Received: 16 June 2022 | Revised: 3 May 2023 | Accepted: 4 June 2023

DOI: 10.1002/ejp.2145

EJP European Journal of Pain

ORIGINAL ARTICLE

Task-dependent functional connectivity of pain is associated with the magnitude of placebo analgesia in pain-free individuals

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Abstract

Background: Task-based functional connectivity (FC) of pain-related regions resulting from expectancy-based placebo induction has yet to be examined, limiting our understanding of regions and networks associated with placebo analgesia.

Methods: Fifty-five healthy pain-free adults over 18 ($M = 22.8$ years, SD = 7.75) were recruited (65.5% women; 63.6% non-Hispanic/Latino/a/x; 58.2% White). Participants completed a baseline followed by a placebo session involving the topical application of an inactive cream in the context of an expectancy-enhancing instruction set. Noxious heat stimuli were applied to the thenar eminence of the right palm using an fMRI-safe thermode. Stimulus intensity was individually calibrated to produce pain ratings of approximately 40 on a 100-point visual analogue scale.

Results: A total of 67.3% of the participants showed a reduction in pain intensity in the placebo condition with an average reduction in pain across the whole sample of 12.7%. Expected pain intensity was associated with reported pain intensity in the placebo session ($b = 0.32$, $p = 0.004$, $R^2 = 0.15$). Voxel-wise analyses indicated seven clusters with significant activation during noxious heat stimulation at baseline ($p_{FDR} < 0.05$). Generalized psychophysiological interaction analysis suggested that placebo-related FC changes between middle frontal gyrus-superior parietal lobule during noxious stimulation were significantly associated with the magnitude of pain reduction ($p_{FDR} < 0.05$).

Conclusions: Results suggest that stronger expectancy-based placebo responses might be underpinned by greater FC among attentional and somatosensory regions.

Significance: This article provides support and insight for task-dependent functional connectivity differences related to the magnitude of placebo analgesia. Our findings provide key support that the magnitude of expectation-based placebo response depends on the coupling of regions associated with somatosensory and attentional processing.

1 | INTRODUCTION

Chronic pain is an aversive and multifaceted experience that occurs in various disease conditions and imposes a substantial individual and public health burden. Over 100 million Americans and 27.5% of individuals globally (Zimmer et al., 2022) experience chronic pain, resulting in $560 billion in healthcare costs, and is the greatest cause of disability worldwide (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011; Wu et al., 2020). Despite chronic pain's high prevalence, long-term treatment options are limited and often do not result in acceptable reductions in pain intensity (Moore et al., 2013; Tompkins et al., 2017). This is concerning as inadequate pain treatment is associated with impairment to functionality and health, such as physical functioning, sleep and other deleterious health outcomes (Sinatra, 2010). A potential approach to mitigating this gap is to use methods that enhance treatment efficacy.

Placebo analgesia (PA) has been shown to reduce an individual's pain through indirect mechanisms, including expectancy and conditioning manipulations (Amanzio et al., 2011; Bingel et al., 2011; Price et al., 2006). The magnitude to which PA influences pain ratings depends on various psychological constructs and neuronal systems (Dodd et al., 2017; Frangos et al., 2021; Schaefer et al., 2018). Additionally, PA enhances responses to treatments with specific biomedical or psychosocial targets and treatments without a specific biomedical or psychosocial target (Bingel et al., 2011; Kisaalita et al., 2016), even under open-label PA paradigms (Carvalho et al., 2016; Chung et al., 2007; Locher et al., 2017; Mundt et al., 2017). Importantly, PA is viewed as an acceptable treatment among groups that have been most commonly studied (i.e. middle-class, non-Hispanic/Latino/a/x White adults), especially where there is no known effective treatment and the condition is not life-threatening (Kisaalita et al., 2016; Millum & Grady, 2013; Wolter & Kleinmann, 2018). Further research is needed with more inclusive samples to fully understand the acceptability of PA.

Despite robust research characterizing PA's effects, individual factors associated with PA responses are less understood. Meta-analytic research has found reductions in the thalamus, somatosensory cortices, striatum, amygdala, insula and anterior cingulate cortex in placebo compared with baseline conditions (Atlas & Wager, 2014; Colloca, 2019). However, PA-related functional connectivity (FC) is less established, and most FC research has been done in the context of the resting-state paradigm.

Assessing FC is important because the brain processes stimuli through networks of functional connections (Cohen & D'Esposito, 2016). Understanding how brain regions are functionally connected during PA responses may allow for additional manipulation approaches, such as neuromodulation, to further enhance the magnitude of PA. Lastly, patients and physicians who do not view an open-label placebo as an acceptable treatment suggest unknown biological mechanisms as a reason against its acceptability (Bishop et al., 2014; Tandjung et al., 2014). Characterizing PA's task-specific neural mechanisms may increase PA's acceptability in clinical practice.

In this study, we aimed to (1) reproduce previous work showing PA-based activation changes in pain-related brain regions (Atlas & Wager, 2014; Zunhammer et al., 2021) and (2) extend our understanding of PA mechanisms by examining task-dependent FC changes among these regions. We hypothesized that: (1) BOLD activation in response to noxious stimulation in the PA condition compared with baseline would be significantly reduced in pain-related regions (thalamus, insula, somatosensory cortices) and increased in regions typically associated with PA (precuneus, superior parietal lobule, middle temporal gyrus) we also hypothesized that PA-based FC changes among pain-related regions would be significantly associated with percent pain reduction.

2 | METHODS

The present study was a secondary data analysis from a larger study investigating brain and spinal cord mechanisms underlying PA (NIH: R01AT001424). Although the original study consisted of four fMRI data collection sessions (i.e. baseline, placebo, repeated baseline and placebo match), two of these sessions were included in the present analyses (baseline and placebo). The current study uses a within-subjects design to examine changes in functional activation and task-dependent FC associated with PA in response to noxious heat stimulation. The first session was a baseline condition in which participants received an individually calibrated painful heat stimulus to the thenar eminence of the nondominant hand. The second session is a placebo condition in which participants receive an expectancy-enhancing instruction set and receive an inactive cream before undergoing the same noxious stimulation as the baseline condition. This study was approved by the University of Florida Institutional Review Board and performed at the University of Florida McKnight Brain Institute and Center for Pain Research and Behavioural Health in Gainesville, FL. All participants provided informed consent prior to data collection.

2.1 | Participants

Healthy, pain-free adults between the ages of 18 and 65 were recruited for this study. Participants completed standard demographic and health history questionnaires to assess

for exclusion criteria. Exclusion criteria included: a history of chronic pain (e.g. chronic low back pain, fibromyalgia), reported regular use of analgesics (i.e. weekly), history of psychological disorder (e.g. major depressive disorder), hypertension or thyroid disease that is not adequately regulated, history of neurological disease (e.g. multiple sclerosis, epilepsy, traumatic brain injury), history of substance dependence and previous participation in a placebo study.

2.2 | Project timeline

Participants completed up to five study visits for the study. The first three study visits were used for this present analysis, including the screening evaluation and baseline testing (visit 1) and two MRI sessions (visits 2 and 3). Participants underwent pain sensory testing during the screening visit to obtain individually calibrated pain responses. Structural and functional MRI scanning was completed during visits 2 (baseline session) and 3 (PA session).

2.3 | Noxious calibration procedure

Participants who met the study criteria completed a series of noxious stimulation trials to calibrate individualized temperatures associated with standardized pain intensity rating using a visual analogue scale (VAS). During calibration and fMRI scanning sessions, noxious heat stimuli were administered using a 3×3-cm MRI-compatible contact thermode (Medoc Heat Sensory Analyser, TSA-2001). Participants underwent a series of ascending 18-s heat pulses that increased by 1°C per pulse to the thenar eminence of the nondominant hand. The starting temperature of the thermode was 43°C. After each pulse, participants rated their pain using a 0–100 electronic VAS ranging from 'no pain' to 'most intense pain imaginable'. The thermode temperature increased by 1°C after each rating until the participant reported a VAS rating of 40 or a maximum temperature of 49 or 51°C was achieved. Changes in safety lockout temperature associated with software upgrades early in the study limited the maximum temperature to 49°C for most participants. Participants who did not report a VAS rating of at least 40 at 51°C were discontinued from the study for safety reasons.

2.4 | MRI data acquisition

MRI data were acquired utilizing a 3T Phillips Achieva and Phillips Ingenia Elition scanner equipped with a 32-channel head coil. The 3T Phillips Achieva scanner was replaced with the Ingenia Elition scanner during the study. A total of 38 participants (69.1%) were scanned on the Phillips Achieva and 17 (30.9%) were scanned on the Phillips Ingenia Elition (see Table S1 for comparison between scanners). The scanning sequence was the same for all participants. Functional data were collected in the transaxial orientation using an EPI sequence (XYZ dimension = 80×80×39; field-of-view [RL (right-to-left direction), AP (anterior-to-posterior direction), FH (foot-to-head direction)—mm] 240, 240, 126; slice thickness [mm] = 3; gap thickness = 0; voxel dimension [mm] = 3×3×3; repetition time [milliseconds] = 2242, TE = 30, FA = 90°). Acquisition time was 2 min and 18 s. High resolution structural brain images were collected using a 3-dimensional (3D) T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with a field-of-view (FOV) = 240 mm (FH)×240 mm (AP)×180 mm (RL), voxel-wise resolution = 1 mm^3, TR = 8.1 ms, TE = 3.7 ms, FA = 8°. Acquisition time was 4 min and 50 s.

2.5 | Noxious heat paradigm

Functional MRI was collected during visits 2 and 3. For both visits, before receiving noxious stimulation, participants were asked to rate the intensity of the pain they expected to experience during the session using an electronic VAS ranging from 'no pain' to 'most intense pain imaginable' with an MR-compatible scroll wheel. Then, participants underwent 12 functional runs consisting of 60 s of warm stimulation (38°C), followed by 18 s of individually calibrated noxious heat and an additional 60 s of warm stimulation applied to the thenar eminence of the nondominant hand. This stimulation protocol was adapted from previous work by Stroman et al. (2018, Bosma & Stroman, 2015) and was used to facilitate comparison with functional and spinal cord imaging data (not included in this analysis).

2.6 | Placebo analgesia

Prior to scanning during visit 3, participants received an expectancy manipulation instruction set designed to induce a placebo effect. Participants were told, 'today, you will complete MRI tasks just like you did during the last study visit. This time, however, we are going to put a cream on your palm called 'TriOxycaine.' When applied, TriOxycaine has been shown to powerfully reduce pain in some people'. TriOxycaine, which consisted of an inert cold cream mixed with oil of thyme, was then applied to the thenar eminence of the nondominant hand.

Participants were asked to rate their expected pain intensity on a 0–100 VAS scale ('Please rate your expected pain intensity', anchored from 'no pain' to the most intense pain imaginable).

Participants then completed the same noxious heat paradigm as visit 2 using individually calibrated stimuli temperatures. Oil of thyme was selected for inclusion due to its use in previous PA studies (Geers et al., 2010, 2019; Sevel et al., 2015), strong odour with a distinct medical scent (Mundt et al., 2017) and lack of empirically demonstrated analgesic effects in animal or human subjects (Aydın et al., 1996).

2.7 | Functional data processing

SPM12 (Wellcome Trust Centre for Neuroimaging) and the CONN toolbox v18b (Whitfield-Gabrieli & Nieto-Castanon, 2012) were used to preprocess fMRI data. Steps included slice-time correction, realignment, registration, normalization to MNI space, spatial smoothing (8 mm FWHM kernel) and signal to artefact reduction using the Artefact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect). Outliers were those where mean global signals exceeded 3 standard deviations, translation exceeded 0.5 mm or rotation exceeded 0.02 radians from the previous image (Chai et al., 2014). Component-based noise correction for physiological and other noise source reduction was implemented in the CONN toolbox and applied to the first-level processing as additional regressors. Regression was used to reduce the influence of five principal components each from signal within the CSF and deep cerebral white matter, all six movement parameters and their first-order derivatives.

2.8 | Task-based activation

Task-based functional activation was assessed via a voxel-wise general linear model in the SPM12 toolbox. Heat stimulations during baseline and placebo conditions were convolved with the haemodynamic response function. First-level analyses were performed to assess the main effect of baseline and placebo in response to noxious heat compared with non-noxious warmth. At the second level, a random-effects voxel-wise GLM was used to analyse the main effect of baseline and placebo conditions between participants, as well as the difference of noxious heat-related activation between conditions ($p < 0.05$). Regions were labelled using the Automated Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002). Areas undefined by the AAL atlas were defined using the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA; Joliot et al., 2015). Areas within the cerebellum were labelled using the Spatially Unbiased Infratentorial and cerebellar Template (SUIT; Diedrichsen, 2006; Diedrichsen et al., 2011).

2.9 | Generalized psychophysiological interaction

Task-based connectivity changes related to percent pain reduction were assessed using a generalized psychophysiological interaction (gPPI) in the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). We used a previously validated gPPI approach to assess context-dependent FC (McLaren et al., 2012). In this approach, at the first level, there are task regressors for each condition (i.e. baseline, placebo), a time series regressor for each seed region (e.g. precuneus) and an interaction term for the product of the task regressor by the time series regressor for each condition. Thus, there were five regressors in this analysis used to measure their association with percent pain reduction: baseline stimulation blocks, placebo stimulation blocks, seed region time series, baseline stimulation by time interaction and placebo stimulation by time interaction. This approach has previously been shown to improve overall model fit and have greater sensitivity and specificity than standard psychophysiological methods (McLaren et al., 2012). We used the significant clusters from the main effect of stimulation in the baseline condition and extracted 6 mm spheres around their peak voxel coordinate as the seed regions for a second-level whole-brain voxel-wise analysis characterizing the association between difference in connectivity between baseline and placebo with percent pain reduction (between-subjects contrast: subject, percent pain reduction [0 1]; within-subjects contrast: baseline condition, placebo condition [−1 1]; $p_{height} < 0.001$, uncorrected; $p_{cluster} < 0.05$, FDR). As such, the second-level contrast measures the change in FC during stimulation blocks in the placebo condition from the baseline condition associated with percent pain change.

2.10 | Statistical analyses

Analyses were conducted using Jamovi version 2.3 and R version 4.1. We used a paired-sample *t*-test of pain intensity ratings collected during scanning to examine whether placebo manipulation resulted in a reduction in pain. Further, we used linear regression to assess the association between expected pain and reported pain by each condition.

3 | RESULTS

3.1 | Participants

A total of 110 participants were screened for eligibility. Seventy-two participants were deemed eligible and returned for the baseline session and 58 participants returned for the placebo scanning session. Only participants who had complete baseline and placebo session scans were included in the analysis. Thus, a total of 55 subjects were included in this analysis. The sample's average age was 22.8 years (SD = 7.75, range = 18–62). The sample consisted of mainly female (65.5%) and non-Hispanic/Latino/a/x (63.6%) participants. Most individuals identified as White (58.2%), followed by Asian (23.6%), Black (7.3%) or more than one race (10.9%). The average number of years of education was 15.3 (SD = 2.17, range = 12–24).

3.2 | Pain intensity ratings

At baseline, participants reported a mean pain intensity of 43.9 (SD = 12.8, range = 17.1–76.8). During the placebo session, participants reported a mean pain intensity of 37.7 (SD = 15.4, range = 9.85–69.1). There was a significant difference between the mean baseline pain intensity ratings and the mean placebo pain intensity ratings ($t(54) = 3.27$, $p = 0.002$, $d = 0.44$). The mean percent pain reduction was 12.7% (SD = 32.2, range = −108%–74.2%) across the sample. The percentage of participants who demonstrated any reduction in pain intensity (i.e. percent pain change >0) was 67.3% ($n = 37$). Among the placebo responders, there was a mean percent pain reduction of 30.3% (SD = 17.4, range = 2.0%–74.2%). Linear regression was used to assess the association of expected pain intensity rating prescan and mean pain intensity ratings during scanning. Results demonstrated a nonsignificant association between expected pain and reported pain intensity in the baseline session ($b = 0.08$, $p = 0.340$, $R^2 = 0.018$). However, there was a significant association between expected pain and reported pain intensity ratings in the placebo session ($b = 0.32$, $p = 0.004$, $R^2 = 0.15$). Results demonstrated an expectancy effect during the placebo session, and the expectancy-based manipulation significantly decreased mean pain intensity ratings in response to noxious heat stimulation.

3.3 | Task-based activation

There were seven significant and large clusters in the baseline condition in response to noxious heat stimulation compared with non-noxious warm stimulation (Figure 1; Table 1). Peak voxel structures consisted of the left precuneus ($T = 8.81$), right olfactory cortex ($T = 6.35$), left middle frontal gyrus ($T = 5.87$), right temporal gyrus ($T = 5.12$), right superior frontal gyrus ($T = 4.89$), left cerebellum VIIIa ($T = 4.29$) and the left inferior parietal lobule ($T = 4.03$). There were nine significant clusters in the placebo condition in response to noxious heat stimulation (Figure 2; Table 2). The peak voxel structures were located in the left precuneus ($T = 7.88$), left parahippocampal gyrus ($T = 6.98$), right gyrus rectus ($T = 5.39$), two clusters in the right middle temporal gyrus ($T = 5.97$ and $T = 5.84$), left middle temporal gyrus ($T = 5.42$), right middle temporal pole ($T = 4.44$) and right anterior insular gyrus ($T = 4.46$; Table 2). There were two clusters with large effect sizes where greater noxious heat-related activations in the placebo session compared with the baseline session (Figure 3; Table 3). Peak voxel structures consisted of the left middle temporal gyrus ($T = 4.58$) and the right middle occipital gyrus ($T = 4.39$). There were no significant clusters where placebo < baseline.

3.4 | Task-based functional connectivity (psychophysiological interaction)

Task-dependent FC differences associated with percent pain reduction during the placebo session compared with baseline were assessed using the seven significant baseline activation clusters as seed regions (i.e. precuneus, olfactory cortex, middle frontal gyrus, middle temporal gyrus, superior frontal gyrus, cerebellum VIIIa and inferior parietal lobule). Using the left middle frontal gyrus as a seed, results revealed greater FC during noxious stimulation in the placebo session than baseline associated with percent pain reduction in a cluster spanning the left superior parietal lobule and left postcentral gyrus. (Figures 4 and 5; Table 4; $b = 0.58$, $p < 0.001$, $R^2 = 0.34$). There were no significant FC differences associated with percent pain reduction in any other seed region.

4 | DISCUSSION

The aims of the study were to reproduce previous work showing PA-based activation changes in pain-related brain regions (Atlas & Wager, 2014; Zunhammer et al., 2021) and to extend our understanding of PA mechanisms by examining task-dependent FC changes among these regions. Overall, we found large, highly significant clusters of activation in response to noxious stimuli in the baseline condition and a similar but attenuated activation pattern in the placebo condition. There were two clusters where

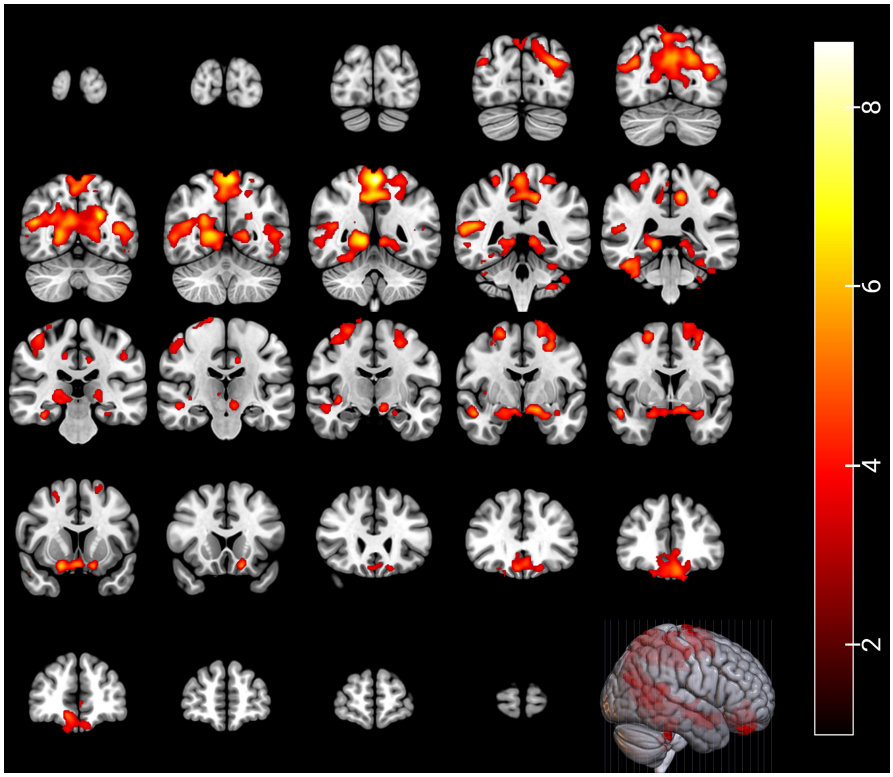

FIGURE 1 One-sample *t*-test results where painful stimulation > warm stimulation during the baseline condition.

TABLE 1 Global peak and local peaks and cluster coordinates of the main effect of stimulation during baseline condition.

Peak voxel structure	*k*	*x*	*y*	*z*	*T*	$p_{FDR\text{-}cor}$
L. precuneus	13,462	−2	−50	64	8.81	<0.001
R. lingual		12	−52	2	7.20	
L. superior occipital gyrus		−22	−66	26	7.12	
R. olfactory cortex	3193	18	12	−18	6.35	<0.001
L. olfactory cortex		−16	14	−16	6.30	
R. anterior insular gyrus		4	8	−16	5.95	
L. middle frontal gyrus	970	−30	−6	52	5.87	<0.001
L. precentral gyrus		−30	−2	60	4.80	
L. precentral gyrus		−24	−10	64	4.74	
R. middle temporal gyrus	446	50	−2	−18	5.85	<0.001
R. middle temporal gyrus		50	−18	−10	4.58	
R. insula		36	−12	−4	4.51	
R. superior frontal gyrus	1531	20	−2	62	5.52	<0.001
R. postcentral gyrus		38	−32	58	5.05	
R. superior frontal gyrus		24	−8	66	5.02	
L. cerebellum VIIIa	179	−30	−42	−48	4.71	0.027
L. cerebellum crus I		−46	−44	−38	4.22	
L. cerebellum crus II		−38	−40	−44	3.83	
L. inferior parietal lobule	154	−44	−36	50	4.37	0.039
L. inferior parietal lobule		−48	−28	40	4.07	

activation in the placebo session was significantly greater compared with the baseline session. We also importantly found that greater FC during noxious stimulation in the placebo condition than baseline was associated with greater percent pain reduction. Specifically, greater FC between the left middle frontal gyrus and a cluster with

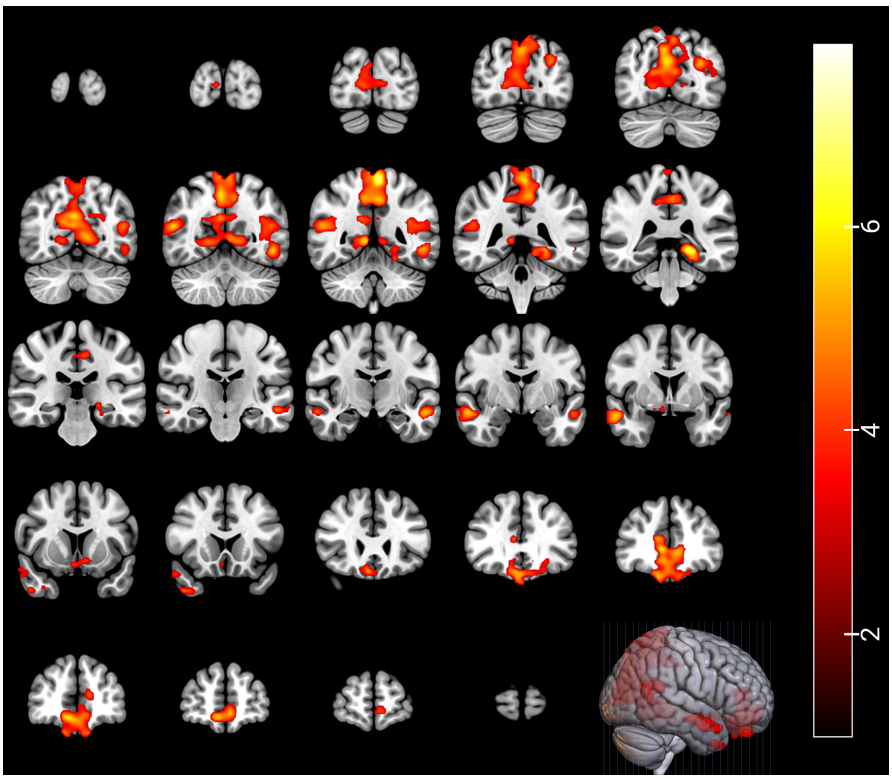

FIGURE 2 One-sample *t*-test results where painful stimulation > warm stimulation during the placebo condition.

TABLE 2 Global peak and local peaks and cluster coordinates of the main effect of stimulation during placebo condition.

Peak voxel structure	*k*	*x*	*y*	*z*	*T*	$p_{FDR\text{-}cor}$
L. precuneus	10,172	−4	−46	64	7.88	<0.001
R. precuneus		6	−56	48	6.23	
R. precuneus		4	−68	30	6.15	
L. parahippocampal gyrus	628	−20	−34	−6	6.98	<0.001
L. lingual gyrus		−24	−46	−6	5.02	
L. cerebellum V		−22	−50	−16	4.27	
R. gyrus rectus	3077	4	30	−22	5.39	<0.001
R. superior orbital gyrus		12	42	−26	6.18	
R. medial orbital gyrus		12	52	−12	6.17	
R. middle temporal gyrus	630	56	0	−18	5.97	<0.001
R. middle temporal pole		56	14	−26	4.14	
R. superior temporal gyrus		66	−2	−10	3.33	
R. middle temporal gyrus	758	52	−56	18	5.84	<0.001
L. middle temporal gyrus	375	−54	−14	−14	5.42	0.001
L. middle temporal gyrus		−62	2	−16	3.41	
R. middle temporal pole	157	44	16	−40	4.44	0.045
R. anterior insular gyrus	160	6	4	−12	4.46	0.045
L. putamen		−12	10	−8	3.76	
R. olfactory cortex		4	16	−12	3.29	

attentional and somatosensory regions was associated with greater percent pain reduction during noxious heat stimulation for the placebo condition compared with the baseline condition. A substantial body of work has been conducted on changes in functional activation in response to noxious stimulation related to PA (Atlas & Wager, 2014; Zunhammer et al., 2021).

Our findings echo previous meta-analyses by demonstrating peak activations during noxious stimulation in commonly identified pain-related regions such as the

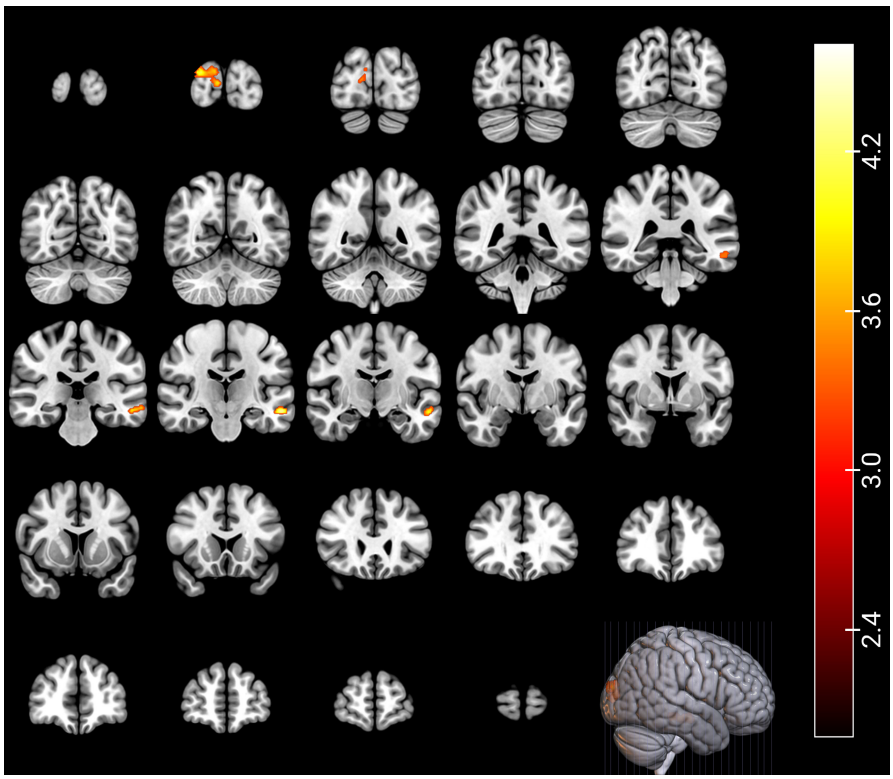

FIGURE 3 Paired-sample *t*-test results where placebo > baseline for painful stimulation > warm stimulation.

TABLE 3 Global peak and local peaks and cluster coordinates and effect size of placebo-baseline paired-sample *t*-test.

Peak voxel structure	*k*	*x*	*y*	*z*	*T*	$p_{FDR\text{-}cor}$	Effect size (*d*)
L. middle temporal gyrus	325	−54	−24	−14	4.58	0.005	1.25
L. middle temporal gyrus		−58	−16	−14	4.51		
L. middle temporal gyrus		−58	−34	−10	3.98		
R. middle occipital gyrus	323	30	−94	22	4.39	0.005	1.19
R. calcarine cortex		8	−96	8	3.87		
R. cuneus		12	−94	18	3.83		

precuneus, middle frontal gyrus, superior frontal gyrus, cerebellum and inferior parietal lobule (Duerden & Albanese, 2013). In the placebo condition, we found a similar pattern of pain-related regional activation but with significantly greater activation in the middle temporal gyrus and middle occipital gyrus, which have been found to have increased activation associated with pain reduction following cue-based expectancy manipulation (Atlas & Wager, 2014; Zunhammer et al., 2021).

Among the regions identified during the noxious stimulation in the baseline condition, the olfactory cortex has not traditionally been associated with pain processing. The olfactory cortex is commonly engaged with odour perception; however, evidence suggests that the olfactory cortex is highly involved with associative memory and threat encoding (Haberly & Bower, 1989; Li, 2014). The olfactory cortex also has anatomical connections with the hippocampus that directly relates to sensory memory processing (Aqrabawi & Kim, 2018). In addition, there is preliminary evidence that pain and olfaction share similar neural mechanisms (Sandri et al., 2021; Zufall et al., 2012). We used the AAL atlas, which labelled this region as olfactory cortex; however, we also used AICHA, which labelled this region as inferior orbitofrontal gyrus. It is also possible that previous studies have labelled this region as inferior orbitofrontal gyrus. The orbitofrontal cortex has been previously shown to be activated in response to pain and changes in FC have been shown to mediate pain intensity (Becker et al., 2017). Activity proximal to this cluster has been implicated with expectations for reward and familiar stimuli (Bollinger et al., 2010; Cohen et al., 2007) and involved with violations of expectancy (Murty & Adcock, 2014). These results suggest that the right olfactory cortex may be an important region for pain processing with associations related to sensory stimulation and associative memory.

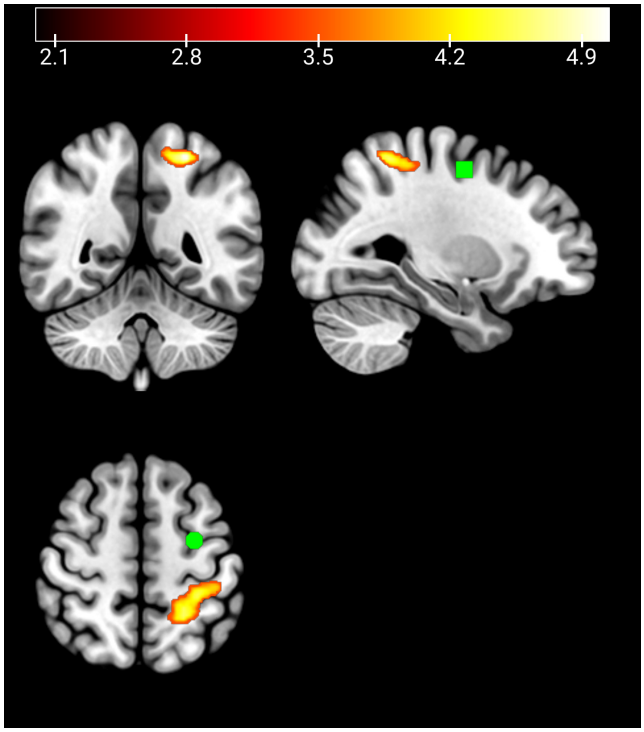

FIGURE 4 Left middle frontal gyrus (green; −30, −6, 52) and a significant cluster associated with the left superior parietal lobule (−24, −50, 60) where greater functional connectivity during the placebo condition compared with the baseline was associated with greater percent pain reduction.

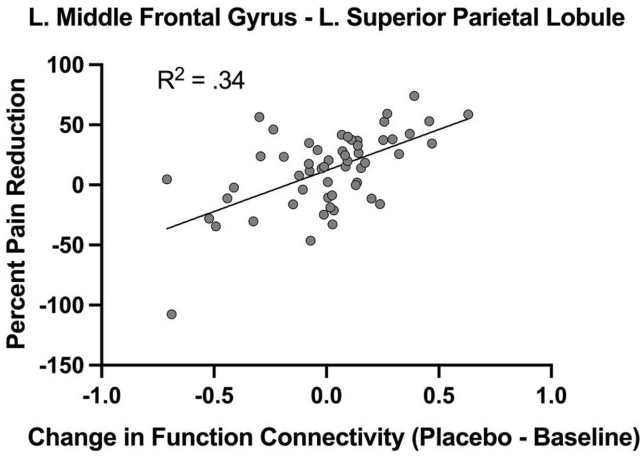

FIGURE 5 Scatterplot demonstrating the significant generalized psychophysiological interaction association between change in functional connectivity (placebo – baseline) and percent pain reduction between the left middle frontal gyrus and a cluster predominately located in the left superior parietal lobule.

We found significant differences in activation in the placebo session compared with the baseline in the left middle temporal gyrus and middle occipital gyrus. The middle temporal gyrus has been found to be activated during placebo treatment in meta-analyses (Zunhammer et al., 2021). Wager et al. (2011) included the middle temporal gyrus in their pain-processing network that was derived using a mega-analytic approach of regions that were activated in response to high- compared with low-intensity noxious thermal stimulation in the left forearm. This finding also replicates an earlier finding from a previous study that found the left middle temporal gyrus to have greater activation in response to placebo than baseline (Craggs et al., 2008). The middle occipital gyrus is most commonly implicated in visual processing; however, it has also been related to processing spatial tactile stimuli (Renier et al., 2010). The middle occipital gyrus can be divided into the inferior and superior lateral occipital cortex. Both the inferior and superior occipital cortices have been shown to have decreased activation in response to pain and increased activation during placebo treatment in meta-analyses (Zunhammer et al., 2021). Changes in activity in a proximal cluster were associated with auditory stimuli expectations (Bueti & Macaluso, 2010). These results further replicate previous research that has implicated greater activation in the left middle temporal gyrus and right middle occipital gyrus in PA.

Interestingly, greater FC of the left middle frontal gyrus with regions related to attention and somatosensory areas was associated with greater placebo-related pain reduction. The cluster consisted of the left superior parietal lobule, left postcentral gyrus and the precuneus cortex. The middle frontal gyrus has been indicated to be involved with PA (Zunhammer et al., 2021). It also is important in attentional control (Andersson et al., 2009; Japee et al., 2015). The left superior parietal lobule has been reliably implicated structurally and functionally in expectancy-enhanced placebo manipulation (Atlas & Wager, 2014; Cherkasova et al., 2022; Makary et al., 2018; Schnitzer et al., 2018). Further, this finding replicates previous work that found that increased left middle frontal gyrus and left superior parietal lobule FC was associated with lower delayed onset muscle soreness (Bush et al., 2021). Together, both the left middle frontal gyrus and left superior parietal lobule have been found to be independently associated with PA and their functional correlation is associated with lower pain intensity. These findings suggest that FC between regions related to attentional and somatosensory areas may be an essential mechanism underlying the degree of PA.

4.1 | Strengths and limitations

The present study's findings represent an important step in clarifying PA's neural mechanisms and their association with reductions in pain intensity. Specifically, changes in FC associated with noxious heat in the context of PA were associated with placebo-related pain reduction, supporting the utility of gPPI approaches for characterizing placebo mechanisms and understanding individual

TABLE 4 Cluster coordinates and regions where placebo-related FC changes during stimulus application were associated with percent pain reduction.

ROI	*x*	*y*	*z*	*k*	Cluster region	Voxels in region	Coverage (%)	$p_{FDR\text{-}cor}$
Middle frontal gyrus	−24	−46	48	259	Left superior parietal lobule	130	9	<0.001
					Left postcentral gyrus	82	2	
					Not labelled	47	0	

differences in PA responses. While the study's findings contribute to our understanding of neural networks involved in PA, they should be considered within the context of the study's limitations. This study focussed on the association of placebo-related pain reductions with changes in whole-brain seed-to-voxel FC patterns. However, there are a variety of other ways that a given region may contribute to a functional process, such as being the centre of a hub or part of a distributed network. Future research should further integrate other analytic approaches (e.g. graph theory, dynamic causal modelling) to further elucidate PA network dynamics. Second, 32.7% of our sample reported increased pain during the placebo session. The gPPI approach models a linear relationship between FC and percent pain reduction. Placebo nonresponders and responders may demonstrate a nonlinear FC and percent pain reduction relationship. Thus, the results of this study probed only the linear relationship between pain-related changes in FC and percent pain reduction. Future studies should consider nonlinear methods or separating the sample to assess for differential effects. Third, healthy, pain-free adults between the ages of 18 and 65 who were well-educated were selected for inclusion in the study, limiting the generalizability of these findings to the larger adult population or individuals with chronic pain. Fourth, the study design did not randomize the order of sessions. As such, it is possible that some of the explained variance may be the result of repeated stimulation. Future studies should randomize the order of conditions per participant and include repetitions of each condition in order to increase validity. Lastly, we used VASs for participants to select their reported pain intensity, which did not display a numeric anchor while participants selected their ratings. While VASs have a number of strengths compared with numeric rating scales, they may result in natural fluctuations between conditions despite a participant experiencing a similar percept. Future studies should repeat conditions in order to account for these natural fluctuations.

4.2 | Summary

The present study set out to examine patterns of task-based FC during PA as it is associated with self-reported pain perception changes. We found that FC between regions activated in response to noxious stimulation and attentional and somatosensory-related areas was associated with greater pain reduction during PA. Our results provide key support for the role of task-based FC in PA and call for further investigations of CNS mechanisms underlying PA that integrate multimodal neuroimaging metrics.

ACKNOWLEDGEMENTS

Support for this work was provided by the National Institutes of Health (R01AT001424; MER, PI, JB, Co-I; K23NS124935, JEL, PI). A portion of this work was performed in the McKnight Brain Institute at the National High Magnetic Field Laboratory's Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility, which is supported by the National Science Foundation Cooperative Agreement No. DMR-1644779* and the State of Florida. JEL is part of a research team that received an equipment grant from Oura Health, Ltd; those data are not associated with the present study.

FUNDING INFORMATION

Support for this work was provided by the National Institutes of Health (R01AT001424; MER, PI, JB, Co-I; K23NS124935, JEL, PI).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report. This article was prepared while JEL was employed at Johns Hopkins University. She is now employed through the National Institutes of Health. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services or the United States government.

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How to cite this article: Bush, N. J., Boissoneault, J., Letzen, J., Staud, R., & Robinson, M. E. (2023). Task-dependent functional connectivity of pain is associated with the magnitude of placebo analgesia in pain-free individuals. *European Journal of Pain*, *27*, 1023–1035. https://doi.org/10.1002/ejp.2145