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Neural correlates of altered reward-driven attention in chronic pain and opioid use

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While attentional processing of reward may be altered in chronic pain, the neural circuits underlying these alterations, and impact from opioid use have remained unclear. To investigate the neural representation of attentional processing in chronic pain, we collected brain fMRI data from patients (fibromyalgia; taking vs. not taking opioids) vs. pain-free controls during performance of a reward task. We selected the inferior frontal gyrus (IFG) and lateral occipital cortex (LOC) as attention-relevant regions of interest. While IFG and LOC responses were not significantly different across groups, we observed decreased IFG response during reward anticipation in patients (uncorrected, p = 0.05). When evaluating LOC-IFG functional connectivity, vs. controls, we observed significantly reduced LOC-IFG connectivity in patients (p-FDR corrected = 0.026), driven by reduced connectivity in non-opioid patients. Further in non-opioid patients, we observed that the relationship between LOC-IFG connectivity and task performance was moderated by pain duration (post-hoc moderation analysis, p = 0.031), indicating cumulative influences of pain duration on attentional processing behavior/circuits. As suggested by our results, attentional processing of reward is altered in fibromyalgia within LOC-IFG brain circuits, possibly to a lesser degree in patients who take opioids, and with potential cumulative effects of longer pain duration.

Keywords Chronic pain, Brain activity, Value, Functional MRI, Attention, Opioids

Chronic pain is a debilitating condition impacting millions of people worldwide. In addition to experiencing physical discomfort, patients with chronic pain often report symptoms of cognitive dysfunction. As shown by many prior studies, patients with chronic pain demonstrate dysfunctional cognitive performance with poor performance in associative learning tasks[1] and memory recall tests[2], as well as more generally impaired attention and executive functions[3–5]. Patients' daily lives can be significantly impacted by cognitive dysfunction, making it more challenging to complete basic tasks, maintain relationships, and manage pain[6].

As a fundamental aspect of daily life, reward processing involves multiple cognitive functions such as memory, decision-making, and attention. In the brain, reward processing closely relates to attentional processing. For example, as compared to low/no-value reward stimuli, high-value reward stimuli capture more attention[7]; such high-value reward stimuli activate the brain's value-driven attentional network. The value-driven attentional network includes the early visual cortex, caudate tail, intraparietal sulcus, and lateral occipital cortex (LOC)[8]. When learning patterns of visual stimuli (i.e., visual regularity), high-value reward patterns enhance individuals' learning. This enhanced learning relates to increased activity in the LOC and inferior frontal gyrus (IFG)[9] which are two brain areas that activate during attentional processing[10,11]. Broader frameworks such as predictive coding and dynamic attending theory can explain value-driven attentional processing. These models suggest that the brain optimizes attentional resources by integrating, updating, and predicting reward signals[12]. Additionally, the dopaminergic system plays an important role in modulating value-driven attention, influencing cognitive control and synaptic plasticity[8,13]. Given that chronic pain is associated with cognitive dysfunction and altered dopaminergic signaling[14–16], chronic pain-related neuroplasticity may impact reward-attention dynamics.

As suggested by mounting evidence, patients with chronic pain exhibit altered brain reward systems[17–23] as well as altered brain attentional processing[24]. Compared to individuals reporting no or low pain, patients with high-intensity pain demonstrate worse impaired performance on attentionally-demanding tasks[25,26]. While clear evidence exists for both altered reward and altered attentional processing in chronic pain, no studies in chronic

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pain patients have yet empirically evaluated brain-based interactions between altered reward and attention processes. In this study, we aimed to investigate the interactions between changes within reward and attentional neural processes in chronic pain. For this aim, we analyzed region-specific neural correlates of attentional processes during patients' performance of a monetary incentive delay (MID) reward task. We included a chronic pain cohort of patients with fibromyalgia, due to fibromyalgia being characterized as a condition of widespread pain[27], with documented presence of altered brain reward systems/behavioral response[21,28], and symptoms of cognitive disturbance[29]. We chose to include patients with fibromyalgia in particular, given existing research highlighting the presence of attentional deficit symptoms in fibromyalgia[30–32].

Currently, from the chronic pain literature, evidence is mixed regarding how opioids impact cognitive functions, such as attention[33]. As indicated by some studies, patients with long-term opioid use demonstrate poor memory performance and impaired attention[34,35]. In sharp contrast, as indicated by another study with patients taking high and low dose opioids, patients taking high dose opioids demonstrate relatively improved cognitive performance – this suggests that opioid-imparted pain relief may thereby improve cognition and attention[36]. As compared to non-opioid chronic pain patients who demonstrate blunted neural response to anticipated rewards, chronic pain patients who take opioids exhibit less blunted brain reward responses[22]. Despite the mixed findings of the relationship between opioid use in chronic pain and cognitive function, it remains unclear how opioids use may influence neural and behavioral mechanisms of reward-related attention processing. Further, patients with fibromyalgia demonstrate dysregulated opioid systems in the brain, as evidenced by reduced mu-opioid receptor binding and increased endogenous opioid cerebrospinal fluid levels[37,38]. Considering that opioid mechanisms play a role in modulating attentional processes[39], dysregulated opioid systems in fibromyalgia may contribute to symptoms of cognitive dysfunction. Greater understanding of how opioid use influences attention processes in patients with fibromyalgia is needed to aid in appropriate treatment selection for concurrent pain and cognitive symptoms.

In the present study, among groups of pain-free controls and patients with fibromyalgia (taking and not taking opioids), we examined how attentional processing is represented in the brain during a task involving reward. We hypothesized patients with fibromyalgia (non-opioid) would exhibit altered attentional response to reward within the LOC and IFG regions, and that patients taking opioids would exhibit more altered attentional response in these regions due to side-effects of opioids. As outlined in a pre-registered plan published on the Open Science Framework (OSF, https://osf.io/dx83h), our analyses focused on brain activity within value-dri ven attentional network regions (i.e., LOC and IFG). To determine how neural responses related to attention processing are shaped in the context of fibromyalgia and opioid use, we investigated MID task-correlated activity within these regions, as well as functional connectivity between these two regions and within relevant brain networks of interest. By conducting additional comprehensive correlational and exploratory analyses, we further probed how LOC and IFG brain activation and connectivity relate to behavioral performance (i.e., task-related reaction time and accuracy) and clinical measures. Lastly, to explore the unique brain mechanisms associated with pain chronicity (vs. resolution) and the possible effects of increasing neural and behavioral deficits with longer duration of pain, we conducted a moderation analysis to investigate how these relationships are impacted by pain duration.

Results

Demographics

We collected task-based fMRI data from a total of 37 patients with fibromyalgia who were not taking opioids (non-opioid patients), 26 patients with fibromyalgia who were taking opioids (opioid patients), and 37 pain-free controls (all female). The full dataset represents data collected as part of two separate studies (one at Stanford University and one at Duke University) conducted by the same investigator (KTM). We have previously reported neural responses (using different ROIs from the ones used in the present study) from some of the same participants, as published elsewhere[21,22,40]. However, we have not previously analyzed and reported on the opioid patient dataset from Duke University. As indicated in the Methods, we included a total of 35 non-opioid patients, 26 opioid patients, and 35 controls in the final analysis, after excluding participants with fMRI registration and motion issues. We also excluded participants who had missing behavioral data from any analyses associated with the missing data. Among the included patients, the duration of pain symptoms ranged from 9 months-28 years (non-opioid patients: M = 9.08 years, SD = 7.35 years; opioid patients: M = 9.08 years, SD = 7.35 years). We provide demographic data in Supplementary Table S1.

Medication use

No controls reported taking any pain or mood-altering medications. Patients in the non-opioid group had no prior opioid use or reported less than a month of lifetime use with no opioid intake within the prior 90 days.

Among the 35 non-opioid patients, 28 were taking medications, and seven patients reported not taking any pain or mood-altering medications. In the opioid group, patients reported taking opioids for periods ranging from 3 months to 16 years, with one individual reporting 40 years. The median duration of opioid use was 5 years (average = 7.08 years), with the median morphine equivalent daily dose of 9 mg (range: 1–90 mg, average = 23.13 mg). (See medications in Supplementary Table S2).

MID task reaction times and accuracy rates

Across three groups, we observed a significant main effect based on the trial type, where anticipation of both higher gain (+$5) and loss (−$5) resulted in faster reaction times [$F(5,455) = 11.9$, $p < 0.001$]. While we observed no main effect for group differences in reaction times [$F(2,455) = 1.6$, $p = 0.199$], we observed a significant interaction between group and trial types on reaction times [$F(10,455) = 2.1$, $p = 0.025$]. These results indicated

that more salient trials led to faster reaction times for all groups and also implied similar levels of task engagement across groups.

For accuracy rate, we observed a main effect of trial type with percent hits higher in gain (+$5) and loss (−$5) trials compared to no gain/no loss trials [F (5, 465) = 9.7, $p < 0.001$], no main effect of group [F (2,465) = 0.5, $p = 0.614$], and a significant interaction effect between group and trial type [F (10, 465) = 2.6, $p = 0.004$]. Again, these results suggested that all groups responded more correctly to highly salient trials, reflecting comparable levels of task engagement.

ROI activation: IFG and LOC

As revealed by ANCOVA, IFG GVNant nor IFG NVLout fMRI beta values [GVNant: gain vs. no-gain anticipation, which compared gain (+$5) trials to no-gain (+$0) trials during the anticipation phase; NVLout: no-loss vs. loss outcome, which compared hits (−$0 outcome) versus misses (−$5 outcome) during the outcome phase] were not significantly influenced by our included age and site covariates (all $p > 0.43$). We observed no significant group differences in IFG response during gain anticipation (GVNant) (F (2, 91) = 3.10, $p = 0.05$) (Fig. 1A). Additionally, we observed no significant group differences in IFG response to non-punishment outcomes (NVLout; $p = 0.33$) (Fig. 1B). Within the LOC ROI, we did not observe group differences in response to gain anticipation (GVNant; $p = 0.26$) or non-punishment outcomes (NVLout; $p = 0.059$). As revealed by the ANCOVA design, the LOC GVNant and LOC NVLout fMRI beta values were not significantly influenced by our included age and site covariates (all $p > 0.063$) (Fig. 1C and D). While none of our ROI activation results reached significance (i.e., corrected $p < 0.0125$), we observed in both patient groups (opioid and non-opioid) a pattern of decreased IFG response during gain anticipation.

Brain network functional connectivity during gain anticipation

As described in our pre-registration, we tested functional connectivity during gain anticipation among the IFG, LOC, ventral DMN, and visuospatial network. When including age and site as covariates, we identified

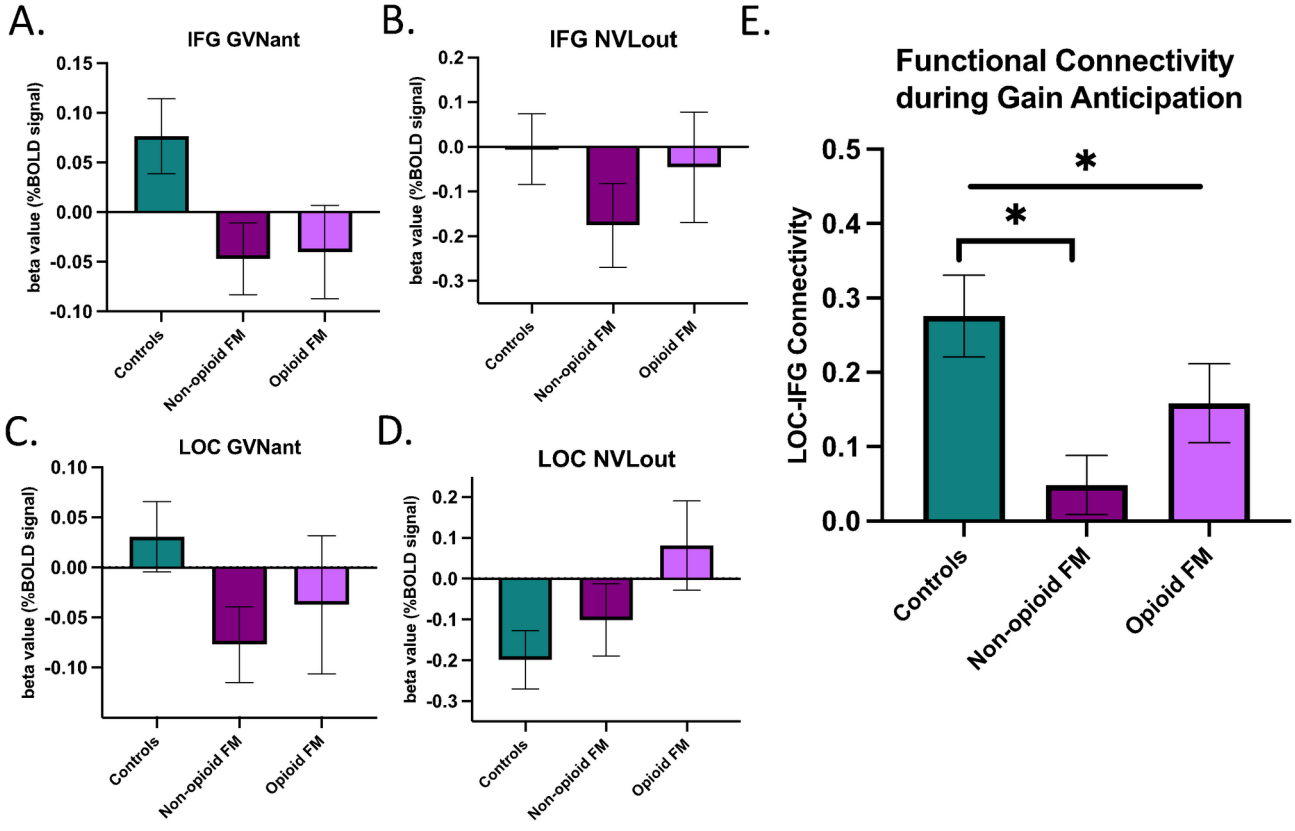

Fig. 1. IFG and LOC Reward Task Responses and LOC-IFG Gain Anticipation Functional Connectivity. (**A**) Contrast beta values extracted from the bilateral IFG ROI during gain anticipation (GVNant, +$5 > $0 trials). (**B**) Contrast beta values extracted from the bilateral IFG ROI during non-punishment outcome (NVLout; -$5 hit vs. miss). (**C**) Contrast beta values extracted from the LOC ROI during gain anticipation (GVNant, +$5 > $0 trials). (**D**) Contrast beta values extracted from the bilateral LOC ROI during non-punishment outcome (NVLout; -$5 hit vs. miss). (**E**) A significant group difference in the LOC-IFG connectivity during gain anticipation ($5 trials) ($p < 0.05$, FDR corrected). All beta values are shown as 10^{-3}. Abbreviation: FDR, false discovery rate; FM, fibromyalgia; IFG, inferior frontal gyrus; LOC, lateral occipital cortex; ROI, region of interest.

a significant group difference in LOC-IFG connectivity [F (2,91) = 5.31, p-FDR corrected = 0.026]. As revealed using post-hoc t-tests, only non-opioid patients showed significantly reduced LOC-IFG connectivity as compared to controls (p-Bonferroni = 0.005) (Fig. 1E). We did not observe significant group differences for any of the other analyzed networks and associated seeds (all p-FDR > 0.078). These results may indicate impaired integration of attentional and reward-related processing in this group, potentially contributing to cognitive deficits observed in chronic pain. Furthermore, the lack of differences in the opioid patients suggest that opioid use may modulate or compensate for this impairment.

Brain and behavioral/clinical correlation analyses

As planned in our pre-registration, we conducted brain-behavioral/clinical correlational analyses separately for each of the three groups. These analyses included three fMRI brain measures (during gain anticipation): LOC beta value, IFG beta value, and LOC-IFG connectivity; and four primary behavioral/clinical measures: reaction time for gain trials, BDI, PANAS, and PROMIS Fatigue. Therefore, for the primary correlational analyses, the Bonferroni corrected threshold was set at $p < 0.0125$ (4 independent behavioral/clinical measure tests).

From the primary correlational analyses of brain values vs. clinical measures, we observed a negative correlation between LOC-IFG connectivity and RT which was significant in the opioid patients (r = -0.528, $p = 0.008$), but did not pass the corrected threshold ($p < 0.0125$) in controls ($r = -0.387$, $p = 0.022$). Meanwhile, in the non-opioid patients, the relationship between LOC-IFG connectivity and RT was reversed (positive direction, did not pass corrected threshold of $p < 0.0125$) ($r = 0.362$, $p = 0.033$) (Fig. 2A). While we did not identify any other significant correlations from our primary correlational analyses (all $p > 0.019$) (see all results in Supplementary Table S3), these results suggest shorter (faster) RT may relate to higher (more correlated between-region fMRI signal) LOC-IFG functional connectivity among opioid patients and to a lesser degree in controls, while this relationship was not observed in non-opioid patients.

As planned in our pre-registration, we also explored relationships between our fMRI measures (LOC beta value, IFG beta value, and LOC-IFG connectivity) vs. additional behavioral/clinical measures including accuracy rate for gain trials, STAI-State/STAI-Trait, BIS/BAS, POMS, and BPI. For exploratory analyses, we report p-values and results with $p < 0.05$ (uncorrected) for descriptive purposes only (Bonferroni corrected p-value threshold for all 5 independent clusters of primary/exploratory clinical measures was set at $p < 0.01$; see details in Methods). From the exploratory correlation analyses, we observed one correlation that met the corrected significance threshold, and a few additional relationships ($p < 0.05$, uncorrected) (see all results in Supplementary Table S3). In the opioid patient group, we observed a negative relationship between LOC GVNant and anxiety (STAI-Trait) (r= -0.497, $p = 0.014$, uncorrected), and a negative relationship between LOC-IFG connectivity and anxiety (STAI-State) (r = -0.523, $p = 0.009$, significant at corrected threshold).

For the relationship between LOC-IFG connectivity and accuracy rate, we identified a positive relationship in the opioid patients ($r = 0.442$, $p = 0.031$, uncorrected) and in the controls ($r = 0.336$, $p = 0.048$, uncorrected), but not in the non-opioid patients ($r = 0.046$, $p = 0.795$) (Fig. 2B). As suggested by these results, higher LOC-

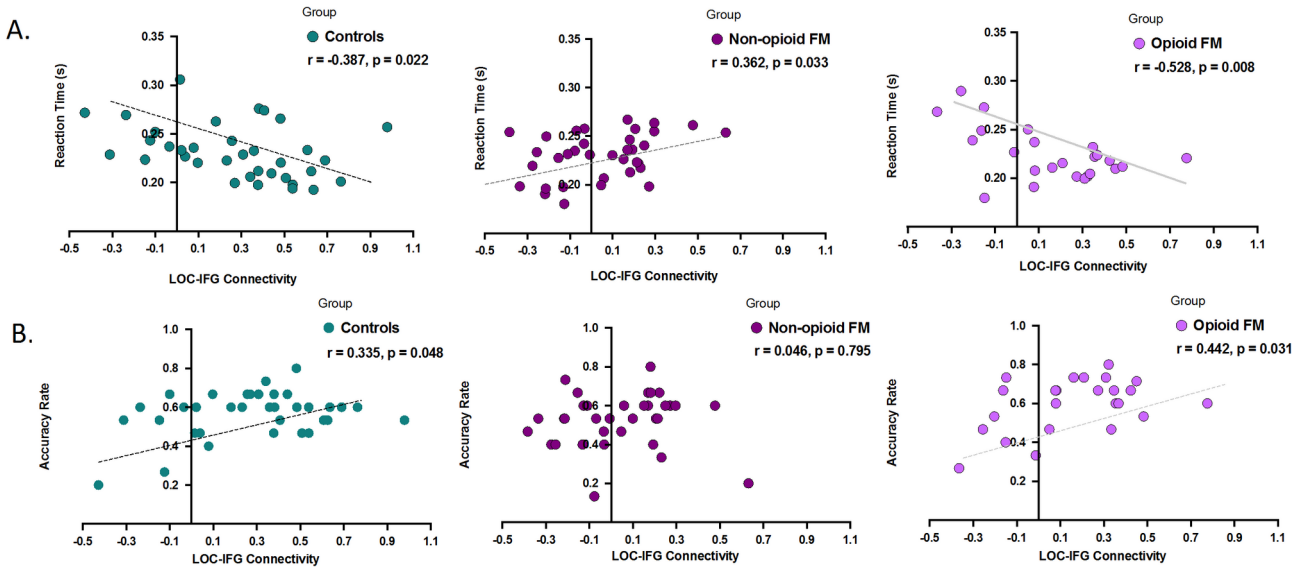

Fig. 2. Brain – Behavioral Correlation Analyses. (**A**) Primary correlational analysis between LOC-IFG connectivity and RT in controls, non-opioid patients, and opioid patients (left to right). A negative correlation was observed in the opioid group (significant, corrected $p < 0.0125$) and in the control group (not significant, corrected). No relationship was observed in the non-opioid group. (**B**) Results from an exploratory (i.e., uncorrected, p values reported for descriptive purposes only) correlational analysis between LOC-IFG connectivity and accuracy rate. Control and opioid patient groups showed a positive relationship ($p < 0.05$, uncorrected), but no relationship was observed in the non-opioid patient group. Abbreviation: FM, fibromyalgia; IFG, inferior frontal gyrus; LOC, lateral occipital cortex; RT, reaction time.

IFG connectivity (i.e., stronger correlation between regions) may relate to lower anxiety and higher accuracy in opioid patients, but not in non-opioid patients.

Moderation analysis with pain duration as a moderator

We conducted a post-hoc moderation analysis with LOC-IFG connectivity as a predictor, pain duration as a moderator, and RT as the dependent variable. As our primary correlational analyses revealed different patterns only in the non-opioid group compared to opioid group and controls, we performed the moderation analyses in both non-opioid and opioid patient groups to further examine what might impact this altered pattern.

For the non-opioid group, we identified a significant main effect between LOC-IFG connectivity and RT ($Z = 3.29$, $p < 0.001$), and a significant main effect of pain duration on RT ($Z = -2.93$, $p = 0.003$); We identified a significant interaction effect of pain duration on LOC-IFG connectivity and RT ($Z = 2.15$, $p = 0.031$). As revealed by a simple slope analysis, we observed no effect of the LOC-IFG connectivity on RT in the non-opioid group who showed lower-than-average levels of pain duration ($Z = 0.63$, $p = 0.528$). Meanwhile we observed a greater effect of the LOC-IFG connectivity on RT in the non-opioid group who showed higher-than-average/average levels of pain duration ($Z = 3.53$, $p < 0.001$ and $Z = 3.06$, $p = 0.002$, respectively). Multicollinearity diagnostics indicated that all variables had acceptable Variance Inflation Factor (VIF) values, suggesting no collinearity concerns (highest VIF = 1.044).

For the opioid group, we observed a significant main effect between LOC-IFG connectivity and RT ($Z = -4.21$, $p < 0.001$), but no main effect of pain duration on RT ($Z = -1.15$, $p = 0.251$); We observed no significant interaction of pain duration on LOC-IFG connectivity and RT ($Z = 1.64$, $p = 0.102$). Multicollinearity diagnostics suggested no multicollinearity among variables (highest VIF = 1.046).

As suggested by these post-hoc moderation analysis results, pain duration appears to moderate the effect of LOC-IFG connectivity on RT in non-opioid patients, but not opioid patients; this suggests a potential effect of longer pain duration resulting in greater alterations in LOC-IFG connectivity and slower RT in patients with fibromyalgia who do not take opioids.

Discussion

In the present study, we aimed to identify how the neural correlates of attentional processing during reward are altered and relate to behavioral/clinical measures in chronic pain (pre-registered in OSF, https://osf.io/dx83h). When evaluating LOC and IFG reward task response during conditions of gain anticipation (GVNant) and non-punishment outcome (NLVout), we observed no significant group differences among opioid patients, non-opioid patients, and controls. However, compared to controls, we did observe reduced (not significant) IFG response during the gain anticipation condition in both patient groups. When examining functional connectivity (among IFG, LOC, ventral DMN, and the visuospatial network) during gain anticipation, we observed a significant group difference in LOC-IFG connectivity, primarily due to reduced connectivity in the non-opioid group vs. controls. Additionally, we identified a negative correlation between LOC-IFG connectivity vs. reaction time (RT) in the opioid patients (significant) and controls (not significant), indicating that higher LOC-IFG connectivity was associated with faster RT. Meanwhile in the non-opioid patients, this pattern was not observed. Similarly, while in the opioid patients and controls LOC-IFG connectivity positively related (uncorrected) to accuracy rate (i.e., higher connectivity with higher accuracy), this pattern was not observed in the non-opioid patients. Finally, through our post-hoc investigation of the potential moderating effect of pain duration on altered brain-behavioral relationships, we identified significant main effects of LOC-IFG connectivity and pain duration on RT, and a significant interaction, suggesting that the LOC-IFG connectivity's impact on RT was moderated by pain duration, but only in non-opioid patients.

Numerous prior studies have explored the attentional network within the human brain, with a particular focus on the well-known dorsal frontoparietal network[41]. However, attentional processing encompasses a wide range of functions, including pre-allocating attentional resources, directing attention to a specified location, and selecting relevant information while inhibiting irrelevant information[42]. Given the specific focus of our study on attentional processes during a reward task, it was crucial to concentrate on brain regions that have been shown to activate during attention tasks involving rewards[8,9,13]. The LOC region is a key component of the value-driven attentional network[8]. For example, while performing a target-searching task, participants exhibit greater activation in the LOC region when the target is associated with a high reward compared to a low reward[8]. Likewise, the IFG not only demonstrates increased activation during a target detection task, but also exhibits heightened activation when processing stimuli associated with high rewards compared to no rewards during the Stroop task[43]. During visual statistical learning, activation in the IFG and LOC regions is increased when processing high-value images in contrast to low-value images[9], suggesting the involvement of attentional processes in stimulus-reward associations[44–46]. While LOC-IFG connectivity has been examined in controls during attentional processing involving rewards[47], our study is, to our knowledge, the first to investigate functional connectivity between these regions during reward-related attentional processing in chronic pain patients.

Despite our prediction in the pre-registration (OSF, https://osf.io/dx83h) that patients (vs. controls) would show significantly reduced activity in the LOC and IFG, both patient groups demonstrated only (non-significant) reduced IFG reward anticipation response. However, we observed a significant difference group in LOC-IFG functional connectivity (during gain anticipation), primarily driven by reduced LOC-IFG connectivity in the non-opioid group vs. controls. This reduced connectivity in the non-opioid group may suggest a lesser engagement of attentional processes related to rewards. Given the role of LOC and IFG in visual salience and attentional control[48,49], respectively, this disruption may reflect impaired top-down attention regulation during reward anticipation. Specifically, aligning with prior evidence of disrupted attentional processes in fibromyalgia[24], the

disengagement of the LOC-IFG circuit may reflect regionally disrupted coordination between the visuospatial network (which includes LOC) and the ventral default mode network (which includes IFG).

As compared to controls, we did not observe a significant difference in LOC-IFG connectivity during reward gain anticipation in the opioid patients. There is conflicting evidence regarding the impact of opioid medication on cognitive function[33]. While some studies have reported cognitive deficits associated with long-term opioid usage[35,50,51], other findings have not revealed cognitive dysfunction in patients with chronic nonmalignant pain receiving opioid medication[52,53]. In a previous study utilizing the MID task, individuals with fibromyalgia who were not taking opioids exhibited altered medial prefrontal cortex (MPFC) response during gain anticipation and non-punishment outcomes, whereas those taking opioids displayed MPFC response more similar to that of pain-free controls[22]. Similarly, our present results suggest that opioid-taking patients may have more intact LOC-IFG connectivity during attentional processing involving rewards. Among opioid users more generally, observed improvements in cognitive performance may be potentially attributed to pain relief[36,54]. While the neural mechanisms for how opioid-mediated pain relief may lead to preserved cognitive performance are largely unknown, our results suggest that LOC-IFG connectivity may relate to the degree of cognitive/attention impairment, at least in reward/value contexts.

Aside from potential mechanisms of opioid-associated pain-relief, higher LOC-IFG connectivity in our opioid-taking patients may relate to increased sensitivity to rewards by opioids. Among patients undergoing methadone treatment for opioid dependence, patients exhibited greater difficulties (vs. controls) in disregarding distractors previously associated with monetary rewards during a target search task[55], suggesting enhanced attention to rewards in opioid dependence. Opioids are known to dramatically influence brain reward circuits[56], with changes in cortical and subcortical networks involving multiple neurotransmitter systems in individuals who take opioids long-term[57,58]. While we did not identify group differences in reward task behavior (i.e., reaction time and accuracy rate) between our opioid and non-opioid groups, it is highly possible that opioid use would influence attentional processing circuits (i.e., LOC-IFG) and even broader cognitive functions during performance of reward-related tasks in our opioid-taking patients.

During reward anticipation in the opioid patients and controls, we observed relationships of LOC-IFG connectivity with RT and accuracy, indicating that higher LOC-IFG connectivity was associated with faster RT and higher accuracy. Notably, we measured LOC-IFG connectivity during the reward anticipation phase, while RT was measured during the presentation of targets (after the anticipation phase). Thus, as based on this identified brain-behavior relationship in the controls and opioid patients, the earlier neural responses during attentional processing involving rewards (i.e., higher LOC-IFG connectivity) may serve to influence the later behavioral performance. The LOC, a key region in the visuospatial network, processes salient visual information, while the IFG, part of the ventral attention network, is involved in top-down attentional processing and cognitive control[13]. Stronger functional connectivity between these regions during reward anticipation may facilitate more efficient attentional engagement, ultimately leading to faster and more accurate responses during task performance.

Meanwhile, the unique absence of these relationships in the non-opioid patients may relate to disrupted attentional processing. Indeed, LOC-IFG connectivity was significantly reduced in the non-opioid patients (vs. controls), which suggests dysfunctional attentional processing despite relatively similar behavioral performance across groups. As revealed by our post-hoc moderation analysis, pain duration appeared to influence the altered brain-behavioral relationships only in the non-opioid patients. Specifically, in the non-opioid patients, pain duration was a significant moderator between LOC-IFG connectivity and RT. As indicated by simple slope analysis, the altered pattern (i.e., positive correlation) between these two factors became more robust with longer pain duration, while no such relationship was observed with shorter pain duration. These findings support evidence that pain chronicity progressively alters neural circuits involved in reward processing and cognitive control[17,59]. Overall, our results suggest that chronic pain impairs attention allocation in reward-related contexts, while highlighting pain duration as an important factor for cognitive dysfunction.

The distinct neural responses observed between the non-opioid vs. opioid groups may be attributable to a combination of various factors that interact across multiple psychological and neurophysiological domains. As suggested by the relatively similar LOC-IFG gain anticipation connectivity in the opioid group vs. controls, individuals with fibromyalgia who take opioids long-term may possess higher expectations of positive outcomes. This heightened expectation could lead to greater engagement of attentional processes. For example, in the opioid group, higher LOC-IFG connectivity was associated with faster reaction times and higher accuracy. Consistent with prior research showing opioid use in chronic pain patients may alleviate cognitive interference and improve task performance[22,36,54], our findings may reflect a potential positive influence of opioid medication on cognitive functions, at least in our included opioid-taking cohort. Further extensive investigations are needed to determine the effects of opioid medication on neural responses during broader cognitive processes and other patient populations.

This study has several limitations which should be considered. First, this study involved a secondary analysis of data collected as part of two studies. While the data from the opioid group collected at Duke University has not been published previously, other components of the datasets were included in prior publications[21,22,40]. Additionally, this study focused on different brain regions of interest compared to the previous studies. Further, the datasets from two different institutions (Stanford and Duke Universities) were not combined in the prior studies. For transparency, we pre-registered the study with carefully planned group analyses (OSF, https://osf.io/dx83h). While site-specific factors can influence fMRI results when combining data from different sites/scanners, the participants across all three groups were proportionally similar for each site, therefore, site-related differences would not be expected to contribute to our observed group differences. As evidence of this, our inclusion of site as a covariate (i.e., correction for site effects) in our neural analyses did not influence the results. Second, we did not directly assess participants' motivation and intention for the reward task. Nonetheless, faster

reaction time for higher reward and higher punishment trials have been described as reflecting participants' task involvement[21,60]. Third, it is important to acknowledge that the present study only included female patients with fibromyalgia. Previous research has shown that males with chronic back pain exhibit different patterns of brain activation during gain anticipation compared to females[61]. Thus, including male participants and different chronic pain conditions in future studies may provide further insights into altered attentional processing during the reward task in patients with chronic pain. Fourth, for the moderation analysis, our sample size, particularly in the opioid group ($n = 26$), may limit the statistical power of our moderation analyses. Future studies with larger samples are necessary to further validate our results. Lastly, while we did not directly measure the impact of medications other than opioids on brain activation, the types of non-opioid pain and mood-altering medications were variable across the opioid and non-opioid patients (see Supplementary Table S2). However, as our sample size was not powered to analyze subgroups of patients taking unique combinations of medications, the effects of various types of medications on attentional processes of reward should be prospectively evaluated in future studies or meta-analyses with larger sample sizes.

Based on preregistered analysis plans (OSF, https://osf.io/dx83h), we examined the neural correlates of attentional processing during performance of a reward-related task in patients with chronic pain with/without opioid use. By focusing our analysis on the LOC and IFG attention-relevant brain regions, we observed significantly reduced LOC-IFG connectivity during gain anticipation in patients, which was related to behavioral performance (i.e., reaction time). While opioid patients and controls displayed relatively similar neural and correlation patterns to each other, the non-opioid patient group exhibited unique deficits in LOC-IFG connectivity and altered brain-behavioral relationships, which appeared to be moderated by pain duration. As suggested by these results, LOC-IFG connectivity appears to mechanistically support attentional processes in the context of reward. Such LOC-IFG attentional processing of reward mechanisms appear to be disrupted in patients with chronic pain (i.e., fibromyalgia), with greater disruption occurring with longer duration of chronic pain. While our study sheds light on how attentional processes are disrupted in chronic pain (and potentially less disrupted in patients who take opioids), future prospective investigations are needed to verify our present results in other chronic pain cohorts with the goal of identifying more effective treatments for cognitive dysfunction in chronic pain.

Methods

Participants

Participants included patients with fibromyalgia who were not taking opioids (non-opioid FM), patients with fibromyalgia who were taking opioids (opioid FM), and controls. We collected data at Stanford University and Duke University [Stanford University: 17 non-opioid FM, 16 opioid FM, and 17 controls; Duke University: 20 non-opioid FM, 10 opioid FM, and 20 controls; all females]. Among these participants, we excluded one non-opioid FM because the structural and functional MRI data of this patient could not be aligned. Additionally, we excluded one non-opioid FM and two controls due to excessive head motion. Therefore, the final analysis included a total of 35 non-opioid FM, 26 opioid FM, and 35 controls. We included only females in this study due to the higher prevalence of fibromyalgia in females.

All participants signed written informed consent. Both the Stanford and Duke University Institutional Review Boards approved study procedures as applicable, and we confirm that all methods were performed in accordance with the relevant guidelines and regulations. All patients with fibromyalgia (non-opioid FM & opioid FM) met the modified American College of Rheumatology 2016 criteria for fibromyalgia[62]. This included (1) a widespread pain index (WPI) score ≥ 7 plus a symptom severity (SS) score ≥ 5, OR WPI score 3–6 plus SS score ≥ 9, (2) symptoms present for at least 3 months, and (3) no disorder that would otherwise explain the pain. In addition, patients had to report experiencing pain in all four areas of their body and have a pain rating of at least 2 on a scale of 0 to 10 over the past month. They also could not have uncontrolled anxiety or depression. Patients in the non-opioid FM group did not have taken any opioid medications in the 90 days leading up to the study and to have used opioids for no more than a month in their entire lifetime. For the opioid FM group, patients reported their ongoing and consistent use of opioid medications for a minimum of 90 days. Pain-free controls had no history of chronic pain, were not to be taking pain medication at the time of the study visit and did not to have any current symptoms of anxiety or depression.

Monetary incentive delay task

We collected data at the Richard M. Lucas Center for Imaging at Stanford University and at the Duke-UNC Brain Imaging and Analysis Center (BIAC). All participants received instructions on the monetary incentive delay (MID) task before the MRI scans. An identical version of the MID task was implemented at both sites/in both studies using MATLAB programming language along with Psychophysics Toolbox v.3 [63,64]. Participants each completed two runs of the MID task. The first run of the MID task consisted of 42 trials (seven presentations of each trial condition), while the second run included 48 trials (eight presentations of each trial condition). Each trial of the MID task consisted of two phases, the anticipation and outcome phases. The anticipation phase consisted of cue and fixation presentations. We presented cues as either circles, representing potential gains (+$5 and +$1 for potential gains, +$0 for no gain), or squares, representing potential losses (-$5 and -$1 for potential losses, -$0 for no loss), along with their corresponding monetary values. Following each cue, we displayed a fixation mark for a duration of 2 s, followed by a triangle target. The target had a variable duration (ranging from 260ms to 280ms), and we instructed participants to press the button box as quickly as possible to either win money or avoid losing it. Target durations were adaptively modified to achieve an approximate 66% hit rate across trials (based on cumulatively tracked performance), consistent with previous studies[21,22,65]. These adaptive modifications are gradual to still allow for the detection of patient vs. control group difference[21,60]. Finally, during the outcome phase, participants received win or loss feedback. If the participant successfully

pressed the button during a gain trial ("hit"), they would win the indicated amount of money, but if they failed to respond ("missed") or pressed the button before or after the target presentation, they would not win any money on that trial. For loss trials, a "hit" meant that participants avoided losing the indicated amount, while a "miss" resulted in the loss of the cued amount. We randomized the presentation of the six types of trial conditions (+$5, +$1, +$0, -$5, -$1, and -$0) throughout the task, and the order of trials and runs remained the same for all participants (i.e., predetermined order). Participants viewed a black screen for 2, 4, or 6 s duration (pseudo-randomized) inter-trial interval period (Fig. 3).

Behavioral and clinical measures

For primary behavioral and clinical measures, as planned in our pre-registration and subject to Bonferroni correction, we included (1) the reaction time during gain anticipation, (2) depression, using the BDI[66], (3) positive and negative affect, using the PANAS[67], and (4) fatigue, using PROMIS Fatigue[68]. As exploratory measures (i.e., additional measures analyzed and presented for descriptive purposes; planned in our pre-registration; not corrected), we included (1) accuracy rate during gain anticipation, (2) anxiety, using the STAI-State and STAI-Trait[69], (3) reward and motivational approach/avoidance behavior, using the BIS/BAS[70], (4) mood disturbance, using the POMS[71], and (5) clinical pain severity and interference, using the BPI[72].

MRI scans

Dataset from Stanford University

We acquired fMRI data on a 3T General Electric scanner using an 8-channel head coil. The scans consisted of the initial preparatory localizer, asset calibration scans, two MID task fMRI scans, and T1 anatomical scan. The MID task fMRI scan parameters were as follows: Gradient Echo Pulse Sequence using spiral in-out acquisition with 32 oblique slices, sequential descending slice order, 2.0 mm x 2.0 mm in-plane resolution, 4.0 mm slice thickness with 0.5-mm slice spacing, TR = 2 s, TE = 30 s, flip angle 76°, pixel size 3.43 mm. The two MID task fMRI scans consisted of 262 and 302 volumes, respectively. The T1 anatomical scan parameters were as follows: 1-mm slice thickness, 256 mm frequency field of view, frequency direction anterior/posterior, flip angle 11°, TR = 6.8, TE = 2.6.

Dataset from Duke University

We acquired fMRI data on a 3T GE Premier UHP system with a 48-channel head coil. The scans consisted of the initial preparatory localizer, asset calibration scans, two MID task fMRI scans, and T1 anatomical scan. The MID

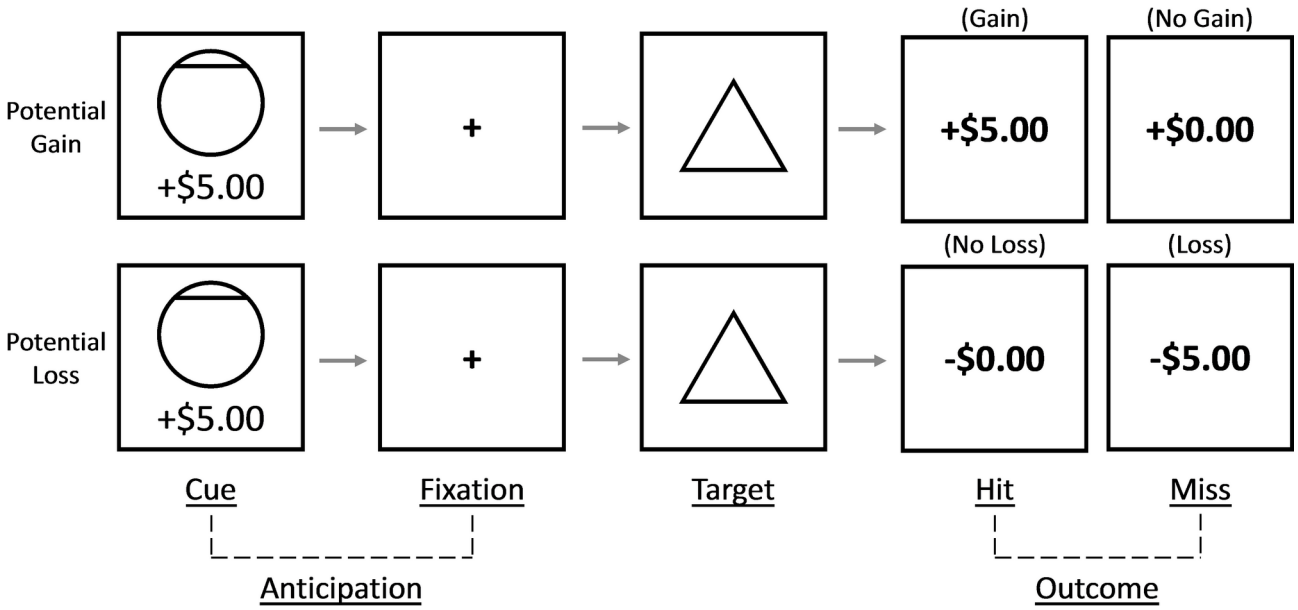

Fig. 3. Structure of Monetary Incentive Delay (MID) Task. Example of potential gain and loss trials in the MID task. Each trial consisted of specific time periods, with trial periods TR-locked (TR = 2 s). The sequence was as follows: TR 1 represented the cue phase (anticipation), TR 2 was the fixation phase (anticipation), TR 3 indicated the target phase, TR 4 denoted the feedback phase (outcome), and TR(s) 5 to 7 represented a variable duration inter-trial interval. During the cue presentation, either circle (indicating potential gains) or square (indicating potential losses) was presented, accompanied by monetary values beneath the respective shapes. After this phase, a fixation mark was lasted for 2 s, initiating the subsequent target phase. During the target phase, a triangle was presented for a variable duration, usually averaging around 265 milliseconds. This duration was determined based on the participant's prior response accuracy to achieve an average hit rate of 66%. At the end of each trial, feedback in the form of win/loss feedback was provided, indicating the monetary gain or loss. Following the feedback phase, a black screen to separate subsequent trials was presented, and the inter-trial interval was pseudo-randomly set to 2, 4, or 6 s.

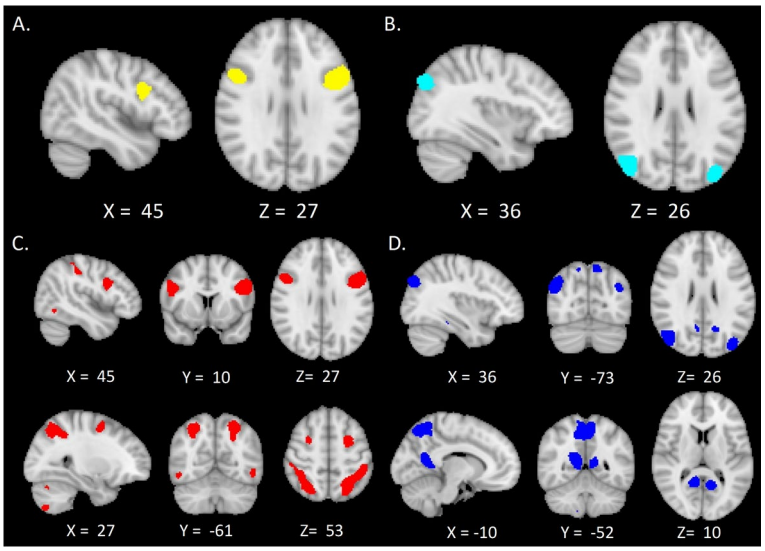

Fig. 4. Regions of Interest. The ROI masks were created using "Functional ROIs" provided by the FIND Lab at Stanford University (Shirer et al., 2012; https://greiciuslab.stanford.edu/resources). (**A**) Location of the bilateral IFG ROI. (**B**) Location of the bilateral LOC ROI. (**C**) Location of the "Visuospatial" network. (**D**) Location of the "ventral_DMN" network. Abbreviation: DMN, default mode network; IFG, inferior frontal gyrus; LOC, lateral occipital cortex; ROI, region of interest.

task fMRI scan parameters were as follows: Gradient Echo Pulse Sequence with 46 slices, interleaved bottom-up slice order, 2.9 mm slice thickness, TR = 2 s, TE = 25 s, flip angle 77°, pixel size 2.9 mm. The two MID task fMRI scans consisted of 262 and 302 volumes, respectively. The T1 anatomical scan parameters were as follows: 1-mm slice thickness, 256 mm frequency field of view, frequency direction anterior/posterior, flip angle 8°, TR = 2.2, TE = 3.2.

fMRI data pre-processing

We pre-processed the fMRI data using Python and AFNI software (Analysis of Functional Neuroimages). We used a GitHub repository (https://github.com/kellyhennigan/MID_processing_example), which included custom scripts, for the pre-processing. By using these scripts, we removed the first 6 lead-in volumes and 4 lead-out volumes, performed slice time correction and motion correction, smoothed the data with a 4 mm (full-width half-maximum, FWHM) Gaussian kernel, and normalized them. We applied a high-pass filter with a threshold of 0.011 Hz to remove the low-frequency signals and transformed the pre-processed functional images to the standard group space. First, we used 3dSkullStrip to strip the skull from the anatomical images and then aligned them to Talairach space using AFNI's @auto_tlrc. To further align the data, we co-registered the first volume of the functional image with the anatomical image, followed by another round of skull stripping. Finally, we co-registered the anatomical image with the functional data and transformed it from its native form into the standard space. To improve the quality of the task-based fMRI data, we applied motion censoring to exclude volumes with motion greater than 0.5 Euclidean norm value[73].

MID task fMRI contrasts

As outlined in the pre-registration (OSF, https://osf.io/dx83h), the focus of the main analysis in the study was on the contrast of (1) **GVNant**: gain vs. no-gain anticipation, which compared gain (+$5) trials to no-gain (+$0) trials during the anticipation phase, and (2) **NVLout**: no-loss vs. loss outcome, which compared hits (−$0 outcome) versus misses (−$5 outcome) during the outcome phase. We convolved the regressors with a single-gamma hemodynamic response function, using a 6-second delay approximation.

Region of interest analyses

In the present study, we conducted primary region of interest (ROI) analyses focused on the IFG (Fig. 4A) and LOC (Fig. 4B). We created the bilateral IFG ROI mask using "Functional ROIs" provided by the FIND Lab at Stanford University[74] (https://greiciuslab.stanford.edu/resources). For the bilateral IFG ROI, we merged the 3rd and 7th ROIs of "Visuospatial" (Fig. 4C), and for the bilateral LOC ROI mask, we merged the 4th and 9th ROI of "ventral_DMN" (Fig. 4D).

Brain functional network connectivity during gain anticipation

We used the CONN toolbox for functional connectivity analysis and followed the CONN toolbox's default pre-processing pipeline and default denoising pipeline. During the denoising step, we applied the anatomical component-based noise correction procedure (aCompCor) to effectively reduce motion-related artifacts across groups (running in MATLAB v.R2020a and SPM12)[75]. For specific set up, we used the intermediate outlier identification setting in CONN, no slice timing correction, and a Gaussian kernel of 4 mm full width half

maximum for smoothing. As outlined in our pre-registration, during gain anticipation, we examined functional connectivity among our primary ROIs, IFG and LOC, and their pre-determined brain networks, Visuospatial network and ventral DMN. We obtained all ROIs and networks from the Stanford University FIND Lab[74]. We used onset time of each gain anticipation trial and 4 s of duration as experiment conditions (within-subject effects) in the CONN toolbox setting.

Correlational and post-hoc moderation analyses

For primary correlational analyses, we investigated relationships between neural correlates during gain anticipation and behavioral and clinical measures (as planned in the pre-registration; https://osf.io/dx83h). First, we focused on the three fMRI measures (LOC beta value, IFG beta value, and LOC-IFG connectivity during gain anticipation) vs. reaction time during gain anticipation trials. Then, we measured correlations between the three fMRI measures and three clinical measures, including BDI, PANAS, and PROMIS Fatigue. Then, as planned in the pre-registration, we conducted exploratory correlational analyses (uncorrected, descriptive only) between the three fMRI measures vs. accuracy rate and clinical measures, including STAI-State and STAI-Trait, BIS/BAS, POMS, and BPI. Following the correlational analyses, we conducted a post-hoc (i.e., not in preregistration plan) moderation analysis to further examine the brain-behavior relationships in both patient groups. We selected pain duration as a moderator based on prior evidence of the duration of pain impacting the heterogeneity of functional connectivity[76].

Statistical analysis

For the behavioral data, we calculated within-group and between-group level statistics for participants' MID task reaction times and accuracy rates. For the ROI analysis of the fMRI data, we conducted both within-group and between-group level statistics for averaged beta values for each ROI and contrast combination. We extracted the beta values using the custom MATLAB scripts (GitHub repository: https://github.com/kellyhennigan/MID_processing_example). We conducted between-group level statistics by using averaged beta values for each ROI and contrast combination. For group analyses, we used one-way analysis of covariance (ANCOVA), correcting for potential effects of age and site differences by including these as covariates. The significance threshold was set at $p < 0.05$. We performed post-hoc t-test (non-opioid FM vs. opioid FM; Controls vs. opioid FM; non-opioid FM vs. Controls) and corrected them for multiple comparisons. The corrected significance threshold for this analysis was set at $p < 0.0125$ (initial $p < 0.05$; Bonferroni corrected for two ROI x two contrast comparisons: IFG x GVNant, LOC x GVNant, IFG x NVLout, LOC x NVLout). For the significance threshold of the functional connectivity analysis, we used a p-value < 0.05, false discovery rate (FDR)-corrected.

To examine the relationship between neuroimaging results and behavior/clinical measures, we conducted correlational analyses. These analyses involved the beta values and functional connectivity values extracted from the fMRI data, and we compared them with the collected behavioral and clinical data. Prior to conducting the correlational analyses, we first tested for significant correlations among the primary behavioral and clinical measures. We identified that the data represented 4 independent cluster measures. Specifically, we included three independent sets of fMRI measures (LOC GVNant, IFG GVNant, and LOC-IFG connectivity) and four primary behavioral and clinical symptom variables (reaction time, BDI PANAS, and PROMIS fatigue). Significant correlations between these variables resulted in the formation of 4 independent clusters of measures: cluster measure (1) LOC-IFG connectivity, cluster measure (2) LOC GVNant and IFG GVNant ($p = 0.009$), cluster measure (3) RT, and cluster measure (4) BDI, PANAS, and PROMIS fatigue (all $p < 0.001$). We adjusted the correlational analyses using Bonferroni correction to account for a total of 4 independent measures. Thus, for the primary correlation analyses, the significance level was set at $p < 0.0125$ (corrected threshold).

For exploratory correlational analyses, we again included three independent sets of fMRI measures (LOC GVNant, IFG GVNant, and LOC-IFG connectivity), as well as additional behavioral and clinical symptom variables (accuracy rate, BAS, BIS, POMS, STAI Trait, STAI State, pain severity, and pain interference). Significant correlations between these variables resulted in the formation of 5 independent clusters of measures. Note that, for this calculation, we added all behavioral and clinical measures from primary and exploratory analyses: cluster measure (1) LOC-IFG connectivity, cluster measure (2) LOC GVNant and IFG GVNant ($p = 0.009$), cluster measure (3) BAS, cluster measure (4) BIS, and cluster measure (5) the rest of the measures (all $p < 0.001$). For these exploratory findings, we adjusted the correlational analyses using Bonferroni correction to account for a total of 5 independent measures, resulted in the significance level set at $p < 0.01$ (corrected threshold). As specified in the pre-registration, we initially planned to use the standard $p < 0.05$ to assess the significance and did not apply a correction for multiple comparisons in the exploratory analyses. Therefore, we report both uncorrected ($p < 0.05$) for descriptive purposes only, as well as corrected results ($p < 0.0125$, significant at Bonferroni corrected threshold) for the exploratory findings. We tested the correlations separately for the non-opioid FM, opioid FM, and control groups and reported both significant and non-significant results. In a moderation analysis, we used the standard $p < 0.05$ to evaluate significance. We addressed multicollinearity in our moderation analyses and calculated Variance Inflation Factor (VIF) values for all variables. A VIF threshold of 5 was used to identify potential multicollinearity issues[77].

Data availability

This study was pre-registered on the Open Science Framework (OSF, https://osf.io/dx83h). None of the data or materials for the experiments reported here is available, but readers seeking access to the data should contact the corresponding author, Su Hyoun Park, or the local ethics committee at the Department of Anesthesiology, Duke University. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data.

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Author contributions

The authors confirm contribution to the paper as follows: S.H.P. and K.T.M. were responsible for the conception and design of the study. S.H.P., A.K.B., and K.T.M. collected the data. S.H.P. and K.T.M. analyzed the data. S.H.P., A.K.B., and K.T.M. were involved in the interpretation of results. S.H.P. produced the initial manuscript draft. S.H.P., A.K.B., and K.T.M. edited and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Declarations

Competing interests
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