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Replication of neural responses to monetary incentives and exploration of reward-influenced network connectivity in fibromyalgia

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Abstract

Neuroimaging research has begun to implicate alterations of brain reward systems in chronic pain. Previously, using functional magnetic resonance imaging (fMRI) and a monetary incentive delay (MID) task, Martucci et al. (2018) showed that neural responses to reward anticipation and outcome are altered in fibromyalgia. In the present study, we aimed to test the replicability of these altered neural responses to reward in a separate fibromyalgia cohort. In addition, the present study was conducted at a distinct U.S. location but involved a similar study design. For the present study, 20 patients with fibromyalgia and 20 healthy controls participated in MID task fMRI scan procedures and completed clinical/psychological questionnaires. fMRI analyses comparing patient and control groups revealed a consistent trend of main results which were largely similar to the prior reported results. Specifically, in the replication fibromyalgia cohort, medial prefrontal cortex (MPFC) response was reduced during gain anticipation and was increased during no-loss (non-punishment) outcome compared to controls. Also consistent with previous findings, the nucleus accumbens response to gain anticipation did not differ in patients vs. controls. Further, results from similarly-designed behavioral, correlational, and exploratory analyses were complementary to previous findings. Finally, a novel network-based functional connectivity analysis of the MID

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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., E.Z.D., A.K.B., and K.T.M. collected the data. S.H.P., E.Z.D., and K.T.M. analyzed the data. S.H.P., E.Z.D., A.K.B., K.H.M., B.K., and K.T.M. were involved in the interpretation of results. S.H.P. produced the initial manuscript draft. S.H.P., E.Z.D., A.K.B., K.H.M., B.K., and K.T.M. edited and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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task fMRI data across patients vs. controls implied enhanced connectivity within the default mode network in participants with fibromyalgia. Together, based on replicating prior univariate results and new network-based functional connectivity analyses of MID task fMRI data, we provide further evidence of altered brain reward responses, particularly in the MPFC response to reward outcomes, in patients with fibromyalgia.

Keywords

Medial prefrontal cortex; Nucleus accumbens; Chronic pain; Value; Total mood disturbance; Monetary incentive delay (MID) task

1. Introduction

Chronic pain is often accompanied by psychological impairments and physical disabilities that can influence motivation (Navratilova and Porreca, 2014), which modulates human cognition and behavior (Daw and Doya, 2006). As the relationship between the experience of pain (i.e., acute or chronic) and motivation is linked, both pain and reward can engage overlapping aspects of neural function, including brain circuits implicated in motivation (i.e., including brain reward systems) (Knutson and Huettel, 2015). For example, in healthy control subjects, relief from acute pain can increase nucleus accumbens (NAcc) activity (Becerra and Borsook, 2008). The NAcc, in the center of the ventral striatum, is a key region involved in brain reward circuits, and dopamine release in NAcc is essential for reward processing (Nicola et al., 2005). Thus, as indicated by neuroimaging evidence of increased NAcc activity in response to pain relief (Becerra and Borsook, 2008), cessation of pain may be experienced as rewarding.

Previous clinical research has implicated alterations of brain reward systems across a variety of chronic pain conditions (Baliki et al., 2012; Berger et al., 2014; Borsook et al., 2016; DosSantos et al., 2017; Martucci et al., 2018, 2019; Park et al., 2022). Fibromyalgia is a condition of widespread musculoskeletal chronic pain which is often accompanied by cognitive and fatigue symptoms (Sluka and Clauw, 2016). As symptoms of fibromyalgia are not only restricted to chronic pain but are also typically accompanied by cognitive deficits, fatigue, and mood disorders, such as anxiety and depression (Sluka and Clauw, 2016), prior studies have focused on how altered motivational systems may represent a key facet of fibromyalgia (e.g., Rosselló et al., 2015). Previous research suggests that relative to healthy controls, patients with fibromyalgia have altered dopaminergic neurotransmission (Albrecht et al., 2016; Ledermann et al., 2017; Wood et al., 2007) and reduced neural responses to anticipated pain relief in regions implicated in reward processing, including the ventral tegmental area (VTA) (Loggia et al., 2014). To date, however, only a few studies have directly measured neural responses to monetary reward and punishment (i.e., to non-nociceptive or non-painful stimuli) in patients with fibromyalgia (Kim et al., 2020; Martucci et al., 2018, 2019). In the present study, we examined brain reward systems in patients with fibromyalgia to replicate and extend prior work demonstrating altered brain response to monetary reward and punishment in fibromyalgia.

Since the turn of the 21st century, researchers have been able to map functional activity in human reward circuits with the help of Functional Magnetic Resonance Imaging (fMRI; Knutson and Cooper, 2005). Comparative research suggests that reward processing involves cortico-subcortical conserved circuits across a network of brain regions which include the NAcc, medial prefrontal cortex (MPFC), VTA, anterior insula (aINS), and anterior cingulate cortex (ACC) (Haber and Calzavara, 2009; Haber and Knutson, 2010; Sescousse et al., 2013). Functional neuroimaging research has implicated these regions in human reward processing (Bush et al., 2002; Haber and Calzavara, 2009; Knutson et al., 2001; Preuschoff et al., 2008) and structural studies have confirmed their interconnection (Chikama et al., 1997; J. H. Fallon, 1981; Fiorillo et al., 2003; Kunishio and Haber, 1994). One specific task used to probe the function of these circuits in humans is the monetary incentive delay (MID) task (Kim et al., 2020; Martucci et al., 2018, 2019). The MID task is designed to probe an individual's response to different stages of reward anticipation and outcome and magnitudes of monetary incentives (e.g., reward magnitudes; +$5, +$1, +$0 and punishment magnitudes; −$5, −$1, −$0) (Knutson et al., 2000). Typically, MID task trials include presentation of a cue followed by a short fixated delay (i.e., anticipation phase), and then target presentation requiring a response (e.g., pressing a button) followed by feedback (i.e., hit or miss; outcome phase).

A previous study by Martucci et al. (2018) combining fMRI with the MID task found that brain responses to monetary reward are altered in patients with fibromyalgia. Compared to healthy controls, patients demonstrated reduced MPFC responses during the anticipation of reward gains, but enhanced MPFC responses in response to non-punishment outcomes. NAcc responses during the anticipation of reward gains, however, did not significantly differ between patients vs. controls (Martucci et al., 2018). In another study applying the MID task to a mixed cohort of patients with chronic low back pain or fibromyalgia, Kim et al. (2020) found that patients had reduced right striatum response to rewarding outcomes. The contrasting results of Martucci et al. (2018) and Kim et al. (2020) thus warrant further investigation to clarify links between fibromyalgia and reward processing.

To test the replicability of previous results (Martucci et al., 2018), we extended a nearly identical study design in a new cohort of patients. As outlined in a pre-registered plan published on the Open Science Framework (OSF, https://osf.io/4yctn), analyses focused on 1) MPFC fMRI-based response during reward anticipation and to non-punishment outcomes, and 2) NAcc fMRI-based response during reward anticipation and to non-punishment outcomes. To further examine the replicability of previous work (Martucci et al., 2018), we also conducted more comprehensive correlational and exploratory analyses in this study (as described in OSF, https://osf.io/4yctn). These correlational analyses included multiple psychological and clinical measures to determine levels of depression, anxiety, behavioral inhibition/approach and motivation, positive and negative affect, mood disturbance, pain severity and interference, and fatigue (see Methods). These psychological/clinical measures were selected for inclusion to 1) explore replication (i.e., of Martucci et al., 2018), and 2) more broadly characterize the fibromyalgia sample. Beyond symptoms of widespread pain, patients with fibromyalgia often report symptoms of anxiety, depression, cognitive deficits, and fatigue (Bernik et al., 2013; Goldenberg et al., 2008; Gracely et al., 2012). Further, in patients with fibromyalgia, positive and negative affect scores are

related to cognitive function (Galvez-Sánchez et al., 2018) and approach/avoidance behavior is altered, relative to healthy controls (Becerra-García and Robles Jurado, 2014). Thus, inclusion of clinical and psychological measures in exploratory analyses, offers a more comprehensive view of how brain reward systems may relate to self-reported psychological and clinical symptoms.

Similar to previous work (Martucci et al., 2018), the present study also included exploratory analyses of reward anticipation response in other regions of interest (i.e., the VTA, aINS, and ACC). The VTA is a key midbrain region involved in reward processing which sends dopaminergic projections to the NAcc (Knutson et al., 2001). The aINS and ACC represent additional essential brain regions for both pain and motivation (Martucci and Mackey, 2018; Medford and Critchley, 2010). Thus, additional exploratory analyses compared activity within these regions for fibromyalgia patients versus controls. Also following previous work (Martucci et al., 2018), analyses further examined neural responses in an extended MPFC region, as well as across the whole-brain to provide a broader perspective of associations between fibromyalgia and incentive processing.

In addition to the replication analyses described above, in this study only, we conducted an additional novel analysis of brain network functional connectivity. Using the same MID task fMRI scan data, these exploratory analyses compared correlated activity across the task (or “functional connectivity”) within selected networks of interest for patients versus healthy controls. As described in prior research, patients with fibromyalgia have shown altered connectivity between regions implicated in reward processing (including the default mode network, or DMN) and other brain regions (including the inferior temporal gyrus, ACC, and superior parietal lobule) while at rest (or while not participating in an overt task) (N. Fallon et al., 2016). Additionally, patients with fibromyalgia at rest have shown increased connectivity both within executive attention regions, and between the DMN and insular cortex relative to healthy controls (Napadow et al., 2010). Thus, patients with fibromyalgia may show altered network-based functional connectivity during both the resting state and task performance, but no research has investigated functional connectivity during performance of a reward task in fibromyalgia. Thus, we conducted an additional exploratory analysis of MID task fMRI data to compare patients versus healthy controls’ functional connectivity across six brain functional networks. These networks included the DMN, dorsal attentional network, salience network, frontoparietal network, sensorimotor network, and visual network, and were selected based on prior research suggesting altered functional connectivity in patients with fibromyalgia (N. Fallon et al., 2016; Napadow et al., 2010; Seo et al., 2012) and networks likely to be engaged during MID task performance (e.g., seeing visual cues and motorically responding to targets). We conducted this network functional connectivity analysis solely as an exploratory analysis to provide further insight for future research investigations.

2. Methods

2.1. Participants

Twenty individuals diagnosed with fibromyalgia and 20 healthy chronic pain free individuals participated in the study. All participants in this study were female. We enrolled only

females because the majority of referred patients with fibromyalgia are women, and sex differences may affect brain activity in response to rewards in patients with fibromyalgia (Baker et al., 2022; Wolfe et al., 2018). Healthy controls were also all female, accordingly. The inclusion criteria for all participants were as follows: 1) female and ages 18–65, 2) ability to read/understand English and give consent to participate, 3) absence of use of opioid medications (no opioid use during the previous 90 days, and no prior use greater than a 30-day period during lifetime), and 4) self-reported or physician diagnosis of fibromyalgia and meeting the American College of Rheumatology (ACR) Criteria for Fibromyalgia OR absence of chronic pain if designated as a healthy participant. Specifically, participants with fibromyalgia were required to 1) meet modified ACR 2016 criteria for fibromyalgia (Wolfe et al., 2016), 2) have pain in all four quadrants of the body, and 3) have an average pain score of at least 2 (0–10 verbal scale) over the prior month.

Exclusion criteria for all participants included: 1) limited ability to participate fully in the behavioral tasks, 2) MRI contraindication (e.g., metal implants, claustrophobia, pregnant or planning to become pregnant), and 3) factors that would adversely affect the participant or integrity of the study which included ongoing legal action or disability claim regarding pain, uncontrolled psychiatric disorder, and prior head/neck injury resulting in concussion. In addition, any participants with missing behavioral/clinical data were excluded from the correlation analysis specific to the missing data (e.g., a participant missing “pain duration” data was excluded from the analyses testing relationships with pain duration, but not excluded from other correlation analyses). All participants were required to have no major and/or uncontrolled depression or anxiety (see Results), and all healthy control participants were required to not be taking any depression- or anxiety-related medications. All participants signed written informed consent acknowledging that they were willing to participate in the study, understood all study procedures, and could withdraw from the study at any time.

2.2. Study procedures

All study procedures were approved by the Duke University Institutional Review Board and were conducted at the Brain Imaging and Analysis Center (BIAC) at Duke University. All participants received instruction for the monetary incentive delay (MID) task and for the arousal and valence ratings and practiced these tasks prior to the MRI scans. In addition, patients with fibromyalgia and healthy controls completed questionnaires including the Beck Depression Inventory (BDI; Beck et al., 1988), State-Trait Anxiety Inventory (STAI-State, STAI-Trait; Spielberger et al., 1970), Behavioral Inhibition System/Behavioral Approach System Scales (BIS/BAS Scales; Carver and White, 1994), Profile of Mood States (POMS; McNair et al., 1971), Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), Brief Pain Inventory (BPI; Keller et al., 2004), PROMIS Fatigue (computer adapted test, bank v1.0) (Cella et al., 2010), and Brief Symptom Inventory, which included subscales for anxiety and depression (BSI; Derogatis and Melisaratos, 1983).

2.3. Monetary incentive delay (MID) task

The MID task was programmed in MATLAB with Psychophysics Toolbox v.3 (Brainard and Vision, 1997; Kleiner et al., 2007), and the procedures were the same as used in Martucci

et al. (2018). All participants performed two runs of the MID task. Each trial consisted of, in order, 1) a cue, 2) a fixation cross, 3) a triangle target, and 4) feedback/outcome. A cue denoted the amount of money that participants could gain or lose [potential gain: +$5 and +$1, no gain: +$0, accompanied with a “circle” symbol; potential loss: −$5 and −$1, no loss: −$0, accompanied with a “square” symbol]. After each cue, a fixation mark was presented for 2 s, and then a triangle target was presented. An initial target duration was set between 260 ms–280 ms, and the target was presented for variable durations. Based on each participant’s performance, the target duration was automatically adjusted by the program to achieve a hit rate of approximately 66% across trials. Participants were instructed to press the button as quickly as possible. Then, after the target presentation feedback was shown on the screen denoting the outcome of the trial. If the participant’s response resulted in a “hit” (i.e., participant pressed the button during the target presentation) on gain trials, they won that amount of money, but if their response resulted in a “miss” (i.e., no button press, or button press before or after presentation of the target), they did not win any money on that trial. For the loss trials, if the participant “hit” they avoided losing the cued amount, but in the case of a “miss,” they lost the cued amount (Fig. 1). The six types of trial conditions (i.e., +$5, +$1, +$0, −$5, −$1, and −$0) were randomly distributed across the task, and the order of trials and runs was the same (i.e., predetermined order) for all participants. The first run of the MID task consisted of 42 trials (i.e., seven presentations of each trial condition) and the second run of the task consisted of 48 trials (i.e., eight presentations of each trial condition).

After the MID task fMRI scans, all participants completed the rating (i.e., arousal, valence) task. For the rating task, participants were instructed to rate their perceived levels of arousal and valence for each of the 6 cues that had been presented during the MID task (e.g., +5 accompanied with a circle symbol). For the each of the 6 cues, two sequential 7-point Likert scales were presented on a screen so that participants could rate via button press their perceived levels of arousal (low – medium – high) and valence (negative – neutral – positive). Participants practiced both the MID task and arousal/valence rating task prior to the MRI scans. For the practice of the MID task, 12 trials were presented (i.e., which included two presentations for each of the 6 trial conditions) and the trial presentation order during practice was distinct from the trial presentation order used in the actual MID task. Prior to practicing the arousal/valence rating task, participants received instruction regarding the meaning of the terms “arousal” and “valence” (i.e., member of the research team read prompts at the beginning of the task which described scenarios for combinations of low vs. high arousal and valence). Following these instructions, participants were able to practice using the arousal and valence scales by using a button box to provide ratings for each of the 6 cues.

Each trial consisted of anticipation and outcome phases, and this example depicts both gain and loss trials. Consistent with Martucci et al. (2018), each trial (TR-locked; TR = 2 s) consisted of TR 1 = cue, TR 2 = fixation, TR 3 = target, and TR 4 = feedback, TR(s) 5–7 = variable duration inter-trial interval. Cues were either circles (potential gains) or squares (potential losses), and they were presented with monetary values. After a fixation period, a target period began. A triangle was presented for a variable duration (~280 ms) during the target period, which was determined based on prior response accuracy to obtain an average

66% hit rate. During the outcome phase, win or loss (i.e., hit or miss) feedback was given. After the feedback, a black screen was presented as a pseudo-randomized inter-trial interval period (2, 4, or 6 s duration).

2.4. Clinical measures

For psychological and clinical measures, we measured the level of 1) depression, using the BDI (Beck et al., 1988) and BSI (Derogatis and Melisaratos, 1983), 2) anxiety, using the STAI-State and STAI-Trait (Spielberger et al., 1970), 3) positive and negative affect, using the PANAS (Watson et al., 1988), 4) reward and motivational approach/avoidance behavior, using the BIS/BAS (Carver and White, 1994), 5) mood disturbance, using the POMS (McNair et al., 1971), 6) clinical pain severity and interference, using the BPI (Keller et al., 2004), and 7) fatigue, using PROMIS Fatigue (Cella et al., 2010). Notably, lower scores of total mood disturbance (POMS) indicates the more stable mood profiles. As described in the Introduction, prior studies have used these measures to asses various domains in fibromyalgia and demonstrated that these measures are differently represented in patients compared to controls (Becerra-García and Robles Jurado, 2014; Bernik et al., 2013; Galvez-Sánchez et al., 2018; Goldenberg et al., 2008; Gracely et al., 2012). For example, patients with fibromyalgia demonstrate lower BAS scores (i.e., approach behavior) compared to controls (Becerra-García and Robles Jurado, 2014), and higher BIS scores (i.e., avoidance behavior) relate to worse pain and psychological function in fibromyalgia (Serrano-Ibáñez et al., 2019).

2.5. MRI scans

Scans were conducted on a 3T GE Premier UHP system with a 48-channel coil at the Duke Brain Imaging and Analysis Center. As in the Martucci et al. (2018) study, the scan sessions consisted of the initial preparatory localizer, asset calibration scans, two MID task fMRI scans, and T1 anatomical scan. The fMRI scan parameters were as follows: Gradient Echo Pulse Sequence with echo time (TE) 25 ms, repetition time (TR) 2 s, interleaved bottom-up slice order, 46 slices, 2.9 mm slice thickness, pixel size 2.9 mm, flip angle 77°. However, unlike the Martucci et al. (2018) study, we did not use a Spiral In-Out scan sequence. The 2 MID task scans consisted of 266 and 302 vol, respectively, and we excluded the first 6 lead-in volumes (12 s) and 4 lead-out volumes (8 s). A T1 anatomical scan (MPRAGE sequence) was acquired for registration of functional images with parameters as follows: whole-brain coverage including the brainstem and cerebellum, 1 mm slice thickness, 256 mm frequency field of view (FOV), frequency direction anterior/posterior, flip angle 8°, TR 2.2 s, TE 3.2 ms.

2.6. fMRI data pre-processing

All neuroimaging data were pre-processed using Python and AFNI software (Analysis of Functional Neuroimages). For pre-processing, the following GitHub repository was used: https://github.com/kellyhennigan/MID_processing_example. Specifically, we used custom scripts for functional images to remove the first 6 lead-in volumes and 4 lead-out volumes, and to perform both slice time correction and motion correction. Next, we spatially smoothed the data with a 4 mm (full-width half-maximum, FWHM) Gaussian kernel and converted the data into units of percent change values (i.e., normalization). We applied

a high-pass filter (a threshold of 0.011 Hz) to remove low-frequency signals. Then, we transformed the concatenated preprocessed functional images to standard group space. Anatomical images were skull stripped (3dSkullStrip) and aligned to Talairach space (AFNI's @auto_tlrc). Next, the first volume of the functional image was co-registered to the anatomical image, and then this volume was skull stripped (3dSkullStrip). Lastly, the anatomical image was co-registered to functional data and transformed from native to standard space.

As part of data pre-processing, we applied motion censoring to exclude any volumes with motion greater than a Euclidean norm value of 0.5, based on evidence suggesting that motion censoring improves the quality of task-based fMRI data (Siegel et al., 2014). For this, we calculated volume-to-volume motion by generating values of the square root of the sum of squares across 6 motion parameter values (i.e., Euclidean norm). Using these values, we calculated the average motion during the MID task for each participant as well as the group difference in head motion.

2.7. MID task fMRI contrasts

Four orthogonal regressors were modeled to contrast participants' responses during anticipation and outcome phases. The use of these regressors resulted in four contrasts: gain vs. no-gain anticipation (GVNant), loss vs. no-loss anticipation (LVNant), gain vs. no-gain outcome (GVNout), and no-loss vs. loss outcome (NVLout). As based on the results reported in the Martucci et al. (2018) study, our main analysis in the present study focused on the following two contrasts (as described in our pre-registered analysis in OSF, https://osf.io/4yctn):

1. gain vs. no-gain anticipation (GVNant contrast): gain (+$5) trials vs. no-gain (+/−$0) trials during the anticipation period.
2. no-loss vs. loss outcome (NVLout contrast): hits (−$0 outcome) vs. misses (−$5 outcome) during the outcome period.

As exploratory analyses, we analyzed two additional contrasts:

1. loss vs. no-loss anticipation (LVNant contrast): loss (−$5) vs. no-loss (+/−$0) during the anticipation period.
2. gain vs. no-gain outcome (GVNout contrast): hits (+$5 outcome) vs. misses (+0 outcome) during the outcome period.

All regressors were convolved with a single-gamma hemodynamic response function, with an approximated 6-s delay.

2.8. Region of interest analyses

As similarly performed in the Martucci et al. (2018) study, in the present study we conducted primary region of interest (ROI) analyses focused on the NAcc and MPFC. For this study, we used the same ROI masks as used in Martucci et al. (2018). The bilateral NAcc ROI was created using the "Left-Accumbens" and "Right-Accumbens" pre-defined masks from the DKD_Desai_MPM atlas which is included in AFNI. After

merging these two masks into one bilateral mask (using AFNI's 3dcalc), the bilateral mask was resampled using AFNI's 3dresample function. A total number of 52 voxels were included in the bilateral NAcc mask. The MPFC ROI was created from two 8-mm diameter spheres centered at±4, 50, −3. As described in the Martucci et al. (2018) study, the MPFC coordinates were selected based on a previous MID task study which defined a bilateral MPFC ROI to analyze data from patients with major depressive disorder (MDD) (4, 50, −4) (Knutson et al., 2008), and these coordinates were slightly adjusted (to±2, 52, −2) based on a prior study which focused on MPFC functional connectivity in patients with chronic pain (Baliki et al., 2012). After creating the two spheres for the bilateral MPFC ROI over the TT_N27+tlrc image, the bilateral MPFC mask image was resampled (using AFNI's 3dfractionize) so that it resulted in a final bilateral MPFC mask of 42 voxels.

2.9. Statistical analysis

Statistical analyses closely matched those reported by Martucci et al. (2018). For the behavioral data, we calculated within-group and between-group level statistics for participants' reaction times and accuracy rates during the MID task. After performing the MID task, participants rated their levels of arousal and valence for each cue (i.e., +$0, +$1, +$5, −$0, −$1, and −$5) that had appeared during the MID task. Using these ratings, we calculated combined values for positive and negative arousal for each participant by first mean-deviating valence and arousal ratings across stimuli within each participant and then combining them like so: (positive arousal = arousal/√(2) + valence/√(2); negative arousal = arousal/√(2) – valence/√(2)) (Knutson, 2005; Knutson et al., 2014), which is consistent with the circumplex model of affect (Watson et al., 1999). Then, we conducted a two-way mixed effects ANOVAs (between-subject factor: group: patient vs. controls; within-subject factor: cue: +/− $0, $1, $5) to determine group, cue, and interaction effects separately for each variable of arousal, valence, positive arousal, and negative arousal.

For the 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 same custom MATLAB scripts as used in the Martucci et al. (2018) study (GitHub repository: https://github.com/kellyhennigan/MID_processing_example). Additionally, as used in the Martucci et al. (2018) study, and as described in our pre-registration plan (as documented in OSF), the corrected significance threshold for our analysis was set at $p < 0.0125$ (initial $p < 0.05$; Bonferroni corrected for four ROI × contrast comparisons: NAcc × GVNant, NAcc × NVLout, MPFC × GVNant, MPFC × NVLout). For visualization purposes, AFNI's 3dttest++ was used to create activation maps, and the ROI group results were visualized at a voxel-wise threshold of $p < 0.05$.

To explore how the neuroimaging results related to clinical symptoms, we conducted correlational analyses for the extracted fMRI beta values vs. collected questionnaire data. As performed in the Martucci et al. (2018) study, we tested these correlations across combined patient and control groups using JASP (JASP Team, 2020). We included three independent sets of ROI beta values (NAcc GVNant, MPFC GVNant, and MPFC NVLout). Clinical symptom variables included behavioral drive, behavioral reward responsiveness,

and behavioral fun seeking (i.e., 3 BAS subscales), behavioral inhibition (BIS subscale), positive affect (PANAS subscale), negative affect (PANAS subscale), total mood disturbance (POMS), depression (BDI), trait anxiety (STAI Trait), state anxiety (STAI State), pain severity (BPI), pain interference (BPI), fatigue (PROMIS Fatigue), and the depression and anxiety subscales of the Brief Symptom Inventory (BSI). Prior to running the planned correlational analyses, we tested for significant correlations between the clinical variables, and as such, we identified that the questionnaire data represented 3 independent clusters of measures: Cluster measure 1) BAS fun and BAS reward ($p < 0.001$), cluster measure 2) BAS drive and BIS ($p < 0.001$), and cluster measure 3) all other measured clinical symptom variables ($p < 0.025$). Accordingly, based on our inclusion of 3 independent sets of ROI fMRI beta values with 3 independent sets of clinical symptom variables, the correlational analyses were Bonferroni corrected for a total of 6 independent measures used and therefore were determined to be significant at the level of $p < 0.008$ (corrected threshold). For any initial combined-group significant correlation (i.e., corrected $p < 0.008$), we also conducted post-hoc analyses to test for within-group (i.e., separately for patients and controls) correlations.

2.10. Additional contrasts and ROIs for post-hoc analyses

As exploratory ROI analyses, we analyzed the NAcc and MPFC ROIs using two exploratory task contrasts for: 1) loss vs. no-loss anticipation (LVNant): loss (−$5) trials vs. no-loss (+/−$0) trials during the anticipation period; and 2) gain vs. no-gain outcome (GVNout): hits (+$5 outcome) vs. misses (+$0 outcome) during the outcome period.

As based on prior research showing less pronounced brain response to smaller incentives (Knutson et al., 2003, 2005), the Martucci et al. (2018) study did not include +$1 and −$1 trials in their analysis. However, as part of separate exploratory analyses, we analyzed the main contrasts [gain anticipation (GVNant) and non-punishment outcomes (NVLout)] with −$1 and +$1 trials included; this analysis allowed us to provide more comprehensive information about whether inclusion of lower reward/punishment incentives influenced the primary results.

Next, we extracted fMRI beta values from additional ROIs of the VTA, aINS, and ACC. For these analyses, we used the same ROI masks as used previously (Martucci et al., 2018). Specifically, the VTA ROI was created using the structural landmark demarcation as defined previously (Hennigan et al., 2015); the bilateral aINS ROI was created by merging the “Left-Anterior Insula” and “Right-Anterior Insula” masks from the DKD_Desai_MPM Atlas in AFNI; and the ACC ROI was created by combining two 4 mm radius spheres (centered at±8, 11, 34) as defined previously (Knutson et al., 2008). All ROIs were resampled to functional image dimensions (using AFNI’s 3dfractionize, clip 0.1) and transformed back to Talairach space. For these post-hoc analyses with additional ROIs and contrasts, we did not correct the results for multiple comparisons since these analyses were exploratory (as described in OSF, https://osf.io/4yctn).

2.11. Whole-brain and expanded anterior medial prefrontal cortex mask post-hoc analyses

In the present study, we conducted post-hoc whole brain and expanded anterior MPFC (aMPFC) region analyses. These analyses were conducted to 1) confirm the ROI results in the present study, and 2) to examine the replicability of post-hoc whole-brain and expanded aMPFC results performed previously (Martucci et al., 2018). For the whole-brain mask, we used TT_N27+tlrc image (AFNI). For the aMPFC mask, we used a functionally-defined extended MPFC ROI (i.e., "kmeans_3.nii" created by de la Vega et al., 2016; https://www.neurovault.org/media/images/1458/kmeans_3.nii.gz) as used previously (Martucci et al., 2018). For visualization purposes, the results were thresholded at $p < 0.05$ ($z = 1.975$) with cluster correction (AFNI's Clustsim) set at a minimum cluster size of 20 voxels with first-nearest neighbor clustering (i.e., all voxels must touch a face for inclusion in a cluster, NN set to = 1).

2.12. Brain functional network connectivity during the MID task

All MID fMRI data were preprocessed using the CONN toolbox's (v.20b) default pre-processing pipeline (running in MATLAB v.R2020a and SPM12) (Whitfield-Gabrieli and Nieto-Castanon, 2012). Pre-processing consisted of realignment, interleaved bottom-up slice order slice-timing correction, and outlier identification. Identification of outliers was performed based on subject measured motion and observed global BOLD signal; for this we used the intermediate outlier identification setting in CONN. Next, T1-weighted structural data and functional data were segmented into grey matter, white matter, and cerebrospinal fluid tissue classes. After normalizing images to Montreal Neurologic Institute (MNI) space, functional images were smoothed using a Gaussian kernel of 4 mm full width half maximum. After pre-processing, we followed CONN's default denoising pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012). The denoising process consisted of the following steps: anatomic component-based noise correction procedure (aCompCor), correction for potential confounding effects, subject-motion parameter estimation, outlier scan identification/scrubbing, and bandpass filtering to 0.008–0.09 Hz.

Across six functional networks, pre-defined targeted seeds were selected from CONN's functional network atlas: four seeds within the default mode network (DMN), three seeds within the sensorimotor network, four seeds within the visual network, seven seeds within the salience network, four seeds within the dorsal attentional network, and four seeds within the frontoparietal network. The coordinate locations for these target seeds were all pre-defined based on the results from CONN's independent component analyses (ICA) of the human connectome project dataset (HCP, 497 subjects). Functional connectivity of targeted seeds within and between the networks was compared for patient vs. control groups (two-sample *t*-test). For the significance threshold, we used a p-value < 0.05, false discovery rate (FDR)-corrected.

3. Results

3.1. Clinical, behavioral, and psychological measures

Data from a total of twenty patients and 20 healthy controls were included in the final analysis (Table 1). As indicated in the Methods, participants who had missing behavioral/clinical data were excluded from any analyses associated with the missing data. All questionnaire measures administered in this study, except for BIS, were also administered in the Martucci et al. (2018) study (Table 1; *the presented significance values (P-Value) are not corrected for multiple comparisons as results are provided only for descriptive purposes*). As compared to the control group, clinical symptoms of anxiety, depression, mood disturbance, fatigue, number of pain areas, pain severity, and pain interference were all significantly higher in the patient group. However, behavioral inhibition (measured using the BIS subscale) did not significantly differ between groups. Notably, the majority of patients did not report severe levels of depression (BDI scores from 18 patients were less than 28, 1 scored 41, 1 did not complete the BDI) or anxiety (STAI scores from 18 patients were less than 61, 1 scored 66, 1 did not complete the STAI). The number and location of painful body areas reported per patient are shown in Supplementary Fig. 1.

In the present study, there was a significant difference in age between patient and control groups, such that patients were younger than healthy controls. We tried to minimize the age differences during recruitment, but due to challenges with recruiting patients (particularly due to the Covid-19 pandemic), could not precisely match age between groups. In the primary analyses, we reported results of a one-way analysis of covariance (ANCOVA), including age as a continuous covariate. As reported by patients, the duration of fibromyalgia-related chronic pain ranged from 9 months to 20 years (M = 6.03, SD = 5.33).

3.2. Medication use

All healthy controls reported taking no pain or mood-altering medications. All patients were opioid-naïve (i.e., reported less than one month of opioid use within their lifetime and no opioid use within at least 90 days prior to the study). Sixteen of the patients were taking nonsteroidal anti-inflammatory drugs (NSAIDs, N = 3), acetaminophen (N = 2), serotonin-norepinephrine reuptake inhibitors (SNRIs, N = 7), selective serotonin reuptake inhibitors (SSRIs, N = 5), serotonin antagonist and reuptake inhibitors (i.e., trazodone, N = 1), tricyclic antidepressants (TCAs, N = 3), other anxiolytics (e.g., buspirone hydrochloride, N = 1), triptans (N = 1), antiepileptics (N = 3), muscle relaxants (N = 5), gamma-aminobutyric acid (GABA) analogs (e.g., pregabalin and gabapentin, N = 4), benzodiazepines (N = 3), and norepinephrine–dopamine reuptake inhibitors (NDRI, N = 3). Four patients reported not taking any pain or mood-altering medications.

3.3. MID task reaction times and accuracy rates

Across both patient and control groups, a significant main effect of trial type indicated that higher gain (+$5 anticipation) and loss (−$5 anticipation) trials elicited shorter reaction times [F(5,190) = 4.2, p = 0.001]. A nonparametric test (Durbin test; JASP team, 2020) also consistently showed a significant main effect of trial type, $X^2(5) = 17.43$, p = 0.004, Kendall's W = −18.79. No group [F(1,190) = 0.0, p = 0.842; Durbin test: $X^2(1) = 0.04$, p

= 0.83, Kendall's W = −3164.99] or group by trial interaction effects [F(5,190) = 1.5, p = 0.186] were observed.

We used a version of the MID task that was programmed to track performance and target 66% accuracy rates (consistent with Martucci et al. (2018)). Despite this adaptive manipulation, percent hits were greater for gain and loss trials as compared to no gain/no loss trials [F(5, 190) = 5.3, p < 0.001]. A Durbin test revealed a significant main effect of trial type, $X^2(5) = 10.82$, p = 0.05, Kendall's W = −26.92. No group [F(1,190) = 0.0, p = 0.844; Durbin test: $X^2(1) = 0.18$, p = 0.67, Kendall's W = 659.74] or group by trial interaction effects [F(5,190) = 1.7, p = 0.129] were observed. These behavioral results suggested similar engagement and performance of the MID task across both patient (N = 20) and control (N = 20) groups.

3.4. MID task cue ratings: arousal, valence, positive arousal, and negative arousal

Due to a technical issue (i.e., data not saved), one patient was not included in the cue rating analyses. All descriptive data for cue ratings are reported in Supplementary Table 1.

3.4.1. Arousal—A two-way repeated measures ANOVA (group × cue) for arousal ratings revealed no significant main effect of group [F(1,185) = 1.1, p = 0.301; Durbin test: $X^2(1) = 1.80$, p = 0.18, Kendall's W = 396.55], indicating similar arousal ratings between patients (N = 19) and controls (N = 20). A significant main effect of cue was observed for arousal [F(5,185) = 37.3, p < 0.001; Durbin test: $X^2(5) = 66.37$, p < 0.001, Kendall's W = −60.28], but no group by cue interaction was observed [F (5,185) = 0.1, p = 0.993] (Supplementary Fig. 2A).

3.4.2. Valence—As we observed several instances of positive valence ratings to negative cue values, our data indicated potential confusion among participants regarding our instructions for the valence ratings. Therefore, valence ratings and positive and negative arousal ratings in this study should be interpreted with caution. A two-way repeated measures ANOVA (group × cue) for valence ratings revealed no significant main effect of group [F(1,185) = 0.7, p = 0.425; Durbin test: $X^2(1) = 0.11$, p = 0.73, Kendall's W = 172.73], indicating similar valence ratings between patients (N = 19) and controls (N = 20). A cue effect was observed for valence [F(5,185) = 20.8, p < 0.001; Durbin test: $X^2(5) = 67.07$, p < 0.001, Kendall's W = 49.73], but no interaction was observed [F(5,185) = 0.6, p = 0.732] (Supplementary Fig. 2B).

3.4.3. Positive arousal—A two-way repeated measures ANOVA (group × cue) for positive arousal ratings revealed no effect of group [F(1,185) = 0.8, p = 0.367; Durbin test: $X^2(1) = 0.06$, p = 0.80, Kendall's W = −4193.39], indicating similar positive arousal ratings in patients (N = 19) and controls (N = 20). A main effect of cue was observed for positive arousal [F(5,185) = 39.6, p < 0.001; Durbin test: $X^2(5) = 103.59$, p < 0.001, Kendall's W = −25.62], but no interaction was observed [F(5,185) = 0.2, p = 0.954] (Supplementary Fig. 2C).

3.4.4. Negative arousal—A two-way repeated measures ANOVA (group × cue) for negative arousal ratings revealed no effect of group [F(1,185) = 1.1, p = 0.306; Durbin

test: $X^2(1) = 0.53$, p = 0.46, Kendall's W = 10528.39], indicating similar negative arousal ratings in patients (N = 19) and controls (N = 20). A main effect of cue was observed for negative arousal [F(5,185) = 8.0, p < 0.001; Durbin test: $X^2(5) = 34.99$, p < 0.001, Kendall's W = −26.00], but no group by cue interaction was observed [F(5,185) = 0.4, p = 0.838] (Supplementary Fig. 2D; note – as described in 3.4.2., due to possible errors in reporting of valence by participants, positive and negative arousal in this study should be interpreted with caution).

3.5. Participant motion

None of the fMRI data indicated significant motion during scanning, therefore no participants' data were excluded from the final analysis. Additionally, no group differences in volume-to-volume motion were observed (p = 0.92 [Euclidean norm, patients: M = 0.068, SD = 0.031; controls: M = 0.069, SD = 0.028]).

3.6. ROI activation: nucleus accumbens

Robust NAcc response during gain anticipation (GVNant) was observed for both patient and control groups, and no group difference was observed (Fig. 2C). In addition, we observed no significant group differences in NAcc activity in response to non-punishment outcomes (NVLout) (Fig. 2E). An ANCOVA revealed that the age covariate was not significantly associated with the NAcc GVNant and NAcc NVLout fMRI beta values (all p > 0.09). Further, no significant group difference in the NAcc GVNant and NAcc NVLout fMRI beta values were observed after controlling for age (all p > 0.6). As described in the Methods, for these analyses, the significance threshold (Bonferroni corrected) was set at p < 0.0125.

The correlational analysis with NAcc GVNant fMRI beta values vs. clinical measures (across patient and control groups combined, N = 40) did not reveal any significant correlations (all p > 0.07). As described in the Methods, the results for the correlational analyses between ROI fMRI beta vs. clinical symptom data, here and in the following analyses, were all evaluated for significance at the Bonferroni-corrected threshold p < 0.008.

3.7. ROI activation: medial prefrontal cortex

During gain anticipation, reduced MPFC activity was observed in patients, indicating less MPFC response in patients relative to controls (Fig. 3C). Even though this result did not reach our corrected statistical threshold of p < 0.0125, the trend was similar to prior results demonstrating reduced MPFC activity in patients compared to controls (Martucci et al., 2018). An ANCOVA analysis revealed that the age covariate was not significantly related to the MPFC GVNant fMRI beta values (F(1,37) = 0.009, p = 0.923). Additionally, no significant group difference in the MPFC GVNant fMRI beta values was observed after controlling for the effect of the age (F(1,37) = 3.142, p = 0.085). The correlational analyses between the MPFC GVNant fMRI beta values vs. clinical symptoms did not reveal significant results.

In response to non-punishment outcomes (NVLout contrast), we identified greater MPFC response in patients as compared to controls (Fig. 4A). While these results did not meet the corrected statistical threshold of p < 0.0125, the trend was again similar to prior results

(Martucci et al., 2018). As determined from the ANCOVA analysis, the age covariate was not significantly related to the MPFC NVLout fMRI beta values ($F[1,37] = 2.007$, $p = 0.165$). After controlling for the effect of the age, we still observed a trend (which did not meet the pre-determined significance threshold) of greater MPFC NVLout fMRI beta values in patients vs. controls ($F[1,37] = 4.418$, $p = 0.042$).

Across combined patient and control groups, MPFC NVLout fMRI beta values were significantly correlated with mood disturbance (POMS) ($r = 0.45$, $p = 0.004$). As confirmed by post-hoc within-group analyses (i.e., correlation analyses which were performed separately for the patients or controls), a within-group positive correlation between MPFC NVLout and mood disturbance was only significant in the patient group ($r = 0.582$, $p = 0.007$) (Fig. 4D). While the BSI was not collected in the Martucci et al. (2018) study, this study included the BSI as an additional measure, and the BSI anxiety score was significantly correlated with MPFC NVLout extracted beta values across patient and control groups combined ($r = 0.548$, $p < 0.001$). Post-hoc within-group analyses revealed a significant positive correlation of BSI anxiety and MPFC NVLout response only in the patient group ($r = 0.659$, $p = 0.002$). Additional results from the correlational analyses of ROI betas (i.e., for NAcc GVNant, MPFC GVant, and MPFC NVLout contrasts) vs. clinical measures are reported in Supplementary Table 2.

3.8. Additional ROIs and contrasts for post-hoc analyses

First, we analyzed the NAcc and MPFC ROIs using two exploratory task contrasts for: 1) gain vs. no-gain outcome (GVNout): hits (+$5 outcome) vs. misses (+$0 outcome) during the outcome period; and 2) loss vs. no-loss anticipation (LVNant): loss (−$5) trials vs. no-loss (+/−$0) trials during the anticipation period. For responses to reward outcome (GVNout contrast) and loss anticipation (LVNant contrast), both groups showed increased MPFC BOLD signal during reward outcome and reduced MPFC activity during loss anticipation. No significant group differences in NAcc activity during gain outcome (GVNout) and loss anticipation (LVNant) were revealed (Supplementary Fig. 3).

Second, from our additional exploratory analyses which included +$1 and −$1 trials (i.e., averaged beta values for each ROI and contrast combination; MPFC GVNant, MPFC NVLout, NAcc GVNant, NACC NVLout), we did not identify notable changes in the results as compared to results of the primary ROI analyses (i.e., with +$5 and −$5 data only). Consistent with the results of the main analyses which indicated no significant group differences, patients demonstrated slightly decreased MPFC GVNant response ($p = 0.138$) and increased NVLout response ($p = 0.052$) relative to controls (Supplementary Fig. 4).

Third, post-hoc fMRI analyses were conducted for GVNant response within additional ROIs which included the VTA, aINS, and ACC. No significant group differences in GVNant response were observed in the VTA or ACC, however, we observed reduced bilateral aINS GVNant response in the patient group relative to controls ($p = 0.035$, Supplementary Figs. 5A and 5B). Inconsistent with Martucci et al. (2018), the ACC response was similar across patient vs. healthy control groups. We ran a whole-brain analysis to explore this discrepancy further by focusing on a larger ACC region. The contrast activation map showed a similar

pattern of nearby ACC activation, slightly anterior to the originally selected ACC ROI (Supplementary Fig. 5C).

Fourth and finally, post-hoc fMRI analyses were conducted within an expanded aMPFC region and across the whole brain, as previously implemented by Martucci et al. (2018). The expanded aMPFC mask analysis revealed the presence of activation outside of the targeted MPFC ROI for both GVNant and NVLout contrasts (Supplementary Fig. 6). As expected, the confirmatory whole-brain analysis demonstrated group differences across reward-associated brain regions (Supplementary Fig. 7). For visualization purposes, these results were thresholded at $p < 0.05$ ($z = 1.975$), and cluster correction was set at a minimum cluster size of 20 voxels (see Supplementary Fig. 6 and Supplementary Fig. 7).

As described in the Methods, all of the above post-hoc analysis results were not corrected for multiple comparisons. They were, however, planned and documented in the pre-registration (OSF, https://osf.io/4yctn) as exploratory analyses.

3.9. Brain network functional connectivity during MID task performance

As identified through network-based analysis of MID Task fMRI data, functional connectivity within the DMN significantly differed between groups, such that patients showed greater within-DMN functional connectivity compared to controls. Functional connectivity values for each of the connections between the four DMN seeds were as follows: MPFC - left lateral parietal cortex, $t(38) = 3.54$, p-FDR corrected = 0.026; left lateral parietal cortex - posterior cingulate cortex, $t(38) = 3.36$, p-FDR corrected = 0.022; right lateral parietal cortex - posterior cingulate cortex, $t(38) = 3.70$, p-FDR corrected = 0.016) (Fig. 5). No group differences were observed for any of the other analyzed networks and associated seeds.

4. Discussion

As the main goal of the present study, we aimed to evaluate replicability of previous results from which demonstrated altered brain reward processing in patients with fibromyalgia (Martucci et al., 2018). For this replication study, we included a new cohort of patients with fibromyalgia, and we pre-registered the analysis plan on the Open Science Framework (OSF, https://osf.io/4yctn). We predicted that patients with fibromyalgia would show altered brain reward response, relative to healthy controls. As previously demonstrated (Martucci et al., 2018), NAcc response to reward anticipation was similar in patients and controls, while MPFC response to both reward anticipation and non-punishment outcomes (i.e., avoidance of punishment) was altered in patients. Although this replication study did not produce significant group differences, similar trends of NAcc and MPFC reward responses mirrored the prior study's results. For example, consistent with previous results, NAcc response to reward anticipation did not differ between patient and control groups, but patients showed lesser MPFC response to reward anticipation and greater MPFC response to non-punishment outcome (i.e., no-loss vs. loss outcome). Also, the present findings established replicability of an association between greater MPFC punishment avoidance response and higher total mood disturbance. Lastly, a new analysis of network-based functional connectivity during MID task performance suggested greater connectivity within the DMN

in patients with fibromyalgia vs. controls, consistent with enhanced DMN engagement during reward processing in patients. Together, these results generally replicate previously-observed patterns (Martucci et al., 2018) and extend these findings with new neuroimaging evidence about alterations of incentive processing in individuals with fibromyalgia.

As observed previously (Martucci et al., 2018), patients with fibromyalgia showed blunted MPFC response to reward anticipation, but heightened MPFC response to non-punishment outcomes. In the present replication study, MPFC activity showed a non-significant trend toward similar patterns. Specifically, patients demonstrated a trend for reduced MPFC response during gain anticipation but enhanced response in response to non-punishment outcomes. Thus, with the consistent directionality of MPFC alterations which were observed as trends, the present results support prior observations and contribute to the evolving characterization of an altered reward-response brain signature in patients with fibromyalgia. Also consistent with previous findings, MPFC activity distinguished no-loss from loss outcomes (i.e., −$5 hit vs. miss, NVLout contrasted data; non-punishment outcomes) in patients to a greater extent than in controls. These findings imply that patients with fibromyalgia may experience avoidance of punishment (i.e., as experienced during the no-loss outcome condition) as more reinforcing and salient than the anticipation or even acquisition of reward. As discussed by Martucci et al. (2018), altered MPFC responses during reward processing may be related to altered midbrain dopamine function in fibromyalgia (Wood et al., 2007), altered prefrontal cognitive function (Glass, 2009; Seo et al., 2012), or a combination of the two.

Also consistent with previous findings (Martucci et al., 2018), we observed relatively robust NAcc response during gain anticipation in patients that did not differ from healthy controls. While consistent across both current and previous work, the relative normalcy of NAcc response during reward anticipation in these cohorts of patients with fibromyalgia might be considered surprising, since other researchers have reported altered NAcc/ventral striatum function in fibromyalgia. For example, other studies indicate both reduced (e.g., Wood et al., 2007) and enhanced brain response to reward (e.g., Ledermann et al., 2017) in patients with fibromyalgia. In addition, patients with chronic back pain and fibromyalgia demonstrate reduced reward anticipatory response in the right striatum (i.e., proximal to the location of the NAcc within the ventral striatum) (Kim et al., 2020). In contrast, considering that in both the present and previous studies (Martucci et al., 2018), no significant group differences in NAcc activity were observed, several factors could have contributed to these divergent findings. The MID task differed slightly across studies: Kim et al. (2020) used a variable time interval between cue and target presentations (2.25–3.75 s) while in contrast, in the present study, the time interval between cue and target was fixed at 2 s. Thus, it is possible that fixed timing might reduce cue salience and contribute to differences in observed NAcc reward response.

To extend the potential for clinical relevance of fMRI measures, we evaluated relationships between fMRI ROI-based findings and questionnaire-measured clinical symptoms. Further, as part of the replication efforts of the present study, the majority of correlational analyses performed in the present study were similarly performed previously (Martucci et al., 2018). These analyses suggested that across both studies, MPFC response to non-punishment

outcome was positively correlated with individual differences in mood disturbance (i.e., greater MPFC response was related to higher mood disturbance as indicated by higher self-reported POMS scores). Of note, in the present study, this correlation was primarily driven by the patient group's data (i.e., there was no significant correlation within the control group alone). These findings suggest that patients with greater mood disturbance may respond more robustly to non-punishment outcomes. Further supporting this relationship, the MPFC response to non-punishment outcomes was also positively related to BSI-measured anxiety. Therefore, patients with fibromyalgia who have higher levels of anxiety may also respond more robustly to non-punishment outcomes. Thus, the present results confirm early evidence (Martucci et al., 2018) that measures of mood disturbance, and, to some extent, anxiety may relate to an enhanced response to non-punishment outcomes by some patients with fibromyalgia.

An exploratory analysis with additional contrasts (i.e., GVNout and LVNant) did not reveal any group differences, similar to previous findings (Martucci et al., 2018). Thus, in fibromyalgia, brain reward system alterations appear to be prominent in conditions of reward anticipation and no-loss outcome (i.e., rather than conditions of loss anticipation or gain outcome). Further, the exploratory analysis, which included +$1 and −$1 trials, did not notably change the results. Thus, the potentially greater sensitivity from including lower incentives (i.e., with an increased number of trials) may have been countered by a reduced impact of lower incentives, consistent with previous findings (Knutson et al., 2003, 2005). To accentuate the variation in incentives, however, including lower incentive trials in the MID task itself may be important.

While exploratory analyses did not identify differences in ACC or VTA response, they did also imply reduced reward anticipation response in the aINS. As shown in previous exploratory analyses (Martucci et al., 2018), patients with fibromyalgia demonstrate reduced reward anticipatory response in the ACC with a trend for a similar pattern of reduced response in the aINS. Therefore, based on the current similar results, lower aINS response may represent a consistent characteristic of patients with fibromyalgia during reward anticipation. Indeed, the aINS is implicated in both reward processing, specifically for risk and risk avoidance (Rudorf et al., 2012). Further, aINS is an important region of altered structural and functional brain changes in patients with fibromyalgia (Ichesco et al., 2014). Nonetheless, while both the previous and present studies included the aINS as an exploratory reward-related ROI, future investigations designed to focus hypotheses on the aINS could more effectively determine the specific role of altered aINS reward response in fibromyalgia. Notably, further neuroimaging analyses of the expanded aMPFC masked regions of interest and across the whole brain demonstrated results which were largely similar to the previous study (Martucci et al., 2018). Thus, the present findings confirm that group differences in MPFC response are not confined to the relatively focused a priori MPFC ROI, but rather, that a broader area of the MPFC may be implicated in altered reward processing in fibromyalgia.

As a complementary analysis, we analyzed MID task data to characterize network-based functional connectivity, focusing on network-based target seeds. Compared to controls, participants with fibromyalgia showed more correlated activity (or "functional

connectivity") in the regions of the reward circuitry which overlap with the "Default Mode Network" (or DMN; Acikalin et al., 2017). The DMN includes the MPFC, PCC and angular gyrus, regions which historically have shown less correlated activity when individuals engage in demanding cognitive tasks (e.g., working memory) versus passively rest (Andrews-Hanna, 2012), although these same regions show increased activity in response to reward outcomes (Knutson et al., 2003). Accordingly, previous studies comparing clinical versus healthy samples have found that individuals with social anxiety showed increased functional connectivity in the DMN during the MID task (Maresh et al., 2014), and patients with obsessive-compulsive disorder show increased correlated activity between the MPFC and PCC during reward receipt (Koch et al., 2018). No previous studies, however, have examined functional connectivity during a reward task (e.g., MID) in patients with fibromyalgia. Similar to previous research on other clinical groups, fibromyalgia patients showed greater functional connectivity in the DMN during the MID task than healthy controls. These findings imply that the DMN may show more correlation during incentive processing in patients fibromyalgia, as in other anxiety disorders, which may be related to the common cooccurrence of fibromyalgia with anxiety symptoms (Thieme et al., 2004). How this correlated activity specifically links to anxiety symptoms will require further study.

5. Limitations

This replication study has some limitations. The present results did not fully replicate those of the previous study (Martucci et al., 2018). While all results followed a similar trend, they did not meet significance at the predetermined corrected thresholds. Several factors might have contributed to this weaker pattern of results, and while we designed the present study as closely as possible to the previous study's design, some minor deviations were unavoidable. First, while the Martucci et al. (2018) study used a Gradient Echo Pulse Sequence with "spiral in-out" acquisition, the present study used a Gradient Echo Pulse Sequence with echo planar imaging. As the spiral in-out scan sequence may enhance the acquisition of medial prefrontal signal (Glover and Law, 2001), this different imaging acquisition technique may have influenced the results. Second, while age did not significantly differ across groups in the previous study, age did statistically significantly differ between patient and control groups in the present samples. While ANCOVA analyses revealed that the age covariate did not alter the main results, the mean age of the patient group in the present study was younger than in Martucci et al. (2018), and patients' pain duration was also slightly shorter, which may have influenced the results. Third, for a proportion of participants (11 patients and 16 controls), the datasets were collected during the participants' second exposure to the MID task (i.e., initial exposure involved a multi-band pulse sequence which was not optimal for visualizing subcortical activity during the MID task (Srirangarajan et al., 2021)). Thus, while it is possible that these participants may have somewhat altered motivation as a function of repeated exposure, the MID task produces good test-retest reliability in MID task signal, even when repeated in the same session (Srirangarajan et al., 2021).

Additionally, we did not directly assess participants' motivation for the task (e.g., whether they were motivated to win money vs. solely respond rapidly). Nevertheless, higher

incentives for both gain (+$5 anticipation) and loss (−$5 anticipation) trials elicited faster reaction times relative to other conditions, indicating that potential rewards and punishments increased participants' motivation. Therefore, future research using the MID task might explicitly examine the influence of these factors on neural activity and performance. Further, the present replication study and Martucci et al. (2018) included only female participants. Healthy males demonstrate significantly greater striatal activation during reward anticipation compared to females (both healthy or with chronic low back pain) (Baker et al., 2022). Thus, including male participants may provide more insights into altered reward responses in patients with fibromyalgia.

Finally, beyond inclusion and exclusion criteria (as described in the Methods), we did not use the standardized diagnostic interview for mental disorders for screening and did not control for psychotherapy treatment, other mental disorders, smoking, substance use, or other types of addiction. While all participants were not taking opioid medications, this study lacked sufficient power to directly measure the influence of other medications on brain activation. As both opioid and non-opioid medications may affect brain reward processes in fibromyalgia (Martucci et al., 2019), the effects of medications can more effectively be evaluated in sufficiently powered future studies.

6. Conclusions

Previous work first reported altered brain reward response to monetary incentives in patients with fibromyalgia (Martucci et al., 2018). Using predetermined hypotheses (OSF, https://osf.io/4yctn) which focused on NAcc and MPFC activity during reward anticipation and in response to non-punishment outcomes, we conducted the present study to determine the replicability of the prior results. Results indicated a consistent trend of similar results in patients with fibromyalgia, including relatively normal NAcc response to reward, yet altered MPFC response to reward anticipation and non-punishment outcome. Thus, the present findings support the need for targeted future research on reward circuitry, including the MPFC, in patients with fibromyalgia. By focusing on replicable differences in incentive processing, future studies should have enhanced potential to identify robust and clinically-relevant neurophysiological markers of fibromyalgia. Further, a complementary analysis using a network-based functional connectivity analysis suggested greater connectivity in reward circuitry (or overlapping "default mode network") in participants with fibromyalgia. While requiring replication, this novel finding implies a unique engagement of this circuit during reward task states in fibromyalgia. Extending the present findings, continued research along these avenues may improve understanding of the interactions between the experience of pain and altered neurobehavioral processes, and may eventually provide essential insights for improved treatments of fibromyalgia and comorbid affective conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

References

Acikalin MY, Gorgolewski KJ, Poldrack RA, 2017. A coordinate-based meta-analysis of overlaps in regional specialization and functional connectivity across subjective value and default mode networks. Front. Neurosci. 11, 1. [PubMed: 28154520]

Albrecht DS, MacKie PJ, Kareken DA, Hutchins GD, Chumin EJ, Christian BT, Yoder KK, 2016. Differential dopamine function in fibromyalgia. Brain Imaging and Behavior 10 (3), 829–839. 10.1007/s11682-015-9459-4. [PubMed: 26497890]

Andrews-Hanna JR, 2012. The brain's default network and its adaptive role in internal mentation. Neuroscientist 18 (3), 251–270. 10.1177/1073858411403316. [PubMed: 21677128]

Baker AK, Ericksen LC, Koppelmans V, Mickey BJ, Martucci KT, Zubieta J-K, Love TM, 2022. Altered reward processing and sex differences in chronic pain. Front. Neurosci. 16. https://www.frontiersin.org/article/10.3389/fnins.2022.889849.

Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV, 2012. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat. Neurosci. 15 (8), 1117–1119. 10.1038/nn.3153. [PubMed: 22751038]

Becerra L, Borsook D, 2008. Signal valence in the nucleus accumbens to pain onset and offset. Eur. J. Pain (London, England) 12 (7), 866–869. 10.1016/j.ejpain.2007.12.007.

Becerra-García JA, Robles Jurado MJ, 2014. Behavioral approach system activity and self-reported somatic symptoms in fibromyalgia: an exploratory study. Int. J. Rheumatic Dis. 17 (1), 89–92. 10.1111/1756-185X.12034.

Beck AT, Steer RA, Carbin MG, 1988. Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8 (1), 77–100. 10.1016/0272-7358(88)90050-5.

Berger SE, Baria AT, Baliki MN, Mansour A, Herrmann KM, Torbey S, Huang L, Parks EL, Schnizter TJ, Apkarian AV, 2014. Risky monetary behavior in chronic back pain is associated with altered modular connectivity of the nucleus accumbens. BMC Res. Notes 7 (1), 739. 10.1186/1756-0500-7-739. [PubMed: 25331931]

Bernik M, Sampaio TPA, Gandarela L, 2013. Fibromyalgia comorbid with anxiety disorders and depression: combined medical and psychological treatment. Curr. Pain Headache Rep. 17 (9), 358. 10.1007/s11916-013-0358-3. [PubMed: 23904203]

Borsook D, Linnman C, Faria V, Strassman AM, Becerra L, Elman I, 2016. Reward deficiency and anti-reward in pain chronification. Neurosci. Biobehav. Rev. 68, 282–297. 10.1016/j.neubiorev.2016.05.033. [PubMed: 27246519]

Brainard DH, Vision S, 1997. The psychophysics toolbox. Spatial Vis. 10 (4), 433–436.

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR, 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc. Natl. Acad. Sci. USA 99 (1), 523–528. 10.1073/pnas.012470999. [PubMed: 11756669]

Carver CS, White TL, 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J. Pers. Soc. Psychol. 67 (2), 319.

Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, Devellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai J-S, Pilkonis P, Revicki D, et al. , 2010. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J. Clin. Epidemiol. 63 (11), 1179–1194. 10.1016/j.jclinepi.2010.04.011. [PubMed: 20685078]

Chikama M, McFarland NR, Amaral DG, Haber SN, 1997. Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. J. Neurosci. 17 (24), 9686–9705. 10.1523/JNEUROSCI.17-24-09686.1997. [PubMed: 9391023]

Daw ND, Doya K, 2006. The computational neurobiology of learning and reward. Curr. Opin. Neurobiol. 16 (2), 199–204. [PubMed: 16563737]

de la Vega A, Chang LJ, Banich MT, Wager TD, Yarkoni T, 2016. Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. J. Neurosci. 36 (24), 6553–6562. [PubMed: 27307242]

Derogatis LR, Melisaratos N, 1983. The brief symptom inventory: an introductory report. Psychol. Med. 13 (3), 595–605. 10.1017/s0033291700048017. [PubMed: 6622612]

DosSantos MF, Moura B. de S., DaSilva AF, 2017. Reward circuitry plasticity in pain perception and modulation. Front. Pharmacol. 8, 790. 10.3389/fphar.2017.00790. [PubMed: 29209204]

Fallon JH, 1981. Collateralization of monoamine neurons: mesotelencephalic dopamine projections to caudate, septum, and frontal cortex. J. Neurosci. 1 (12), 1361–1368. 10.1523/JNEUROSCI.01-12-01361.1981. [PubMed: 6172572]

Fallon N, Chiu Y, Nurmikko T, Stancak A, 2016. Functional connectivity with the default mode network is altered in fibromyalgia patients. PLoS One 11 (7), e0159198. 10.1371/journal.pone.0159198. [PubMed: 27442504]

Fiorillo CD, Tobler PN, Schultz W, 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. Science. 10.1126/science.1077349.

Galvez-Sánchez CM, Reyes del Paso GA, Duschek S, 2018. Cognitive impairments in fibromyalgia syndrome: associations with positive and negative affect, alexithymia, pain catastrophizing and self-esteem. Front. Psychol. 9. https://www.frontiersin.org/articles/10.3389/fpsyg.2018.00377.

Glass JM, 2009. Review of cognitive dysfunction in fibromyalgia: a convergence on working memory and attentional control impairments. Rheum. Dis. Clin. N. Am. 35 (2), 299–311. 10.1016/j.rdc.2009.06.002.

Glover GH, Law CS, 2001. Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. Off. J. Int. Soc. Magn. Reson. Med 46 (3), 515–522.

Goldenberg DL, Bradley LA, Arnold LM, Glass JM, Clauw DJ, 2008. Understanding fibromyalgia and its related disorders. Prim. Care Companion J. Clin. Psychiatry 10 (2), 133–144. [PubMed: 18458727]

Gracely RH, Ceko M, Bushnell MC, 2012. Fibromyalgia and Depression, vol. 2012. Pain Research and Treatment, 486590. 10.1155/2012/486590.

Haber SN, Calzavara R, 2009. The cortico-basal ganglia integrative network: the role of the thalamus. Brain Res. Bull. 78 (2–3), 69–74. 10.1016/j.brainresbull.2008.09.013. [PubMed: 18950692]

Haber SN, Knutson B, 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology: Official Publ. Am. College of Neuropsychopharmacology 35 (1), 4–26. 10.1038/npp.2009.129.

Hennigan K, D'Ardenne K, McClure SM, 2015. Distinct midbrain and habenula pathways are involved in processing aversive events in humans. J. Neurosci. 35 (1), 198–208. 10.1523/JNEUROSCI.0927-14.2015. [PubMed: 25568114]

Ichesco E, Schmidt-Wilcke T, Bhavsar R, Clauw DJ, Peltier SJ, Kim J, Napadow V, Hampson JP, Kairys AE, Williams DA, Harris RE, 2014. Altered resting state connectivity of the insular cortex

in individuals with fibromyalgia. J. Pain : Official J. Am. Pain Soc. 15 (8), 815–826. 10.1016/j.jpain.2014.04.007e1.

Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS, 2004. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin. J. Pain 20 (5), 309–318. 10.1097/00002508-200409000-00005. [PubMed: 15322437]

Kim M, Mawla I, Albrecht DS, Admon R, Torrado-Carvajal A, Bergan C, Protsenko E, Kumar P, Edwards RR, Saha A, Napadow V, Pizzagalli DA, Loggia ML, 2020. Striatal hypofunction as a neural correlate of mood alterations in chronic pain patients. Neuroimage 211, 116656. 10.1016/j.neuroimage.2020.116656. [PubMed: 32068162]

Kleiner M, Brainard D, Pelli D, 2007. What's new in Psychtoolbox-3?.

Knutson B, 2005. Distributed neural representation of expected value. J. Neurosci. 25 (19), 4806–4812. 10.1523/JNEUROSCI.0642-05.2005. [PubMed: 15888656]

Knutson B, Adams CM, Fong GW, Hommer D, 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci.: The Official J. Soc. Neurosci. 21 (16), RC159.

Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH, 2008. Neural responses to monetary incentives in major depression. Biol. Psychiatr. 63 (7), 686–692. 10.1016/j.biopsych.2007.07.023.

Knutson B, Cooper JC, 2005. Functional magnetic resonance imaging of reward prediction. Curr. Opin. Neurol. 18 (4), 411–417. [PubMed: 16003117]

Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D, 2003. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. Neuroimage 18 (2), 263–272. 10.1016/s1053-8119(02)00057-5. [PubMed: 12595181]

Knutson B, Huettel SA, 2015. The risk matrix. Curr. Opin. Behav. Sci. 5, 141–146.

Knutson B, Katovich K, Suri G, 2014. Inferring affect from fMRI data. Trends Cognit. Sci. 18 (8), 422–428. [PubMed: 24835467]

Knutson B, Taylor J, Kaufman M, Peterson R, Glover G, 2005. Distributed neural representation of expected value. J. Neurosci.. Official J. Soc. Neurosci. 25 (19), 4806–4812. 10.1523/JNEUROSCI.0642-05.2005.

Knutson B, Westdorp A, Kaiser E, Hommer D, 2000. FMRI visualization of brain activity during a monetary incentive delay task. Neuroimage 12 (1), 20–27. 10.1006/nimg.2000.0593. [PubMed: 10875899]

Koch K, Reeß TJ, Rus OG, Gürsel DA, Wagner G, Berberich G, Zimmer C, 2018. Increased default mode network connectivity in obsessive–compulsive disorder during reward processing. Front. Psychiatr 9. https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00254.

Kunishio K, Haber SN, 1994. Primate cingulostriatal projection: limbic striatal versus sensorimotor striatal input. J. Comp. Neurol. 350 (3), 337–356. 10.1002/cne.903500302. [PubMed: 7533796]

Ledermann K, Jenewein J, Sprott H, Hasler G, Schnyder U, Warnock G, Johayem A, Kollias S, Buck A, Martin-Soelch C, 2017. Altered dopamine responses to monetary rewards in female fibromyalgia patients with and without depression: a [^{11}C]raclopride bolus-plus-infusion PET study. Psychother. Psychosom. 86 (3), 181–182. 10.1159/000455927. [PubMed: 28490029]

Loggia ML, Berna C, Kim J, Cahalan CM, Gollub RL, Wasan AD, Harris RE, Edwards RR, Napadow V, 2014. Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia. Arthritis Rheumatol. 66 (1), 203–212. 10.1002/art.38191. [PubMed: 24449585]

Maresh EL, Allen JP, Coan JA, 2014. Increased default mode network activity in socially anxious individuals during reward processing. Biol. Mood Anxiety Disord. 4 (1), 7. 10.1186/2045-5380-4-7. [PubMed: 25075275]

Martucci KT, Borg N, MacNiven KH, Knutson B, Mackey SC, 2018. Altered prefrontal correlates of monetary anticipation and outcome in chronic pain. Pain 159 (8), 1494–1507. 10.1097/j.pain.0000000000001232. [PubMed: 29790868]

Martucci KT, Mackey SC, 2018. Neuroimaging of pain: human evidence and clinical relevance of central nervous system processes and modulation. Anesthesiology 128 (6), 1241–1254. 10.1097/ALN.0000000000002137. [PubMed: 29494401]

Martucci KT, MacNiven KH, Borg N, Knutson B, Mackey SC, 2019. Apparent effects of opioid use on neural responses to reward in chronic pain. Sci. Rep. 9 (1), 9633. 10.1038/s41598-019-45961-y. [PubMed: 31270360]

McNair DM, Lorr M, Droppleman LF, 1971. Manual Profile of Mood States.

Medford N, Critchley HD, 2010. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct. Funct. 214 (5), 535–549. 10.1007/s00429-010-0265-x. [PubMed: 20512367]

Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE, 2010. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 62 (8), 2545–2555. 10.1002/art.27497. [PubMed: 20506181]

Navratilova E, Porreca F, 2014. Reward and motivation in pain and pain relief. Nat. Neurosci. 17 (10) 10.1038/nn.3811. Article 10.

Nicola SM, Taha SA, Kim SW, Fields HL, 2005. Nucleus accumbens dopamine release is necessary and sufficient to promote the behavioral response to reward-predictive cues. Neuroscience 135 (4), 1025–1033. 10.1016/j.neuroscience.2005.06.088. [PubMed: 16165291]

Park SH, Baker AK, Krishna V, Mackey SC, Martucci KT, 2022. Altered resting-state functional connectivity within corticostriatal and subcortical-striatal circuits in chronic pain. Sci. Rep. 12 (1) 10.1038/s41598-022-16835-7. Article 1.

Preuschoff K, Quartz SR, Bossaerts P, 2008. Human insula activation reflects risk prediction errors as well As risk. J. Neurosci. 28 (11), 2745–2752. 10.1523/JNEUROSCI.4286-07.2008. [PubMed: 18337404]

Rosselló F, Muñoz MA, Duschek S, Montoya P, 2015. Affective modulation of brain and autonomic responses in patients with fibromyalgia. Psychosom. Med. 77 (7), 721–732. 10.1097/PSY.0000000000000217. [PubMed: 26186433]

Rudorf S, Preuschoff K, Weber B, 2012. Neural correlates of anticipation risk reflect risk preferences. J. Neurosci. 32 (47), 16683–16692. [PubMed: 23175822]

Seo J, Kim S-H, Kim Y-T, Song H, Lee J, Kim S-H, Han SW, Nam EJ, Kim S-K, Lee HJ, Lee S-J, Chang Y, 2012. Working memory impairment in fibromyalgia patients associated with altered frontoparietal memory network. PLoS One 7 (6), e37808. 10.1371/journal.pone.0037808. [PubMed: 22715371]

Serrano-Ibáñez ER, López-Martínez AE, Ramírez-Maestre C, Esteve R, Jensen MP, 2019. The behavioral inhibition and activation systems and function in patients with chronic pain. Pers. Indiv. Differ. 138, 56–62. 10.1016/j.paid.2018.09.021.

Sescousse G, Caldú X, Segura B, Dreher J-C, 2013. Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. Neurosci. Biobehav. Rev. 37 (4), 681–696. 10.1016/j.neubiorev.2013.02.002. [PubMed: 23415703]

Siegel JS, Power JD, Dubis JW, Vogel AC, Church JA, Schlaggar BL, Petersen SE, 2014. Statistical improvements in functional magnetic resonance imaging analyses produced by censoring high-motion data points. Hum. Brain Mapp. 35 (5), 1981–1996. [PubMed: 23861343]

Sluka KA, Clauw DJ, 2016. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience 338, 114–129. 10.1016/j.neuroscience.2016.06.006. [PubMed: 27291641]

Spielberger CD, Gorsuch RL, Lushene RE, 1970. Manual for the State-Trait Anxiety Inventory. http://ubir.buffalo.edu/xmlui/handle/10477/2895.

Srirangarajan T, Mortazavi L, Bortolini T, Moll J, Knutson B, 2021. Multi-band FMRI compromises detection of mesolimbic reward responses. Neuroimage 244, 118617. 10.1016/j.neuroimage.2021.118617. [PubMed: 34600102]

Thieme K, Turk DC, Flor H, 2004. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. Psychosom. Med. 66 (6), 837–844. [PubMed: 15564347]

Watson D, Clark LA, Tellegen A, 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54 (6), 1063–1070. 10.1037//0022-3514.54.6.1063. [PubMed: 3397865]

Watson D, Wiese D, Vaidya J, Tellegen A, 1999. The two general activation systems of affect: structural findings, evolutionary considerations, and psychobiological evidence. J. Pers. Soc. Psychol 820–838.

Whitfield-Gabrieli S, Nieto-Castanon A, 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2 (3), 125–141. 10.1089/brain.2012.0073. [PubMed: 22642651]

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, Walitt B, 2016. Revisions to the 2010/2011 fibromyalgia diagnostic criteria. In: Seminars in arthritis and rheumatism, Vol. 46, No. 3. WB Saunders, pp. 319–329. [PubMed: 27916278]

Wolfe F, Walitt B, Perrot S, Rasker JJ, Häuser W, 2018. Fibromyalgia diagnosis and biased assessment: sex, prevalence and bias. PLoS One 13 (9), e0203755. [PubMed: 30212526]

Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA, 2007. Fibromyalgia patients show an abnormal dopamine response to pain. Eur. J. Neurosci. 25 (12), 3576–3582. 10.1111/j.1460-9568.2007.05623.x. [PubMed: 17610577]

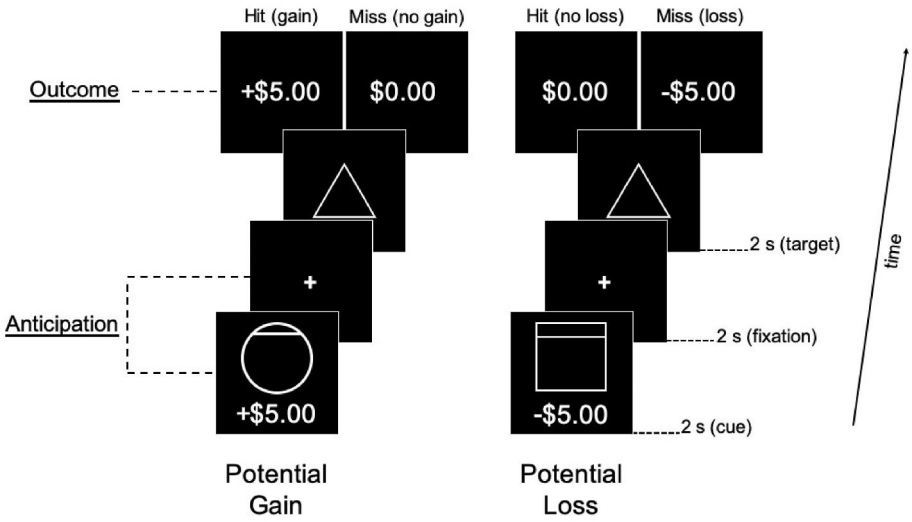

Fig. 1.
Structure of monetary incentive delay (MID) task trials.

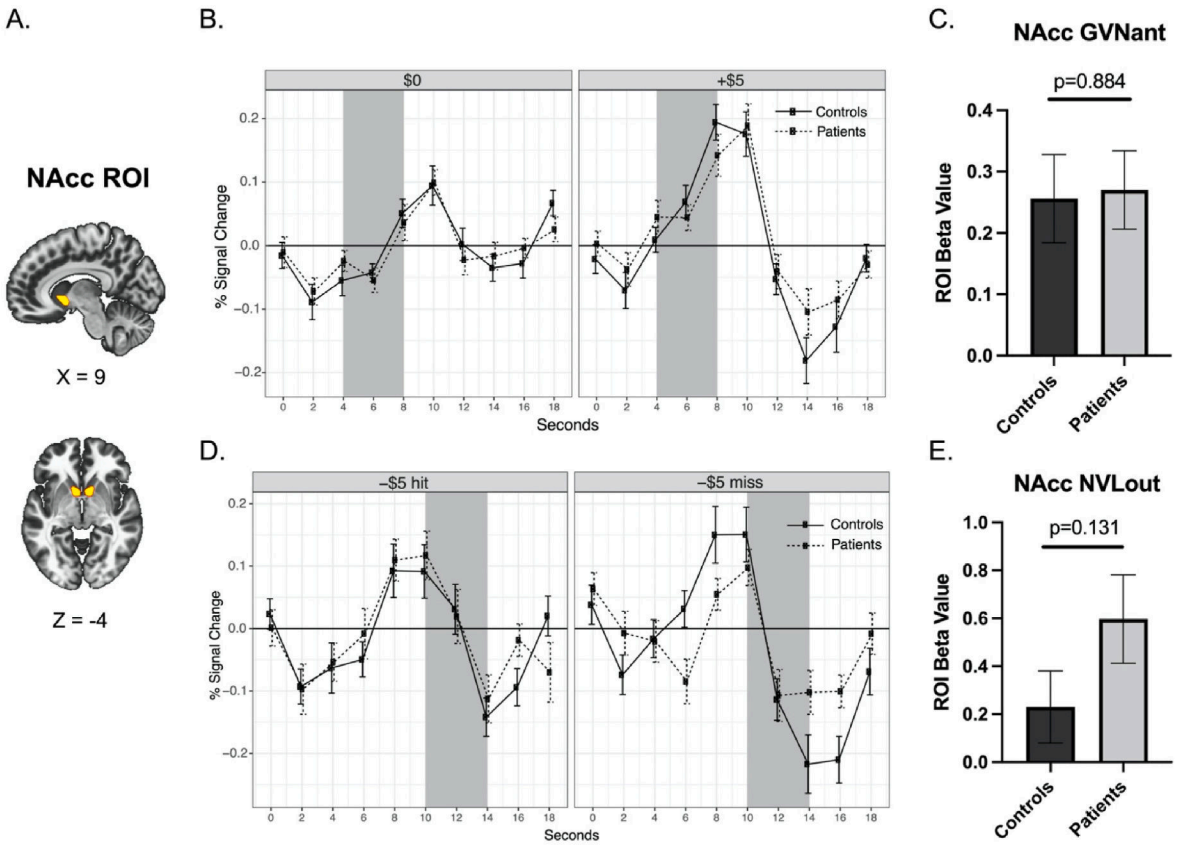

Fig. 2.

Nucleus Accumbens Activity during Reward Anticipation.

(A) Bilateral ROI of the NAcc. The same ROI mask that was used in Martucci et al. (2018) was used in the present analyses. (B) Group means and standard error of raw time course plots of NAcc ROI activity to $0 and +$5 anticipation trials. The shaded area represents the estimated anticipation period (presentation of cue and fixation [0–4 s] plus 4 s to account for hemodynamic response function delay). (C) Contrast beta values extracted from the bilateral NAcc ROI during reward anticipation (GVNant, +$5 > $0 trials). (D) Group means and standard error of raw time course plots of NAcc ROI activity to −$5 hit (i.e., no loss) and −$5 miss (i.e., loss) trials. (E) Contrast beta values extracted from the bilateral NAcc ROI during non-punishment outcomes (NVLout; −$5 hit vs. miss). All beta values are shown as 10^{-3}. Abbreviation: NAcc, nucleus accombens; ROI, region of interest.

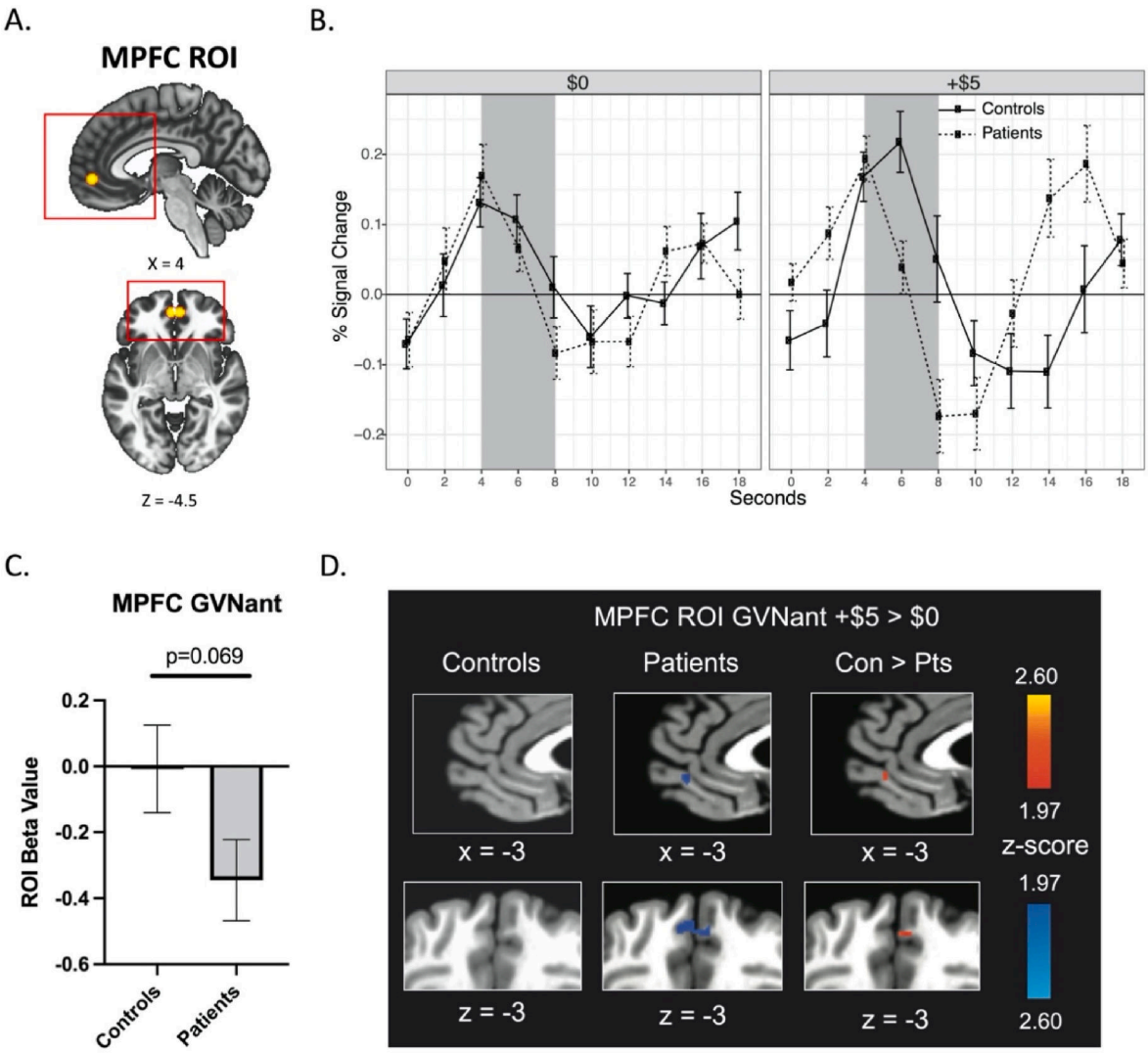

Fig. 3.

Medial Prefrontal Cortex Activity during Reward Anticipation.

(A) Bilateral ROI of MPFC. The same ROI mask from Martucci et al. (2018) was used. Red boxes denote magnification areas of sagittal and axial plane images depicted in Fig. 3D. (B) Group means and standard error for raw time course plots of MPFC ROI activity to $0 and +$5 anticipation trials. The shaded area represents the estimated anticipation period (presentation of cue and fixation [0–4 s] plus 4 s to account for hemodynamic response function delay). (C) Contrast beta values extracted from the MPFC ROI during reward anticipation (GVNant, +$5 > $0 trials). (D) Contrast activation maps of MPFC ROI activity during reward anticipation (GVNant; $p < 0.05$, uncorrected). All beta values are shown as 10^{-3}. Abbreviation: Con, controls; MPFC, medial prefrontal cortex; Pts, patients; ROI, region of interest.

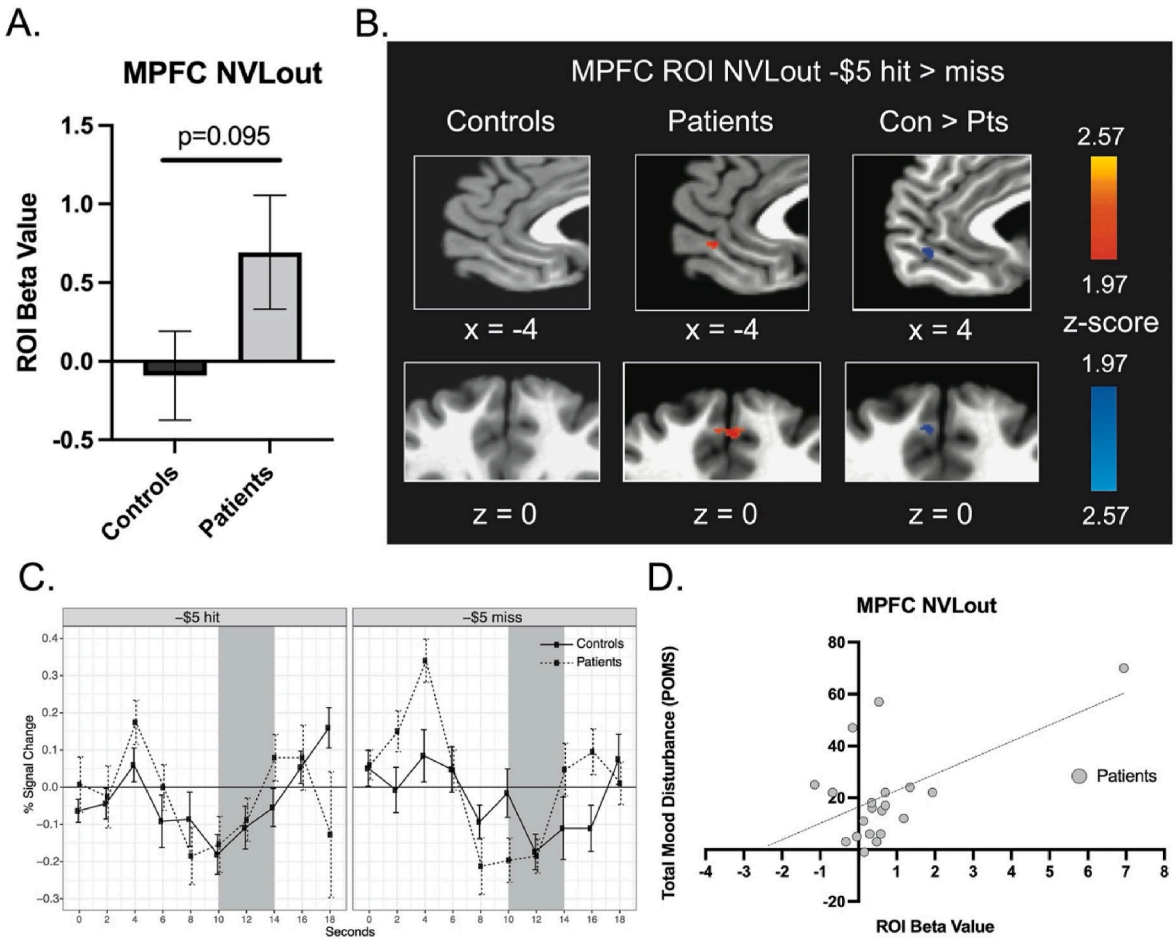

Fig. 4.

Medial Prefrontal Cortex Activity in Response to Non-punishment Outcomes.

(A) fMRI beta values extracted from the MPFC ROI during non-punishment outcomes (NVLout contrast, −$5 hit > miss). (B) Contrast activation maps of MPFC ROI activity during non-punishment outcomes ($p < 0.05$, uncorrected). (C) Group means and standard error of raw time course plots of MPFC ROI activity to outcomes (hits or misses) for −$5 anticipation trials. The shaded area represents the estimated outcome period (presentation of outcome and post-outcome [6–10 s] plus 4 s to account for hemodynamic response function delay). (D) Correlations between MPFC NVLout extracted beta values and total mood disturbance (POMS) in the patient group. One patient with a high MPFC NVLout beta value was kept in the analysis because the fMRI scan volumes were censored for bad movements (greater than a Euclidean norm value of 0.5) during pre-processing, and only 4 vol (among 540 vol) were censored for this individual. Also, this patient did not have as high of a beta value in the NVLout contrast with both −$5 and −$1 data (see results in Supplementary Fig. 4E). Therefore, we believe this to be a true representative signal of MPFC activity for the −$5 NVLout contrast from this individual. Further, the greater total mood disturbance (i.e., worse) in this patient aligns with greater MPFC activation that may be consistent with a greater “relief” experience. Post-hoc analyses excluding this patient resulted in MPFC NVLout beta value for controls vs. patients ($p = 0.174$) and POMS vs. MPFC NVLout beta

values correlation (r = 0.08; p = 0.606). All beta values are shown as 10^{-3}. Abbreviation: Con, controls; MPFC, medial prefrontal cortex; Pts, patients; ROI, region of interest. POMS, Profile of Mood States.

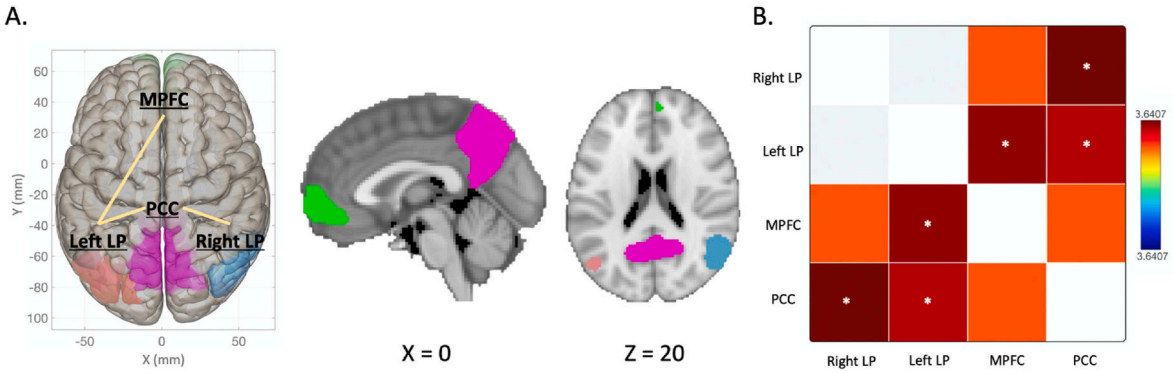

Fig. 5.

Functional Connectivity within the Default Mode Network during MID Task Performance. (A) DMN seeds defined by CONN Toolbox with significant group differences in seed-to-seed connectivity (yellow lines) [Green = MPFC, Blue = Right LP, Peach = Left LP, Magenta = PCC] (B) Significant group differences (fibromyalgia > controls, shown in red with asterisks) in connectivity between DMN seeds ($p < 0.05$, FDR corrected). Abbreviation: DMN, default mode network; FDR, false discovery rate; LP, lateral parietal cortex; MID, monetary incentive delay; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; ROI, region of interest.

Table 1
Participant Demographics and Clinical and Psychological Measures.

A total of 40 participants (patients N = 20, controls N = 20) completed the study. No participants were of race categories for Asian, Pacific Islander, Alaskan, or Native American. “Other” refers to self-identified race other than all of these categories. For clinical and psychological measures, individual participants’ data were missing for the BDI (1 patient and 1 control), STAI-State (1 control), and STAI-Trait (1 patient and 1 control) questionnaires; the total number of participants for each of these measures differs from other measures. Abbreviations: BAS, Behavioral Activation System; BIS, Behavioral Inhibition System; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; BSI, Brief Symptom Inventory; FAF, Fibromyalgia Assessment Form; PANAS, Positive and Negative Affect Schedule; POMS, Profile of Mood States; PROMIS, Patient-Reported Outcomes Measurement Information System; STAI, State-Trait Anxiety Inventory; sd, standard deviation. The presented significance values (P-Value) are not corrected for multiple comparisons as results are provided only for descriptive purposes.

	Patients		Controls		
	N		**N**		
Total Participants (all female)	**20**		**20**		
Righthanded	**19**		**19**		
Self-Identified Race[a,b]					
American Indian	**0**		**1**		
Caucasian	**15**		**17**		
African American	**4**		**2**		
Other	**1**		**0**		
Hispanic or Latina Ethnicity	**1**		**1**		
Employment Status[b]					
Part-time employed	**1**		**1**		
Full-time employed	**14**		**12**		
Unemployed	**5**		**7**		
Income Level[b]					
$0–$34,999	**7**		**3**		
$35,000–$59,999	**5**		**4**		
$60,000 or more	**8**		**11**		
Education Level[b]					
High School	**1**		**0**		
College/University	**13**		**13**		
Advanced Degree	**6**		**7**		
Clinical Measures					
	N	**Mean±sd (Median)**	**N**	**Mean±sd (Median)**	**P-Value**
Age	20	35.9 ± 12.3 (32.5)	20	44.2 ± 12.1 (43.5)	0.037
Positive Affect (PANAS)	20	24.8 ± 5.7 (25.5)	20	34.4 ± 7.9 (36.5)	<0.001

Negative Affect (PANAS)	20	19.0 ± 5.1 (18)	20	15.1 ± 4.9 (13.5)	0.018
Behavioral Drive (BAS)	20	10.8 ± 1.8 (11)	20	11.3 ± 2.3 (11)	0.458
Behavioral Fun (BAS)	20	10.9 ± 1.9 (11)	20	11.6 ± 2.0 (12)	0.246
Behavioral Reward (BAS)	20	17.3 ± 2.4 (17)	20	17.0 ± 2.8 (18)	0.767
Behavioral Inhibition (BIS)	20	22.3 ± 3.8 (23)	20	20.4 ± 4.6 (19.5)	0.17
Total Mood Disturbance (POMS)	20	20.0 ± 18.4 (16.5)	20	−1.1 ± 8.2 (−3)	<0.001
Fatigue (PROMIS)	20	65.5 ± 6.3 (63.9)	20	43.6 ± 8.5 (41.9)	<0.001
Trait Anxiety (STAI)	19	48.2 ± 10.4 (51)	19	37.2 ± 9.9 (37)	0.0018
State Anxiety (STAI)	20	38.7 ± 9.3 (37.5)	19	30.7 ± 7.2 (29)	0.004
Depression (BDI)	19	16.7 ± 8.7 (15)	19	4.5 ± 6.6 (3)	<0.001
Number of Pain Areas (FAF)	20	12.0 ± 3.8 (12)	20	0.3 ± 0.5 (0)	<0.001
Pain Severity (BPI)	20	4.5 ± 1.9 (5.25)	20	N/A	<0.001
Pain Interference (BPI)	20	6.1 ± 2.8 (6.14)	20	N/A	<0.001
	20	3.7 ± 1.6 (3)	20	2.7 ± 1.8 (1)	0.009
Brief Symptom Inventory (BSI), Anxiety					
Brief Symptom Inventory (BSI), Depression	20	4.4 ± 1.6 (4)	20	3.0 ± 2.7 (1)	0.005

[a] One patient and one control self-identified with two racial categories.

[b] Chi-square tests of homogeneity confirmed that patient and control samples did not differ based on self-identified race, X^2 (4, N = 42) = 2.79, p = 0.59, employment status, X^2 (2, N = 40) = 0.49, p = 0.78, income level, X^2 (2, N = 40) = 2.09, p = 0.35, or education level, X^2 (2, N = 40) = 1.08, p = 0.58.