigate the role of pain intensity as a moderator in the relationship between hemodynamic activity in the SMC and emotional functioning outcome of depression, perceived stress, and anxiety and 2) further investigate the role of pain intensity in the relationship between HCC levels and PFC. We propose that studying the interplay between neural activation patterns, as measured by fNIRS and chronic stress biomarkers, such as HCC, alongside emotional functioning measures (e.g., anxiety, depression, perceived stress), will provide preliminary insights into the neurobiological outcomes associated with CPSP. Specifically, we hypothesize that pain intensity will moderate the relationships between 1) resting-state hemodynamic activity in the SMC and emotional functioning outcomes like depression, anxiety, and perceived stress, and 2) PFC activity and chronic stress levels, as measured by HCC. By leveraging fNIRS as a non-invasive neuroimaging modality for capturing cortical brain activity and its relationship with pain and stress, our primary aim is to examine bivariate associations between PFC and SMC activation patterns and outcomes related to emotional functioning and chronic stress levels. Our secondary aim is to evaluate whether pain intensity moderates these associations, thereby clarifying its role as a potential modifier in brain-behavior relationships among individuals with CPSP. And further advancing the understanding of the neurobiological pathways underlying CPSP-related emotional and stress responses.

## Results

### Group demographics, surgical characteristics and outcome measures

The sample included 29 female participants with CPSP (14 – 61 years old, Mean age = 29.21 years, SD = 12.15). Relevant demographic and clinical data are reported in Table 1. Participants reported a mean baseline pain score of 3.41 ± 2.22 at the time of the visit, as well as a mean pain score of 4.55 ± 1.81 in the past week. Means for emotional functioning measures can be found in Table 2 and means for cortisol and TSI in regions of interest can be found in Table 3.

### Primary analysis: Pearson's correlation

The association between emotional functioning measures (anxiety, depression, and perceived stress) with average TSI scores was investigated for 6 ROIs in the lateral and medial PFC, and in the SMC (Fig. 1). Results show a significant positive correlation between depressive symptoms and the left SMC (L.SMC) ($r = 0.505$; $p = 0.006$; $p_{FDR} = 0.036$) and a significant positive correlation between anxiety and the L.SMC ($r = 0.705$; $p = 0.013$;

| | Total Cohort (n = 29) |
|---|---|
| Demographics | |
| Age | 29.21 ± 12.15 (14 – 61) |
| Race (%) | |
| White | 69 |
| Black or African American | 10 |
| Asian, South Asian or Pacific Islander | 7 |
| Hispanic or Latino | 0 |
| Multiracial | 14 |
| Ethnicity (%) | |
| Hispanic or Latino | 10 |
| Other | 90 |
| Clinical information | |
| Lifetime surgeries | 2.83 ± 1.70 (1 – 8) |
| Most recent surgery since study visit (%) | |
| >1 year | 38 |
| 1 – 2 years | 41 |
| 2 – 3 years | 3.5 |
| 3 – 4 years | 3.5 |
| 4 + years | 14 |
| Type of surgery (%) | |
| Orthopedic | 76 |
| Other | 24 |
| Pain experiences | |
| Baseline pain score | 3.41 ± 2.22 (0 – 7) |
| Pain at surgical site (%) | 100 |
| Pain level in past week | 4.55 ± 1.81 (1 – 8) |

**Table 1**. Demographics and clinical information. All participants in the study were cisgender women. The data is expressed as the mean ± SD of a unit or number of patients.

| | Total Cohort (n = 29) |
|---|---|
| Perceived stress | 24.0 ± 7.94 (8 – 42) |
| Anxiety | 18.0 ± 6.57 (8 – 31) |
| Depression | 16.0 ± 7.21 (8 – 32) |

**Table 2**. PROMIS self-report emotional functioning measures.

$p_{FDR} = 0.039$). The relationship between perceived stress and L.SMC was not significant ($r = 0.338$, $p = 0.084$; $p_{FDR} = 0.168$). There were no significant correlational relationships identified in the cohort between right SMC activation.

Correlations between HCC and neural activation patterns in resting state ROIs investigated through Pearson's correlation found a significant negative correlation between HCC and right lateral PFC (R. lPFC) ($r = -0.475$, $p = 0.016$, $pFDR = 0.048$). Significant positive correlation between left lateral PFC and HCC was not significant after Benjamini–Hochberg correction ($r = 0.381$, $p = 0.046$, $pFDR = 0.058$).

## Secondary analysis: pain intensity as a moderator in the relationship between neural activation and emotional functioning

Moderation analyses with pain intensity as a continuous variable were run to test the role of pain intensity as a moderator in significant relationships identified above.

A moderation analysis using PROCESS Model 1 (Hayes, 2022) to examine whether pain intensity moderated the relationship between L.SMC and depression concluded the overall model as significant, $F(3, 24) = 3.41$,

| | Total cohort (n = 29) |
|---|---|
| Cortisol, (pg/mg) | 15.88 ± 31.69 (1 – 171) |
| Left lateral prefrontal cortex, % | 56.14 ± 24.76 (12 – 96) |
| Left medial prefrontal cortex, % | 51.01 ± 26.27 (8 – 93) |
| Right medial prefrontal cortex, % | 62.59 ± 24.63 (5 – 99) |
| Right lateral prefrontal cortex, % | 47.52 ± 23.64 (3 – 93) |
| Left somatosensory cortex, % | 58.06 ± 15.42 (29 – 94) |
| Right somatosensory cortex, % | 47.08 ± 21.11 (6 – 91) |

**Table 3**. Cortisol and TSI in regions of interest.

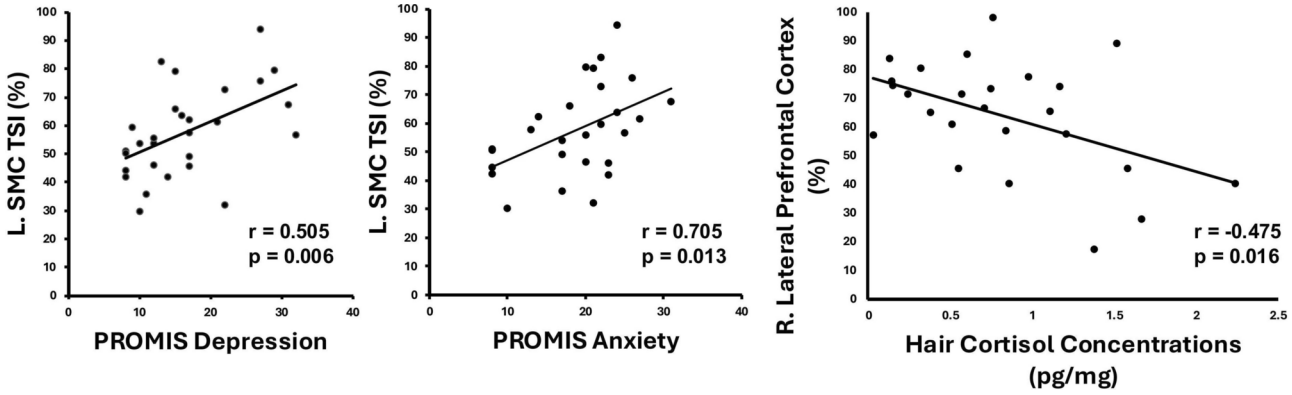


**Fig. 1**. (**a**) A significant positive correlation is observed between depressive symptoms and left SMC (L.SMC) activity (r = 0.505; p = 0.006, $p_{FDR}$ = 0.036),where significance was conserved after False Detection Rate (FDR) adjustment of the p value (r = 0.705; p = 0.013, $p_{FDR}$ = 0.039). (**b**) Significant positive correlation is also reported between anxiety and L.SMC activity (r = 0.654; p = 0.008; $p_{FDR}$ = 0.048). (**c**) A significant negative correlation is present between HCC and right lateral prefrontal cortex (R.lPFC) activity (r = -0.475, p = 0.016, pFDR = 0.048).

$p = 0.0337$, with an $R^2$ of 0.299, indicating that approximately 29.9% of the variance in depression scores was explained by the predictors. There was a significant main effect of L.SMC on depression, b = 0.48, SE = 0.17, t = 2.78, p = 0.0103, with higher L.SMC scores associated with higher depression scores. The main effect of pain intensity (BPS) on depression was not significant, b = 0.06, SE = 0.17, t = 0.33, p = 0.7419, nor was the interaction term between L.SMC and pain intensity, b = -0.23, SE = 0.19, t = -1.19, p = 0.2457. Additionally, the change in $R^2$ due to the interaction term was not significant ($\Delta R^2 = 0.0414$, F(1, 24) = 1.42, p = 0.2457), indicating that pain intensity did not moderate the relationship between l.SMC and depression in this sample.

A secondary moderation analysis examining pain intensity moderating the relationship between L. SMC and anxiety found the overall model was not significant, F(3, 23) = 2.32, p = 0.10, $R^2 = 0.23$. The main effect of L. SMC on anxiety was significant (b = 0.46, p = 0.0181), while pain intensity was not a significant predictor (b = -0.09, p = 0.6353). The interaction between L. SMC and pain intensity also were not significant (b = 0.03, p = 0.8675), indicating that pain intensity did not moderate the relationship between L. SMC and anxiety.

A third moderation analysis was conducted to examine whether pain intensity moderated the relationship between R.lPFC and HCC levels. The overall model was not significant, F(3, 21) = 2.08, p = 0.13, with $R^2 = 0.23$. There was a significant negative association between R.lPFC and cortisol levels (b = -0.58, p = 0.0289), indicating that higher R.lPFC values were associated with lower cortisol levels. Pain intensity was not a significant predictor (b = 0.06, p = 0.7665), and the interaction between R.lPFC and pain intensity was also not significant (b = 0.01, p = 0.9558), indicating that pain intensity did not moderate the relationship between R.lPFC and cortisol levels in this sample.

## Discussion

The present study is the first to our knowledge investigating the mechanistic impact of pain intensity on the relationship between neural activation, emotional functioning, and chronic stress in females across the lifespan (adolescents-older adults) living with CPSP. Specifically, we found neural activation patterns proposing a correlational relationship between the L.SMC and depressive symptoms, as well as between the L.SMC and

anxiety. These findings suggest that in individuals with CPSP, L.SMC hemodynamic activity may be associated with an increase in depressive and anxiety symptoms, overall implicating this region in emotional regulation. While previous literature indicates that perceived pain intensity may be a risk factor for adverse emotional functioning[51,52], the present study did not find pain intensity to be a moderator of the relationship between L.SMC activation and emotional functioning.

The SMC is integral to pain processing networks, particularly for its role in the sensory-discriminative aspects of pain[37]. Neuroimaging studies have consistently shown that the SMC is highly responsive to noxious stimuli, with activity levels correlating directly with reports of pain intensity. The proposed correlational relationship between SMC activity and emotional functioning levels of depression and anxiety in this CPSP cohort further support this body of evidence, also lending support to past research supporting that the SMC's function extends beyond sensory processing to include its involvement in emotional regulation. Moreover, the integration of the SMC into broader pain-processing networks, such as the "pain matrix" that includes regions like the PFC and insula, supports its role in modulating both the sensory and affective components of pain[36]. Previous studies have also demonstrated that increased activity in the SMC is proportional to both pain stimulus and subjective pain rating[53]; however, these experiments often use acute, experimental pain paradigms, only in healthy volunteers of both sexes. This present study is the first, to our knowledge, to show a correlational relationship between SMC activity and depressive and anxiety symptoms in individuals with chronic pain. However, the proposed mechanistic framework linking SMC plasticity to emotional function outcomes being moderated by pain intensity was not supported by the analysis of this cohort. This could further support research suggesting pain intensity is not a major predictor of outcome in CPSP populations and opens future opportunities to research other important pain factors like pain interference or other psychosocial measures. The exploratory nature of this analysis, however, does not attempt to disprove influences of pain intensity on outcomes in CPSP patients, but instead to suggest pain intensity is not a major moderator in the proposed mechanism. Future research should also examine whether pain intensity functions as a mediator in the relationship between somatosensory cortical activation and emotional functioning outcomes, which may help clarify its indirect contributions to the affective experience of chronic pain.

The focus on females allowed for us to hone a level of specificity not available to experimental designs including both sexes. Measures like brain-region activation levels and HCC are both dependent on bodily systems that are highly sex-dependent, creating a confounder in mixed-sex cohorts. The ability to focus this investigation on females significantly strengthens the validity and generalizability of these results to a population at high risk for poor pain outcomes and contributes to research on neural mechanisms underlying emotional regulation in females. While our results highlight important pain-stress interactions in females, future research is needed to determine whether these patterns extend to males or other chronic pain populations. These results could lead to further research that could inform targeted interventions aimed at regulating SMC activity to improve emotional functioning in patients with CPSP.

Our results indicate that there is a negative correlation between activation levels in the R.lPFC and chronic stress via HCC levels. These results support previous research suggesting PFC plays a modulatory role in the stress response both stimulating and inhibiting HPA axis, with results of our correlational analysis specifically supporting the PFC's inhibitory role[46,54]. Secondary analysis examining whether pain intensity moderates the significant correlation between R.lPFC activity and HCC found no evidence that pain intensity plays a significant role in this relationship. Hemodynamic activity patterns involving the PFC have been implicated in multiple acute and chronic stress disorders (i.e. acute stress disorder, post-traumatic stress disorder)[55]. However, specific patterns of activation have implicated subparts of the PFC with deep brain regions, for example, the stimulatory relationship between medial PFC region and the striatum during acute stress events[56], that fNIRS does not have the capabilities of broaching. While our results link PFC activity with HCC, secondary analyses suggest that this neural mechanism is not influenced by pain intensity. However, these results do expand upon the literature on neural mechanisms of chronic stress in females, since so much of the research thus far has focused on animal models. While our current experimental design did allow for the collection of more acute stress over the past month via self-report (PROMIS Perceived Stress) and chronic stress levels (HCC), future directions could also incorporate salivary cortisol data collection to further elucidate the complex relationship between acute and chronic stress, pain, and neural activation patterns.

The integration of chronic stress and emotional regulation into existing chronic pain models could help advance our understanding of CPSP and further efforts in phenotyping this complex population. Proposed SMC and PFC activation and its correlational link to emotional functioning and stress allows for future pain models to be expanded to incorporate neurobiological data and biomarkers. Future research adapting more mature pain models with multi-methodological approaches could account for neural circuits associated with pain as it relates to specific outcomes. This could lead to the development of multi-modal interventions that aim not only to alleviate pain but also to restore normal functioning in key brain regions involved in the stress-pain interaction. The results of this study are, however, exploratory, and aim to provide proof-of-concept evidence for multimodal approaches in chronic pain populations. Such targeted interventions could significantly enhance our ability to manage CPSP more effectively through phenotyping of CPSP, which could transform patient care and improve clinical outcomes. Ultimately, this work aligns with the broader goals of personalized medicine and precision healthcare, offering a pathway to better address the long-term burden of chronic pain on both individuals and the healthcare system.

The present study should be considered in light of its limitations. One limitation is the small sample size of the cohort, which resulted in modest statistical power of our analyses. However, a priori analyses were conducted using G*Power to ensure adequate statistical power for our analyses. For the bivariate correlation analysis, we selected an effect size of $r = 0.50$, corresponding to a large effect as defined by Cohen (1988). This analysis indicated a required sample size of $n = 29$ to achieve 80% power with $\alpha = 0.05$, which is in range of our

study sample. Similarly, for the moderation analysis, we conducted a power analysis using a linear multiple regression model (R2 increase) with an effect size of f2 = 0.35, also classified as a large effect according to Cohen (1988). This calculation yielded a required sample size of n = 29, demonstrating that our sample meets the necessary threshold. Due to the exploratory nature of this investigation, the results are promising and lay the foundation for further analysis of the relationship between neural activation patterns, stress, and emotional functioning outcomes in CPSP populations. Future directions should include a healthy, pain, and surgery-free control group and using longitudinal designs (pre-, peri-, & post-surgical), as well as advanced statistical analysis techniques to investigate neural activation patterns as predictors for cortisol levels and emotional functioning. Further, the cross-sectional design limits our ability to draw definitive conclusions about the causal relationships between chronic stress, pain intensity, and neural activity. Future research should employ longitudinal designs to investigate how these variables interact over time. Further expanding data collection longitudinally would allow for the specific tracking of acute and chronic changes, as well honing in on specific characteristics in the acute to chronic transition related to chronic stress and chronic pain. Additionally, while fNIRS offers a valuable tool for measuring cortical hemodynamic responses, its spatial resolution is limited compared to other neuroimaging methods, such as functional MRI[50]. Multi-modal imaging techniques could provide a more comprehensive understanding of the neural circuits involved in CPSP. Future directions of this research would involve expanding cortisol region coverage of the fNIRS to further investigate diverse pain areas impacted by CPSP, as well exploring other imaging techniques that can access deep-brain hemodynamic activity. With the scope of this investigation being exploratory, and with the aim of capturing baseline cortical activity, resting state activation levels were appropriate to provide preliminary results. However, the absence of task-evoked pain paradigms limits our ability to interpret causality and dynamic functional responses to pain or stress stimuli. This provides a strong future direction as further research can expand upon this work through the incorporation of tasks like conditioned pain modulation and offset analgesia. Furthermore, the exclusion of participants with severe psychiatric disorders may limit the generalizability of our findings to individuals with comorbid mental health conditions, who represent a significant proportion of the chronic pain population. Participants also had a variety of different surgeries leading to the onset of CPSP. However, our work and that of others[6], has demonstrated that surgery type is not predictive of who will transition to CPSP[57,58]. This is likely due to other underlying factors, like the ones investigated in this study, contributing to the central sensitization pain so surgery type is less significant.

In conclusion, our findings propose correlational links between SMC activity and depressive and anxiety outcomes, as well as PFC activity with HCC. Pain intensity was not found to significantly impact these relationships. This study aims to contribute mechanistic understanding of the link between CPSP and emotional functioning outcomes, as well as to further investigate the role of pain intensity in influencing outcomes. This project also aims to further promote the use of biomarkers and multimodal approaches to CPSP research and psychosocial outcomes, and to further phenotype this complex population.

## Methods

### Participants

Twenty-nine participants were recruited from referrals from Boston Children's Hospital, as well as from posters in the hospital and community, and social media posts. Participants presented with chronic pain following surgery, defined as pain persisting at least three months past the expected recovery time. Informed consent was obtained at the beginning of the study visit from all participants. Ethical approval was obtained from the Institutional Review Board at Boston Children's Hospital. All methods were performed in accordance to the Declaration of Helsinki.

Potential research participants were screened by the research team to determine eligibility. The present study is part of a larger ongoing investigation deeply phenotyping CPSP risk across the lifespan (adolescents-older adults). As part of the larger study, 236 people have been screened eligible, while 42 participants have been screened ineligible. No participants have dropped out of the study during the study visit for any reason. Inclusion criteria for this study consisted of having CPSP, therefore pain for at least 3 months following surgery, being at least 12 years old, female, and on stable dosages of all medications during the past 30 days. Participants in this cohort reported mainly orthopaedic surgeries (75.9%) and the participants that reported other surgeries included laryngeal, obstetric, thoracic, orofacial and bariatric. Exclusionary criteria consisted of the following: 1) reported history of significant psychiatric or neurological disorders such as psychosis, schizophrenia, and bipolar disorder, 2) recent or current illicit recreational drug use, 3) use of antipsychotic medication, and 4) recent (within 12 months) traumatic brain injury. Additionally, we adopted a process that limits plasma levels of over the counter (OTC) medications that are taken 'pro re nata' (PRN) (unscheduled) at the time of participation. Specifically, participants could not have taken a non-narcotic pain reliever within 48 h prior to a study visit. If a participant had to take such a PRN medication within 48 h, then their study visit was rescheduled. This is important as OTC analgesics, including Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and acetaminophen are known to alter brain responses[59].

### Experimental design

The study visit involved a one session in-person study visit and included the following data collection: (1) pain and emotional functioning self-report questionnaires administered on an iPad in the lab through Redcap, a secure web-based platform for data collection; (2) collection of a hair sample for HCC data extraction; (3) fNIRS data collection in resting state.

## Measures

The outcomes of this investigation were emotional functioning, HCC, and resting state activation in the SMC and PFC using fNIRSs. The following self-report measures were administered as Redcap questionnaires on an iPad at the beginning of the study visit.

Self-Report.

*Baseline pain score*

Participants used a numeric rating scale (NRS) to rate their baseline pain score at the study visit, which has been validated for measuring post-operative pain and quantifying pain intensity.

*Anxiety*

The *Patient-Reported Outcomes Measurement Information System* (PROMIS)[60] is a tool used to standardize patient-reported outcomes. The *PROMIS anxiety short form* scale is a seven item, five-point scale that assesses the extent to which an individual has experienced anxiety in the past seven days. This scale includes items such as "In the past 7 days… I felt fearful". The *PROMIS Pediatric Anxiety short form* follows the same structure as the adult form, but includes age-appropriate questions such as "In the past 7 days… I felt like something awful might happen".

*Depression*

The *PROMIS Depression short form* is an eight item, five-point scale that assesses the extent to which an individual has experienced depression in the past seven days. The scale includes items such as "In the past 7 days… I felt worthless". The *PROMIS Pediatric Depressive Symptoms short form* follows the same structure as the adult form, but includes age-appropriate questions such as "In the past 7 days… I could not stop feeling sad".

*Perceived stress*

To measure perceived stress in the past month, the *NIH Toolbox Perceived Stress Scale* was used. This includes a pediatric version for ages 13–17 years and an adult version. Both the pediatric and adult versions assess how the individual has perceived their stress to be in the past month. Examples of questions include "In the past month… how often have you been upset because of something that happened unexpectedly?" "In the past month… How often have you been angered because of things that happened that were outside of your control?".

## Chronic stress: HCC collection

Hair sample collection happened during the in-person study visit. A sample was cut from a posterior vertex position as close to the scalp as possible. At minimum, 10 mg of hair for a 3 cm segment was obtained from every participant. Hair is estimated to grow at 1 cm per month, therefore 3 cm samples were analysed and estimated to represent cortisol levels from 3 months prior. Samples were packaged in tinfoil and sent to be assayed at Dresden University of Technology (TU Dresden) in Germany. Liquid chromatography coupled with tandem mass spectroscopy (LCMS/MS) was the method use for HCC extraction, and results were sent back to the lab team for analysis (Detailed description of HCC extraction and analysis is further explained[42]).

## fNIRS CW7 system and experimental setup

A continuous wave near-infrared optical imaging system (CW7, TechEn Inc., Milford, MA, USA) was used to record time courses of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations at a sampling rate of 25 Hz. This system was comprised of 12 laser sources and 24 detectors, each emitting two wavelengths (690 nm and 830 nm) of near-infrared light. Sources and detectors were systematically arranged across the participant's entire head, with a spatial separation of 3.2 cm between adjacent source-detector pairs, providing 46 measurement channels covering the frontal, temporal, parietal, and occipital lobes (see Fig. 2 for the detailed channel layout).

The fNIRS cap was fitted securely onto each participant's head, ensuring good contact between optodes and scalp by adjusting the positioning of the cap and using an adjustable strap under the chin to prevent movement. Participants were given standardized instructions and a practice session to familiarize them with the experimental tasks.

For brain data acquisition, a standard headcap was used to position fNIRS sources and detectors accurately over the cortical ROIs. The fNIRS setup consisted of five light emitters and eight detectors, positioned bilaterally over the prefrontal cortices (PFC), and four emitters and six detectors over the bilateral somatosensory cortices (SMC). This configuration allowed for a total of 12 cortical measurement channels within the PFC and SMC regions, sensitive to detecting hemodynamic changes in deeper cortical structures. To capture superficial hemodynamic signals, nine short-separation source-detector channels (1 cm apart) were situated over key ROIs, providing sensitivity to scalp blood flow and enabling regression of superficial signals from the long-separation channels[61].

The six ROIs selected included the bilateral lateral prefrontal cortices (lPFC), bilateral medial prefrontal cortices (mPFC), and bilateral somatosensory cortices (SMC). These ROIs were chosen based on established neuroimaging literature linking them to pain perception and modulation[7,37,62].

## Resting-state fNIRS data acquisition

To establish a baseline brain activity profile, each participant underwent a resting-state assessment lasting 10 min. During this period, participants were instructed to sit still, remain relaxed, and focus on a black cross displayed centrally on a laptop screen in a dim room. The black cross remained visible for the entire duration of the resting-state session to minimize visual distractions. This protocol allowed for the collection of resting-state

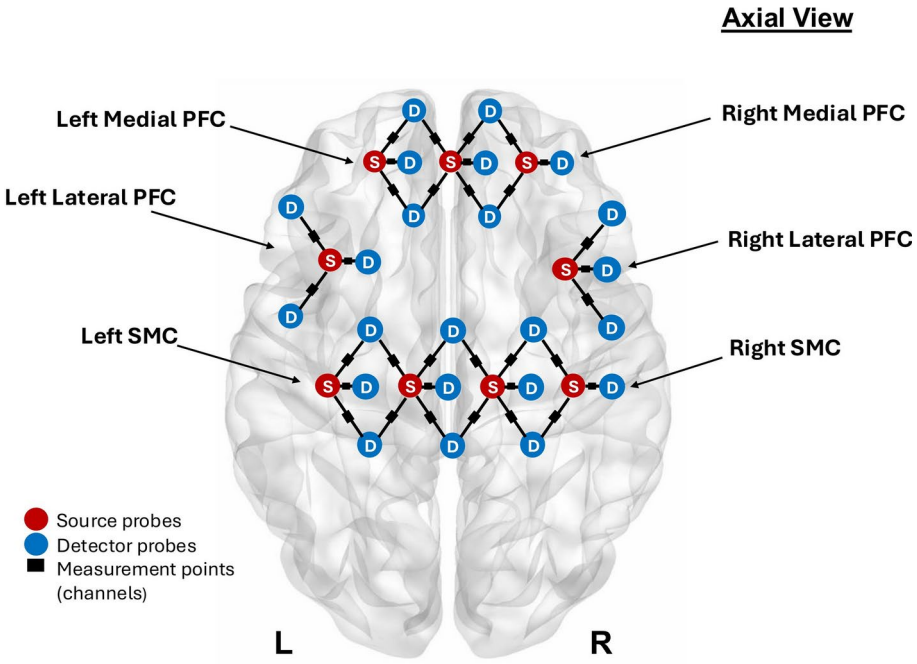


**Fig. 2**. The fNIRS cap source – detector channel layout was created using a built-in Matlab toolbox BrainMap Viewer 1.7 (https://www.nitrc.org/projects/bnv/) and PowerPoint to reflect the specific fNIRS layout used in this study. The channel arrangement is displayed above. Sources and detectors are uniquely placed to capture brain data from the 6 regions of interest that have been chosen due to previously literature implicating these regions in pain and emotional functioning.

hemodynamic signals across predefined ROIs, which were used as a reference for analysing task-evoked brain activity.

## fNIRS data preprocessing

The fNIRS data were pre-processed using a combination of the Homer2 toolbox (Huppert et al., 2009) and custom MATLAB scripts (MATLAB version R2019b, The MathWorks Inc., Natick, MA, USA). Initial quality checks were conducted using the qt-nirs toolbox (https://github.com/lpollonini/qt-nirs), and the scalp-coupling index (SCI) was calculated for each channel, with a threshold of 0.5 used to exclude channels with poor optode-scalp coupling and unreliable signal quality[63]. Raw light intensity signals were converted to optical density (OD) values. The process of converting raw light intensity signals to OD values is a crucial step in fNIRS data preprocessing. The raw light intensity, measured by the detectors in the fNIRS system, reflects the amount of light that has passed through the scalp, skull, and brain tissues. This light intensity varies based on absorption and scattering properties of different tissue types and chromophores, such as hemoglobin. The OD transformation is performed using the formula:

$$OD = log_{10}\left(\frac{I_0}{I}\right)$$

where $I_0$ is the initial light intensity and is the measured light intensity at each time point. This conversion step normalizes the data and reduces the impact of baseline variations in light source power and optode coupling. OD values thus represent relative changes in light absorption, which are then used to calculate changes in hemoglobin concentration.

After conversion to OD, temporal filtering is applied to the time-series data using a bandpass filter with cutoff frequencies between 0.01 and 0.1 Hz. This bandpass filter removes low-frequency components (e.g., slow baseline drift) and high-frequency physiological noise (e.g., cardiac pulsations at 1–2 Hz and respiratory artifacts at 0.2–0.4 Hz) that are unrelated to the hemodynamic response of interest. The low cutoff of 0.01 Hz helps eliminate very slow oscillations, which could be caused by system instabilities or changes in room temperature. The high cutoff of 0.1 Hz helps eliminate physiological noise, which may otherwise obscure or distort the signals of interest. Thus, this bandpass filtering step helps enhance the signal-to-noise ratio, ensuring that only the relevant hemodynamic components are retained for further analysis. This preprocessing step is essential for reducing artifacts and improving the quality of fNIRS data, allowing for more accurate extraction of physiological signals related to neural activity.

The OD values were then transformed into relative changes in HbO and HbR concentrations using the modified Beer-Lambert law[64]. Motion artifacts were detected using a combination of visual inspection and automated metrics (e.g., signal derivatives), and corrected using a spline interpolation algorithm, which replaced

noisy segments with interpolated values based on neighboring non-artifactual data, thereby preserving the temporal and spatial integrity of the hemodynamic response[65]. To minimize contamination from superficial hemodynamic fluctuations, signals from short-separation channels were used to create a reference that was regressed from long-separation channels using a general linear model approach[66], enhancing sensitivity to cortical signals. To incorporate HbO and HbR levels into an absolute measure of brain region activation, we calculated TSI scores using the equation below. This allows for a ratio of oxygen concentration to be calculated, a common measure of blood volume changes in near infrared spectroscopy analysis[67]:

$$TSI = \frac{[HbO]}{[HbO] + [HbR]} \times 100\%$$

This comprehensive preprocessing pipeline ensured that the fNIRS signals were optimized for robust detection and interpretation of brain hemodynamic changes during resting-state and task-evoked conditions.

## Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA). Prior to analysis, the distribution of all continuous variables was assessed using the Shapiro–Wilk test[68]. To meet the assumptions of normality, variables were z-transformed where appropriate. Descriptive statistics were used to summarize demographic characteristics, clinical and surgical histories, and outcome measures, with means and standard deviations (or ranges) reported as applicable.

The primary analysis involved a series of Pearson's bivariate correlation analyses to examine associations between (1) hemodynamic activity in the six resting-state regions of interest (ROIs)—bilateral lateral prefrontal cortex (lPFC), medial prefrontal cortex (mPFC), and somatosensory cortex (SMC)—and (2) psychological and biological outcomes including depressive symptoms, anxiety, perceived stress, and hair cortisol concentration (HCC). These analyses aimed to identify brain-behavior relationships relevant to emotional functioning and chronic stress in individuals with CPSP. Two-tailed p-values were considered statistically significant at $\alpha \leq 0.05$, and the Benjamini-Hochberg [69] procedure was applied to control the false discovery rate (FDR) due to multiple comparisons.

For the secondary analysis, any correlational relationships that remained statistically significant after FDR correction were further examined using moderation analyses to assess whether pain intensity moderated the relationship between neural activation and psychological or stress-related outcomes. Moderation models were implemented using Hayes' PROCESS macro (version 4.2), Model 1, with pain intensity as a continuous moderator variable. The significance of interaction effects was evaluated through the change in $R^2$ ($\Delta R^2$) and associated F-tests. This two-step approach allowed for the investigation of both direct associations and potential conditional effects of pain intensity on brain-outcome relationships.

## Data availability

The data used in this study are available upon request. Researchers can request access to the data by contacting csieberg@mgh.harvard.edu.

Received: 20 December 2024; Accepted: 26 April 2025
Published online: 10 May 2025

## References

1. Einhorn, L. M., Krishnan, P., Poirier, C. & Ingelmo, P. Chronic postsurgical pain in children and adolescents: a call for action. *J. Pain Res.* **17**, 1967–1978. https://doi.org/10.2147/JPR.S464009 (2024).
2. Rosenberger, D. C. & Pogatzki-Zahn, E. M. Chronic post-surgical pain – update on incidence, risk factors and preventive treatment options. *BJA Educ.* **22**(5), 5. https://doi.org/10.1016/j.bjae.2021.11.008 (2022).
3. Thapa, P. & Euasobhon, P. Chronic postsurgical pain: current evidence for prevention and management. *Korean J. Pain* **31**(3), 3. https://doi.org/10.3344/kjp.2018.31.3.155 (2018).
4. Wunsch, H., Wijeysundera, D. N., Passarella, M. A. & Neuman, M. D. Opioids prescribed after low-risk surgical procedures in the United States, 2004–2012. *JAMA* **315**(15), 1654–1657. https://doi.org/10.1001/jama.2016.0130 (2016).
5. Hah, J. M., Bateman, B. T., Ratliff, J., Curtin, C. & Sun, E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. *Anesth. Analg.* **125**(5), 1733–1740. https://doi.org/10.1213/ANE.0000000000002458 (2017).
6. Sieberg, C. B. et al. Predictors and trajectories of chronic postoperative pain following hip preservation surgery. *J. Hip Preserv. Surg.* **4**(1), 45–53. https://doi.org/10.1093/jhps/hnx003 (2017).
7. Karunakaran, K. D. et al. Can pain under anesthesia be measured? pain-related brain function using functional near-infrared spectroscopy during knee surgery. *Neurophotonics* https://doi.org/10.1117/1.NPh.10.2.025014 (2023).
8. Rivera-Ramos, H. et al. Incidence and risk factors of chronic post-thoracic surgery pain: A retrospective study. *Rev. Esp. Anestesiol. Reanim.* https://doi.org/10.1016/j.redare.2024.101644 (2024).
9. Schreiber, K. L. et al. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. *Pain* **154**(5), 660–668. https://doi.org/10.1016/j.pain.2012.11.015 (2013).
10. Honigman, L., Yarnitsky, D., Sprecher, E. & Weissman-Fogel, I. Psychophysical testing of spatial and temporal dimensions of endogenous analgesia: conditioned pain modulation and offset analgesia. *Exp. Brain Res.* **228**(4), 493–501. https://doi.org/10.1007/s00221-013-3580-7 (2013).
11. Yarnitsky, D. et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* **138**(1), 22–28. https://doi.org/10.1016/j.pain.2007.10.033 (2008).
12. Sieberg, C. B. et al. Pilot investigation of somatosensory functioning and pain catastrophizing in pediatric spinal fusion surgery. *Pain Manag. Nurs. Off. J. Am. Soc. Pain Manag. Nurses* https://doi.org/10.1016/j.pmn.2022.11.001 (2023).
13. Kanaan, S. F., Melton, B. L., Waitman, L. R., Simpson, M. H. & Sharma, N. K. The effect of age and gender on acute postoperative pain and function following lumbar spine surgeries. *Physiother. Res. Int.* **26**(2), e1888. https://doi.org/10.1002/pri.1888 (2021).
14. Moretti, B. et al. Influence of sex and gender on the management of late-stage knee osteoarthritis. *Musculoskelet. Surg.* **106**(4), 457–467. https://doi.org/10.1007/s12306-021-00725-8 (2022).

15. Roy, M. & Vachon-Presseau, É. Cortisol increases visceral pain in women but not in men. *Pain* **160**(8), 1691. https://doi.org/10.1097/j.pain.0000000000001580 (2019).
16. Casale, R. et al. Pain in women: a perspective review on a relevant clinical issue that deserves prioritization. *Pain Ther.* **10**(1), 287–314. https://doi.org/10.1007/s40122-021-00244-1 (2021).
17. Gupta, A. et al. Sex-based differences in brain alterations across chronic pain conditions. *J. Neurosci. Res.* **95**(1–2), 604–616. https://doi.org/10.1002/jnr.23856 (2017).
18 Failla, M. D., Gerdes, M. B., Williams, Z. J., Moore, D. J. & Cascio, C. J. Increased pain sensitivity and pain-related anxiety in individuals with autism. *Pain Rep.* **5**, 6. https://doi.org/10.1097/PR9.0000000000000861 (2020).
19 Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B. & Riley, J. L. Sex, gender, and pain: a review of recent clinical and experimental findings. *J. Pain*. https://doi.org/10.1016/j.jpain.2008.12.001 (2009).
20. Mogil, J. S. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *Nat. Rev. Neurosci.* **13**(12), 859–866. https://doi.org/10.1038/nrn3360 (2012).
21. Mogil, J. S. Qualitative sex differences in pain processing: emerging evidence of a biased literature. *Nat. Rev. Neurosci.* **21**(7), 353–365. https://doi.org/10.1038/s41583-020-0310-6 (2020).
22. Engel, G. L. The need for a new medical model: a challenge for biomedicine. *Science* **196**(4286), 129–136. https://doi.org/10.1126/science.847460 (1977).
23. Miaskowski, C. et al. A biopsychosocial model of chronic pain for older adults. *Pain Med.* **21**(9), 1793–1805. https://doi.org/10.1093/pm/pnz329 (2020).
24. Angst, F. et al. Extended overview of the longitudinal pain-depression association: A comparison of six cohorts treated for specific chronic pain conditions. *J. Affect. Disord.* **273**, 508–516. https://doi.org/10.1016/j.jad.2020.05.044 (2020).
25. Boring, B. L., Richter, A. & Mathur, V. A. Higher self-perceived stress reactivity is associated with increased chronic pain risk. *Pain Rep.* **8**(2), e1068. https://doi.org/10.1097/PR9.0000000000001068 (2023).
26 Ew, dH. et al. The association of depression and anxiety with pain: a study from NESDA. *PLoS ONE* https://doi.org/10.1371/journal.pone.0106907 (2014).
27. IsHak, W. W. et al. Pain and depression: a systematic review. *Harv. Rev. Psychiatry* **26**(6), 352–363. https://doi.org/10.1097/HRP.0000000000000198 (2018).
28 Börsbo, B. et al. The complex interplay between pain intensity, depression, anxiety and catastrophising with respect to quality of life and disability. *Disabil. Rehabil.* **31**(19), 1605–1613. https://doi.org/10.1080/09638280903110079 (2009).
29. Fonseca-Rodrigues, D. et al. Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis. *Rheumatology* **61**(1), 53–75. https://doi.org/10.1093/rheumatology/keab512 (2022).
30. Garnæs, K. K. et al. Mental health among patients with chronic musculoskeletal pain and its relation to number of pain sites and pain intensity, a cross-sectional study among primary health care patients. *BMC Musculoskelet. Disord.* **23**(1), 1115. https://doi.org/10.1186/s12891-022-06051-9 (2022).
31. Seminowicz, D. A. & Davis, K. D. Cortical responses to pain in healthy individuals depends on pain catastrophizing. *Pain* **120**(3), 297–306. https://doi.org/10.1016/j.pain.2005.11.008 (2006).
32. Suso-Ribera, C., García-Palacios, A., Botella, C. & Ribera-Canudas, M. V. Pain catastrophizing and its relationship with health outcomes: does pain intensity matter?. *Pain Res. Manag.* **2017**(1), 9762864. https://doi.org/10.1155/2017/9762864 (2017).
33 Lamé, I. E. et al. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. *Eur. J. Pain.* **9**(1), 15–24. https://doi.org/10.1016/j.ejpain.2004.02.006 (2005).
34. Gustin, S. M. et al. Pain and plasticity: is chronic pain always associated with somatosensory cortex activity and reorganization?. *J. Neurosci. Off. J. Soc. Neurosci.* **32**(43), 14874–14884. https://doi.org/10.1523/JNEUROSCI.1733-12.2012 (2012).
35. Kim, W., Kim, S. K. & Nabekura, J. Functional and structural plasticity in the primary somatosensory cortex associated with chronic pain. *J. Neurochem.* **141**(4), 499–506. https://doi.org/10.1111/jnc.14012 (2017).
36. Kuner, R. & Flor, H. Structural plasticity and reorganisation in chronic pain. *Nat. Rev. Neurosci.* **18**(1), 20–30. https://doi.org/10.1038/nrn.2016.162 (2017).
37 Kropf, E., Syan, S. K., Minuzzi, L. & Frey, B. N. From anatomy to function: the role of the somatosensory cortex in emotional regulation. *Rev. Bras. Psiquiatr. Sao Paulo Braz.* **41**(3), 261–269. https://doi.org/10.1590/1516-4446-2018-0183 (2019).
38. Vignaud, P. et al. Can a single session of noninvasive brain stimulation applied over the prefrontal cortex prevent stress-induced cortisol release?. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **121**, 110667. https://doi.org/10.1016/j.pnpbp.2022.110667 (2023).
39. McEwen, B. S. & Morrison, J. H. Brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron* **79**(1), 16–29. https://doi.org/10.1016/j.neuron.2013.06.028 (2013).
40. Arnsten, A. F. T., Joyce, M. K. P. & Roberts, A. C. The aversive lens: Stress effects on the prefrontal-cingulate cortical pathways that regulate emotion. *Neurosci. Biobehav. Rev.* **145**, 105000. https://doi.org/10.1016/j.neubiorev.2022.105000 (2023).
41 Van, A. M. et al. "Hair cortisol and the relationship with chronic pain and quality of life in endometriosis patients. *Psychoneuroendocrinology* https://doi.org/10.1016/j.psyneuen.2018.01.001 (2018).
42. Stalder, T. & Kirschbaum, C. Analysis of cortisol in hair – State of the art and future directions. *Brain. Behav. Immun.* **26**(7), 1019–1029. https://doi.org/10.1016/j.bbi.2012.02.002 (2012).
43. Lynch, R. et al. Perceived stress and hair cortisol concentration in a study of Mexican and Icelandic women. *PLOS Glob. Public Health* **2**(8), e0000571. https://doi.org/10.1371/journal.pgph.0000571 (2022).
44 Xu, Y. et al. Interaction effects of life events and hair cortisol on perceived stress, anxiety, and depressive symptoms among chinese adolescents: testing the differential susceptibility and diathesis-stress models. *Front. Psychol.* https://doi.org/10.3389/fpsyg.2019.00297 (2019).
45. Lunde, C. E. & Sieberg, C. B. Walking the tightrope: a proposed model of chronic pain and stress. *Front. Neurosci.* **14**, 270. https://doi.org/10.3389/fnins.2020.00270 (2020).
46. Radley, J., Morilak, D., Viau, V. & Campeau, S. Chronic stress and brain plasticity: Mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neurosci. Biobehav. Rev.* **58**, 79–91. https://doi.org/10.1016/j.neubiorev.2015.06.018 (2015).
47. Arnsten, A. F. T. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nat. Neurosci.* **18**(10), 1376–1385. https://doi.org/10.1038/nn.4087 (2015).
48. Joëls, M. Corticosteroids and the brain. *J. Endocrinol.* **238**(3), R121–R130. https://doi.org/10.1530/JOE-18-0226 (2018).
49. Joëls, M., Sarabdjitsingh, R. A. & Karst, H. Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. *Pharmacol. Rev.* **64**(4), 901–938. https://doi.org/10.1124/pr.112.005892 (2012).
50 Pinti, P. et al. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. *Ann N Y Acad. Sci.* **1464**, 1. https://doi.org/10.1111/nyas.13948 (2020).
51. Martinez-Calderon, J., Flores-Cortes, M., Morales-Asencio, J. M. & Luque-Suarez, A. Pain-related fear, pain intensity and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. *J. Pain* **20**(12), 1394–1415. https://doi.org/10.1016/j.jpain.2019.04.009 (2019).
52. Unseld, M. et al. Prevalence of pain and its association with symptoms of post-traumatic stress disorder, depression, anxiety and distress in 846 cancer patients: A cross sectional study. *Psychooncology.* **30**(4), 504–510. https://doi.org/10.1002/pon.5595 (2021).
53. Wilcox, C. E. et al. The subjective experience of pain: an FMRI study of percept-related models and functional connectivity. *Pain Med. Malden Mass* **16**(11), 2121–2133. https://doi.org/10.1111/pme.12785 (2015).

54. Ulrich-Lai, Y. M. & Herman, J. P. Neural regulation of endocrine and autonomic stress responses. *Nat. Rev. Neurosci.* **10**(6), 397–409. https://doi.org/10.1038/nrn2647 (2009).
55. Yabuki, Y. & Fukunaga, K. Clinical therapeutic strategy and neuronal mechanism underlying post-traumatic stress disorder (PTSD). *Int. J. Mol. Sci.* **20**(15), 3614. https://doi.org/10.3390/ijms20153614 (2019).
56. Haber, S. N. & Knutson, B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**(1), 4–26. https://doi.org/10.1038/npp.2009.129 (2010).
57. Woolf, C. J. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain* **152**(3 Suppl), S2-15. https://doi.org/10.1016/j.pain.2010.09.030 (2011).
58 Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *The Lancet.* **367**, 9522. https://doi.org/10.1016/S0140-6736(06)68700-X (2006).
59. Ratner, K. G., Kaczmarek, A. R. & Hong, Y. Can over-the-counter pain medications influence our thoughts and emotions?. *Policy Insights Behav. Brain Sci.* **5**(1), 82–89. https://doi.org/10.1177/2372732217748965 (2018).
60. Schalet, B. D. et al. Clinical validity of PROMIS depression, anxiety, and anger across diverse clinical samples. *J. Clin. Epidemiol.* **73**, 119–127. https://doi.org/10.1016/j.jclinepi.2015.08.036 (2016).
61. Wyser, D. et al. Short-channel regression in functional near-infrared spectroscopy is more effective when considering heterogeneous scalp hemodynamics. *Neurophotonics* **7**(3), 035011. https://doi.org/10.1117/1.NPh.7.3.035011 (2020).
62 Ong, W.-Y., Stohler, C. S. & Herr, D. R. Role of the prefrontal cortex in pain processing. *Mol. Neurobiol.* **56**, 2. https://doi.org/10.1007/s12035-018-1130-9 (2019).
63. Pollonini, L. et al. Auditory cortex activation to natural speech and simulated cochlear implant speech measured with functional near-infrared spectroscopy. *Hear. Res.* **309**, 84–93. https://doi.org/10.1016/j.heares.2013.11.007 (2014).
64 Baker, W. B. et al. Modified beer-lambert law for blood flow biomed. *Opt. Express.* **5**, 11. https://doi.org/10.1364/BOE.5.004053 (2014).
65 Jahani, S., Setarehdan, S. K., Boas, D. A. & Yücel, M. A. Motion artifact detection and correction in functional near-infrared spectroscopy: a new hybrid method based on spline interpolation method and Savitzky-Golay filtering. *Neurophotonics.* **5**, 01. https://doi.org/10.1117/1.NPh.5.1.015003 (2018).
66. Gagnon, L., Yücel, M. A., Boas, D. A. & Cooper, R. J. Further improvement in reducing superficial contamination in NIRS using double short separation measurements. *Neuroimage* **85**(1), 127–135. https://doi.org/10.1016/j.neuroimage.2013.01.073 (2014).
67. McKnight, J. C. et al. When the human brain goes diving: using near-infrared spectroscopy to measure cerebral and systemic cardiovascular responses to deep, breath-hold diving in elite freedivers. *Philos. Trans. R. Soc. B Biol. Sci.* **376**, 20200349. https://doi.org/10.1098/rstb.2020.0349 (1831).
68. Shapiro, S. S. & Wilk, M. B. An analysis of variance test for normality (complete samples). *Biometrika* **52**(3/4), 591–611. https://doi.org/10.2307/2333709 (1965).
69. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B Methodol.* **57**(1), 289–300 (1995).



## Acknowledgements
We gratefully acknowledge Dr. Clemens Kirshbaum, PhD and his team at Dresden Labservice for providing HCC analysis as well insightful responses to our questions. We also thank Siya Marwah and Maya Jotwani for helping with data acquisition.


## Author contributions
All authors to the conception and study design presenting in this study. Authors Margaret Moreland, Caitlin Curry, Ziyan Wu, and Madison Vansickel were responsible for data acquisition. Authors Margaret Moreland, Ziyan Wu, and Caitlin Curry led data analysis and interpretation, with Ziyan Wu responsible for all fNIRS data extraction and analysis. All authors contributed significantly to drafting and reviewing the written manuscript. Authors Anthony Wang and Dr. Ziyan Wu, PhD are credited for creating the images and figures for this manuscript. All authors have approved the submitted version of this manuscript.


## Funding
This research is funded by an R35 MIRA Award (R35GM142676) from the National Institute of General Medical Sciences awarded to Dr. Christine B. Sieberg, PhD.


## Declarations

## Competing interests
The authors declare no competing interests.

## Additional information
**Correspondence** and requests for materials should be addressed to C.B.S.

**Reprints and permissions information** is available at www.nature.com/reprints.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.