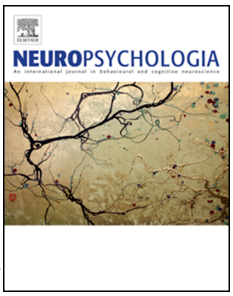

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Modeling neural and self-reported factors of affective distress in the relationship between pain and working memory in healthy individuals

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Abstract

The relationship between pain and cognition has primarily been investigated in patients with chronic pain and healthy participants undergoing experimental pain. Recently, there has been interest in understanding the disruptive effects of non-experimental pain in otherwise healthy individuals. Recent studies suggest that healthy individuals reporting pain also demonstrate decrements in working memory (WM) performance, however factors contributing to this relationship remain poorly understood. The present study examined the association between everyday pain and WM in a large community-based sample of healthy individuals and investigated whether self-reported affective distress and medial frontal cortex activity might help to explain this relationship. To address these research questions, a large publicly available dataset from the Human Connectome Project (N = 416) was sourced and structural equation modeling was utilized to examine relationships between pain intensity experienced over the past 7 days, self-reported affective distress (composite measure), performance on a WM (n-back) task, and task-related activation in the medial frontal cortex. Examining participants who reported non-zero pain intensity in the last 7 days (n = 228), we found a direct negative association between pain intensity and performance on the WM n-back task, consistent with prior findings. Self-reported affective distress was not associated with WM performance. Additionally, pain intensity was indirectly associated with WM performance via WM task-related activity in the ventromedial prefrontal cortex (vmPFC). Our findings suggest that everyday pain experienced outside of the laboratory by otherwise healthy individuals may directly impact WM performance. Furthermore, WM task-related increases in vmPFC activity may be a factor contributing to this relationship.

Key Words: pain intensity; vmPFC; n-back task; affective distress

1. Introduction

Pain is a common experience known to interfere with cognition. Pain-related deficits in executive function and working memory (WM), or the process of maintaining and manipulating information over short periods of time (Baddeley, 1992; Cowan, 2017), have been demonstrated in non-human animals (Boyette-Davis et al., 2008; Braithwaite and Droege, 2016; Glass, 2009; Hayes et al., 1981), patients with chronic pain (Baker et al., 2016; Berryman et al., 2013; Dick et al., 2008; Glass and Park, 2001), and healthy volunteers undergoing experimental pain induction (Houlihan et al., 2004; Legrain et al., 2009; Mylius et al., 2012; Seminowicz and Davis, 2007). More recently, there has been interest in understanding the relationship between pain and cognition outside of the laboratory setting. Very little is known about the impact of naturalistic pain experiences on the cognition and behavior of otherwise healthy individuals, yet these insights may be more generalizable, and thus may have wider implications for understanding human behavior than those found in the laboratory (Eccleston, 2013).

A recent online study of healthy individuals found that self-reported pain due to common conditions such as backache and arthritis was associated with worse performance on the widely used n-back task of WM (Attridge et al., 2015). These findings suggest that pain experienced outside of the laboratory is related to WM performance, although the potential neural and psychological mechanisms contributing to this relationship remain poorly understood. Prior clinical research conducted with chronic pain patients as well as experimental research conducted with healthy samples points to the potential roles of affective distress and medial frontal cortex activation in the relationship between pain intensity and WM capacity. The current research examines the relationship between non-experimental pain and WM in otherwise healthy

individuals, and explores whether affective distress and activation of specific regions within the medial frontal cortex are associated with pain and deficits in WM.

1.1. Pain, affective distress, and working memory deficits

Affective distress is a core component of the experience of pain (Edwards et al., 2016; Rainville et al., 2005; Rhudy and Meagher, 2001, 2003; Wiech and Tracey, 2009). The experience of pain is often (although not always, see Leknes and Tracey, 2008, for a review) associated with feelings of distress including fear, anger, anxiety, and stress (Price, 2000; Taal and Faber, 1997; Vowles et al., 2004). In turn, the experience of pain-related distress is associated with greater attention to pain, difficulty disengaging attention from pain, reduced attentional control, and poorer WM capacity (Crombez et al., 1999; Eccleston, 1994; Eccleston et al., 1997; Keogh et al., 2013). Independent of the experience of pain, affective distress has been shown to interfere with WM capacity by disrupting attentional control, for example in the recollection of negative biographical memories (Allen et al., 2014), word recall and semantic processing (Ellis et al., 1984), and conflict-driven executive control (Padmala et al., 2011).

1.2. Shared neural underpinnings of pain, affective distress, and working memory deficits

Activity in brain regions associated with pain-related distress are also implicated in cognitive control, specifically the dorsal medial frontal cortex (dMFC), anterior midcingulate cortex (aMCC), and ventromedial prefrontal cortex (vmPFC). For example, in a study of healthy individuals receiving experimentally induced pain, higher levels of pain catastrophizing (distressing cognitions about pain) were associated with increased activity in the insular cortex and anterior cingulate cortex (ACC) (Seminowicz and Davis, 2006), brain regions previously implicated in the negative emotional component of pain (Woo et al., 2015). The ACC and other medial structures have been theorized to mediate the effects of pain-related distress on cognitive

impairment in patients with chronic pain (Hart et al., 2003). Pain-related activity in the aMCC has been found to mediate the relationship between acute stress-related physiological responding and pain unpleasantness in chronic back pain patients (Vachon-Presseau et al., 2013). Speaking to the central role of this brain region in pain, affective distress, and cognitive control, in a review of neuroimaging studies of healthy individuals, Shackman et al. (2011) identified overlapping regions of the aMCC involved in all three processes.

The vmPFC has been implicated in both the affective component of pain as well as the disruptive effects of pain on executive function. At a broad level, the vmPFC is hypothesized to be involved in attention to emotion (Pessoa et al., 2002) and assigning affective meaning to a range of processes including pain (Roy et al., 2012). With regards to pain, although vmPFC activity is associated with decreased pain in healthy individuals receiving experimentally induced pain (Atlas et al., 2014), it is associated with increased pain in individuals with chronic pain (Apkarian et al., 2011). Furthermore, there is evidence implicating the vmPFC and broader medial frontal cortex in the transition from acute to chronic pain, specifically via altered functional connectivity with emotion and reward circuitry (Baliki et al., 2012; Hashmi et al., 2013). The vmPFC is a key node of the default mode network (DMN), a collection of functionally connected frontal and parietal regions whose activity reliably characterizes the brain "at rest" (Uddin, 2015; Uddin et al., 2009), and which is strongly implicated in mind wandering (Christoff et al., 2009). Hence, the DMN is typically (although not always, see Spreng, 2012) de-activated during cognitive tasks requiring attentional control (Anticevic et al., 2012). In patients with chronic pain, however, there is evidence of attenuated deactivation of the DMN during tasks of attentional control (Baliki et al., 2008), in addition to a broad reorganization of the DMN at rest (Baliki et al., 2014).

Given that multiple regions of the medial frontal cortex have been implicated in pain, affective distress, and cognitive control, Kragel et al. (2018) utilized multivariate patterns of brain activity across multiple studies to identify domain-specific and generalizable representations. Their results speak to the structural and functional proximity of pain, affective distress, and cognitive control representations in the brain, and provide a basis for examining medial frontal cortex activity as a factor involved in all three processes.

1.3. Overview of the current research

Following prior research (Attridge et al, 2015), the current study examined whether pain experienced outside of the laboratory in otherwise healthy individuals was associated with worse WM as indicated by performance on the n-back task, investigated the role of affective distress in the relationship between pain and WM, and explored the shared neurobiological underpinnings of pain, affective distress, and deficits in WM performance. We utilized the large and publicly available Human Connectome Project (HCP) dataset in order to model the relationship between pain experienced over the past 7 days, affective distress, WM, and WM task-related brain activation in the dMFC, aMCC, and vmPFC. We hypothesized that pain report would be directly associated with worse WM task performance, and that pain report would be indirectly associated with WM task performance via contributing factors related to self-reported affective distress and WM task-related brain activity.

2. Methods

2.1. Participants

Data used in the preparation of the analyses described herein were obtained from the 1200 subject release of the MGH-USC Human Connectome Project (HCP) database. The goal of the HCP was to recruit healthy participants across a broad spectrum with respect to behavioral,

ethnic, and socioeconomic diversity (Van Essen et al., 2012). We aimed to maximize our study sample size within the constraints of using the previously collected HCP data, namely by using the largest HCP data release to date (the 1200 subject data release), and selecting within that data release one subject from each family, resulting in a sample of 416 unrelated, healthy, right-handed subjects (216 female, M_{age} = 28.59, SD = 3.72). As the stated aim of our study was to examine the effect of pain in otherwise healthy individuals on working memory task performance, we further restricted our sample for structural equation modeling analyses to the 228 individuals who reported experiencing > 0 pain intensity in the past 7 days.

Inclusion criteria for HCP participants were age 22-35 at time of phone screening and ability to give valid informed consent. HCP participants were excluded if they had significant history of psychiatric disorder, substance abuse, neurological or cardiovascular disease, which included participant report of a diagnosis, hospitalization lasting two days or longer, or current pharmacologic or behavioral treatment for a period of 12 months or longer. Additional exclusion criteria included history of seizures/epilepsy, any genetic disorder, multiple sclerosis, cerebral palsy, brain tumor or stroke, history of head injury, premature birth, current or past history of chemotherapy or radiation, thyroid treatment, diabetes treatment, or the use of daily prescription medications for migraines in the past month. Full inclusion and exclusion criteria are described in Van Essen et al. (2013).

Participant data were collected at Washington University over the course of a 2-day visit. NIH Toolbox Behavioral Tests were conducted on Day 1, along with resting state and task fMRI scan session #1. Non-NIH Toolbox Behavioral Tests and a second session of resting state and task fMRI scanning was conducted on Day 2. All participants provided informed consent during the first day of testing procedures. Data analysis and research procedures for the present study

were approved by the Institutional Review Board (IRB) at the University of Miami. HCP research protocols and data collection procedures were approved by the HCP-affiliated university review boards.

2.2. Measures

2.2.1. Pain. Pain ratings were made by participants as part of a battery of behavioral assessments on the first day of the 2-day HCP study visit. As the primary predictor in our models, we examined participant ratings of pain intensity using the National Institutes of Health (NIH) Toolbox Pain Intensity Survey (Cook et al., 2013). Participants' level of pain intensity experienced over the past 7 days was assessed with a single item, 0-10 numeric rating scale (0 = "No pain", 10 = "Worst imaginable pain"). The Pain Intensity Survey was repeated for 20 participants in the final sample due to test-retest validation by HCP, the results of which are outside the scope of the present study. As a result, we chose to retain only the first score (corresponding to the original study session visit) for each affected participant. To ensure that the results of our analyses reflected only those individuals who reported being in pain in the last 7 days, we included only subjects who reported > 0 pain intensity (n = 228) in subsequent analyses. To further characterize participants who reported non-zero pain intensity, we examined two additional measures of pain, pain interference and sleep disruption due to pain.

Pain interference was measured using a computerized adaptive test (CAT) as part of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) (Cella et al., 2010; Rothrock et al., 2010). Participants were instructed to report the degree to which pain interfered with their social, cognitive, emotional, physical, and recreational activities in the past seven days. The NIH PROMIS pain interference assessment also contains items about sleep quality and life enjoyment. Each item was assessed on a 5-point scale ranging from "not at all" to

"very much." In addition, we included a single item from the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) assessing sleep disruption due to pain. The PSQI assesses different aspects of sleep and sleep quality. The item assessing pain asks, "During the past month, how often have you had trouble sleeping because you…Have Pain?" Participants are asked to respond on a scale from 0 = "Not during the past month," 1 = "Less than once a week," 2 = "Once or twice a week," or 3 = "Three or more times per week."

2.2.2. Working memory (WM). Participants completed a WM n-back task (Owen et al., 2005) as part of the fMRI cognitive performance battery (for more details of the overall battery see Barch et al., 2013). The task was presented in the fMRI scanner and consisted of two runs of 8 task blocks (10 trials each) and 4 fixation blocks each. Participants viewed 4 stimulus category types (places, tools, faces, body parts), where each stimulus category was presented in separate blocks within the run. Half of the blocks presented to subjects in each run tested WM using a 2-back load level. Participants were instructed to respond when the current stimulus matched that which appeared two trials prior. The other half of the blocks consisted of a control 0-back load level, where participants were instructed to respond when a trial stimulus matched a target cue presented at the start of the block. After a 2.5 second cue at the start of each block indicating the task type (and target if a 0-back block), participants viewed each picture for 2 seconds, with picture stimuli separated by a 500 millisecond inter-trial interval (ITI). Within each block, 2 trials were designated targets and 2-3 trials were designated non-target "lures," or targets appearing in the incorrect n-back position. The entire task took approximately 10 minutes to complete. Each participant's average accuracy score across all stimulus category types in the 2-back condition was used as the behavioral measure of WM.

In addition to the n-back task, HCP participants also completed the List Sorting Task (Tulsky et al., 2014) during the NIH Toolbox behavioral testing session. The List Sorting Task assessed WM through the presentation of sequences of visually and orally presented stimuli. Participants were asked to sort the sequences of stimuli by various characteristics of the stimuli. Higher scores indicated higher levels of WM. We examined the age-adjusted List Sorting score, which is normed using the age appropriate band of the NIH Toolbox norming sample (bands of ages 18-29, or 30-35). A List Sorting score of 100 indicates a score that is the national average, while a score of 85 indicates a score that is 1 standard deviation below the national average for that participant's age band.

2.2.3. Self-reported affective distress. The HCP includes several behavioral measures categorized as "Negative Affect," specifically Anger-Affect, Anger-Hostility, Anger-Physical Aggression, Fear-Affect, Fear-Somatic Arousal, and Sadness. In addition, there are several measures of related constructs, including social distress and perceived stress (Loneliness, Perceived Stress, Perceived Rejection), that have been previously identified as associated with pain perception and cognitive performance (Bushnell et al., 2013; Hart et al., 2003; Shackman et al., 2011; Villemure and Bushnell, 2002). Measures used for analyses in the present study include Anger-Affect, Fear-Affect, Sadness, and Perceived Stress. The Anger-Affect Survey is a CAT administered measure comprising items from the PROMIS Anger Item bank that assess anger as an affective experience over the past 7 days (Pilkonis et al., 2013). The Fear-Affect survey was administered from items compiled from the PROMIS Anxiety Item Bank and assess self-reported fear and anxious misery over the past 7 days (Pilkonis et al., 2013). The Sadness Survey is a CAT administered measure of sadness in respondents over the past 7 days. The Perceived Stress Survey is a CAT administered measure of how unpredictable, uncontrollable

and overloaded participants feel about their lives over the past month (Kupst et al., 2015). All surveys were scored such that higher scores indicate higher levels of the construct (e.g., anger).

2.3. Data analytic technique

2.3.1. Self-reported affective distress. Because there were a number of potential self-report measures included in the HCP dataset pertaining to affective distress, we used a data-driven approach to identify a positively correlated cluster of measures that we then included as indicators for a latent construct using confirmatory factor analysis (CFA). We conducted Pearson correlation analyses using R Version 3.5.2 in order to choose the indicators for our latent construct. To aid in the identification of correlated measures, we used the Ward error sum of squares hierarchical clustering method (Murtagh and Legendre, 2014) as implemented in the *corrplot* R package (Wei and Simko, 2016). The following NIH Toolbox measures comprising the largest significantly correlated hierarchical cluster were chosen as the final indicators for the affective distress latent construct: Anger-Affect Survey, Perceived Stress Survey, Sadness Survey, and Fear-Affect Survey (Fig. 1a). Because the latent construct has no natural metric, we fixed the loading for the Anger-Affect indicator to 1 to provide a metric for the latent construct.

2.3.2. fMRI data preprocessing. A minimal-preprocessing pipeline for the surface-based HCP structural and functional data was used (Glasser et al., 2013) that included artifact removal, head motion correction using FSL's MCFLIRT (Jenkinson et al., 2002), segmentation, and registration to standard MNI-space. Surface-based activation maps were derived from task-fMRI data collected on a 3T Siemens Skyra scanner with a 32-channel head coil (TR = 720 ms, TE = 33.1 ms, flip angle = 52˚, FOV = 208mm × 180mm, matrix size = 104 × 90, 72 slices, 2mm isotropic voxels). Each subject's volume scans in MNI-space were mapped to CIFTI "grayordinate" standard space (32k Conte69 mesh) using a cortical ribbon-based volume to

surface mapping. A 2mm FWHM surface-based smoothing kernel was applied using a geodesic Gaussian algorithm. Subsequent preprocessing included extra surface-based smoothing using a geodesic Gaussian algorithm with 4mm FWHM. Computation of surface-based activation maps for each subject was performed using a standard general linear model (GLM) analysis using FSL's FILM (FMRIB's Improved Linear Model) with autocorrelation correction (Woolrich et al., 2001). Task-condition regressors were constructed by convolution with a canonical hemodynamic response function (HRF; Glover, 1999). Temporal derivatives of each convolved regressor were included in the GLM to account for timing differences but estimates for these terms were not used further analysis. A '2-back > 0-back' contrast was used to isolate increases in 2-back task-related brain activity.

2.3.3. 2-back task-related brain activity. Following conventions for best-practices in selecting ROIs for analysis (Poldrack, 2007), 2-back task-related brain activity was taken from regions-of-interest (ROIs) chosen *a priori* due to their prior implication in pain, affective distress, and cognitive control (Hashmi et al., 2013; Kragel et al., 2018; Woo et al., 2015). The ROIs selected as potential factors underlying the relationship between pain and WM task performance were the anterior midcingulate cortex (aMCC), dorsal medial frontal cortex (dMFC), and ventromedial prefrontal cortex (vmPFC). Because HCP fMRI data is in surface file format (CIFTI), we utilized a surface-based resting state functional connectivity-derived parcellation of cortical areas (Gordon et al., 2016) to define each ROI. In order to create surface-based ROIs that were comparable to those identified in prior studies implicating the MFC in pain, affective distress, and cognitive control (Kragel et al., 2018), individual parcels were combined to create each of the final ROIs used in our analyses. Mean parameter estimates from a

contrast of 2-back task-related brain activity (2-back vs. 0-back) were extracted for each participant in each ROI for inclusion in structural equation models.

2.3.4. Structural equation modeling (SEM). Pain intensity was examined in a structural equation model predicting 2-back task accuracy. To build the model, we first fit a measurement model testing self-reported affective distress (composite measure). We then fit a structural equation model testing the direct association between pain intensity and 2-back task accuracy, with self-reported affective distress (composite measure) included as an additional factor that we hypothesized might be involved in an indirect relationship between pain and WM. Finally, we tested a model where we added brain activity from the three 2-back task-related ROIs. At each step, model fit was evaluated using previously recommended criteria (Hooper et al., 2008) for the following indices: χ^2 (chi-square) test (acceptable if χ^2 p-value > .05), the Root Mean Square Error Approximation (RMSEA, acceptable if ≤ .08), the Comparative Fit Index (CFI, acceptable if ≥ .95), and the Standardized Root Mean Square Residual (SRMR, acceptable if ≤.08).

We specified paths from pain intensity to 2-back task accuracy via affective distress and each of our task-related ROIs, as we hypothesized that participants' self-reported affective distress could influence the strength of task-related brain activity and therefore be negatively associated with WM. The proposed structural equation model, with hypothesized direct and indirect associations, can be viewed in Fig. 2.

Although there are known age-related deficits in WM task performance (West, 1999), age was not included in the model because our sample was relatively young with a small standard deviation (M = 28.7, SD = 3.78, range: 22-36), and a prior study (Attridge et al., 2015) found no evidence for an age × pain interaction on n-back task performance using a similarly aged subject population. The zero-order correlation between age and pain intensity in our sample was not

significant, $r = .003$, $t(226) = 0.04$, $p = .968$, nor was the correlation between age and WM task performance, $r = -.099$, $t(223) = -1.49$, $p = .138$. Finally, when available we used age-adjusted variables included in the HCP dataset.

2.3.5. Model assumptions. Analyses were conducted using R Version 3.5.2 and RStudio Version 1.1.463 (R Studio Team, 2016). Measurement and structural equation models were specified using the *lavaan* package in R (Rosseel, 2012). Because Shapiro-Wilk tests revealed evidence of non-normality in several of our model variables (specifically the 2-back task accuracy dependent variable, pain intensity predictor variable, NIH Toolbox Anger-Affect Survey, and NIH Toolbox Fear-Affect Survey), we employed robust maximum likelihood (MLR) estimation for all models. MLR adjusts model fit indices and utilizes the Huber-White "sandwich" estimator to correct inflated standard errors due to kurtosis and non-normality (Huber, 1967). No predictors in our model had a variance inflation factor (VIF) greater than 3, suggesting no problematic multicollinearity in our structural equation models.

2.3.6. Outliers. Examination of the dependent task performance variable for univariate outliers revealed one observation that was greater than 3 standard deviations below the mean accuracy score. However, because the dependent variable had acceptable levels of skewness and kurtosis (skewness = -0.77, kurtosis = 3.16) based on previously published guidelines (skewness < 2 and kurtosis < 7; Ryu, 2011), we opted to retain all observations. Examining the pain intensity predictor revealed four univariate outliers. However, because this variable also had acceptable levels of skewness and kurtosis (skewness = 1.59, kurtosis = 5.36), we retained all observations. Additionally, checking for multivariate outliers using Cook's Distance (Cook, 1977) did not reveal any influential outliers.

2.3.7. Missing data. The 2-back task accuracy dependent variable had 3 missing values. Missing values were removed with listwise deletion in structural equation models.

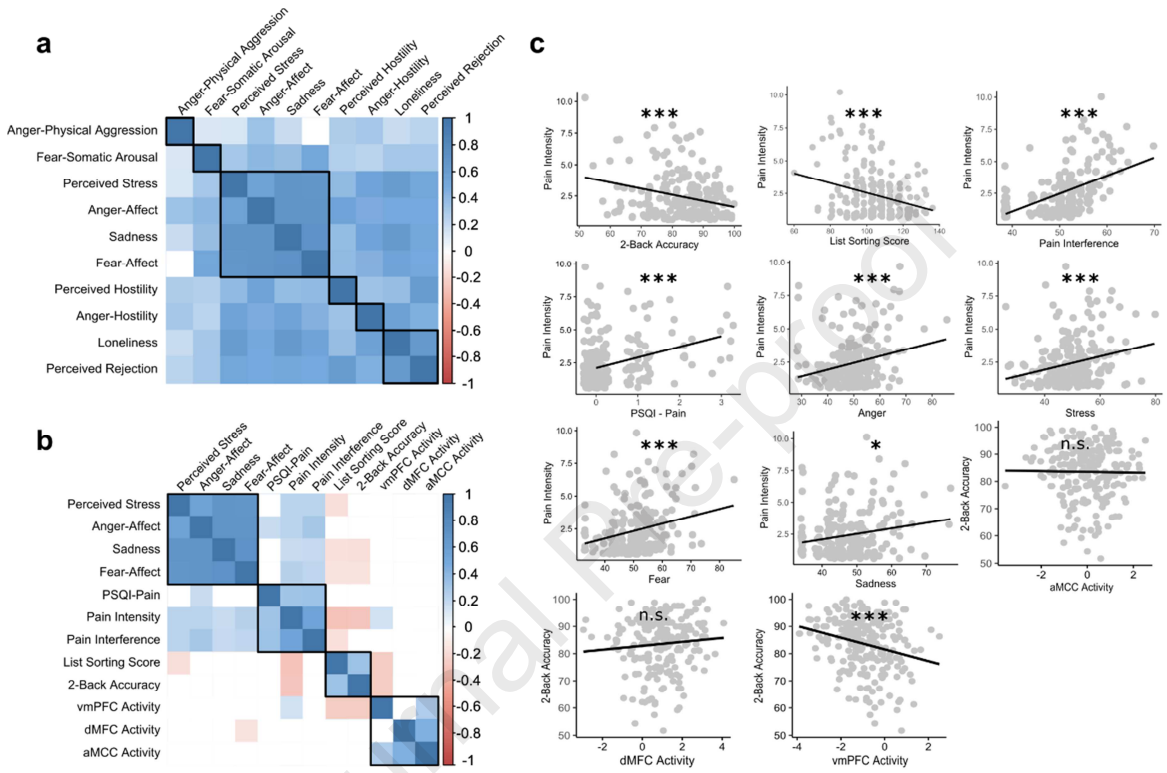

Figure 1. Pearson correlation matrices of HCP variables of interest in the current study in participants who reported > 0 pain intensity in the last 7 days. Positive correlations are represented with blue backgrounds; negative correlations are represented with red backgrounds. The intensity of the color in each cell is proportional to the strength of the correlation coefficient. The *p*-values within each matrix were adjusted for multiple comparisons using false discovery rate (FDR) correction. Cells with white backgrounds had FDR-corrected *p*-values > .05. Black outlines indicate hierarchical clustering of correlated variables using the Ward criterion. (a) Relationships between HCP measures of self-reported affective distress. The largest cluster, comprising the NIH Toolbox Perceived Stress Survey, Anger-Affect Survey, Sadness Survey,

and Fear-Affect Survey were chosen as the indicators for the self-reported affective distress latent construct; (b) Relationships between measures of interest related to pain, affective distress, and working memory task performance. (c) Scatter plots demonstrating the correlations reported in (b), including between pain intensity in the past 7 days and working memory measures, pain intensity in the past 7 days and other Human Connectome Project (HCP) measures of pain, correlations between pain intensity in the past 7 days and measures of affective distress, and correlations between 2-back task performance and 2-back task-related activation in a priori ROIs. *Note.* * $p < .05$, ** $p < .001$.

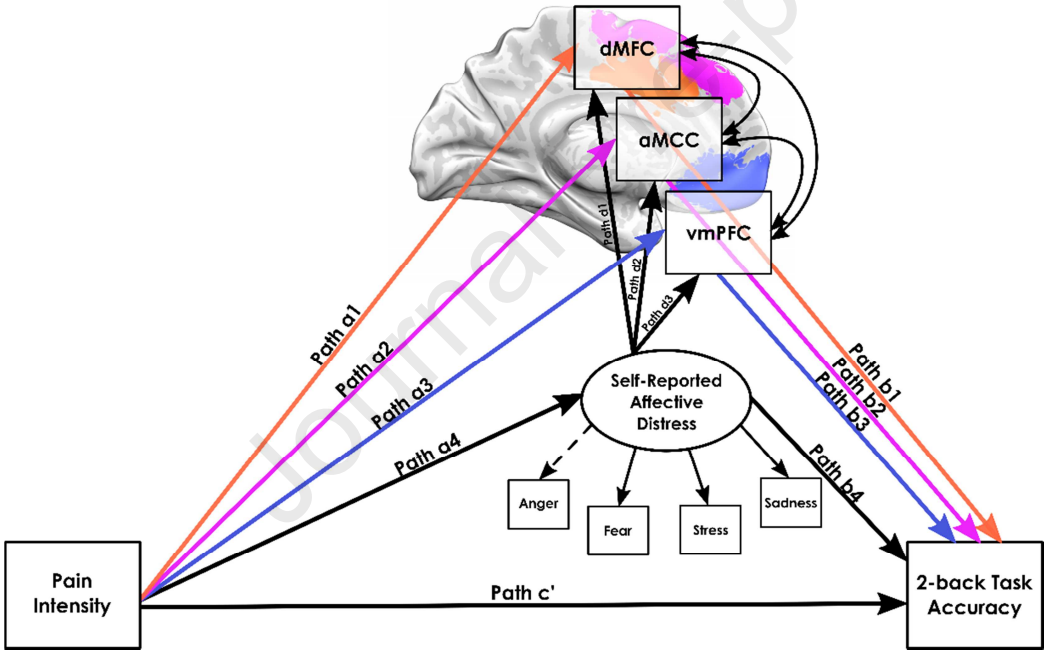

Figure. 2. Proposed structural equation model (SEM) testing the association between pain intensity and 2-back task accuracy. Different colors denote the indirect paths that were tested. Note: dMFC = dorsal medial frontal cortex; aMCC = anterior midcingulate cortex; vmPFC = ventromedial prefrontal cortex; Anger = NIH Toolbox Anger-Affect Survey; Fear = NIH Toolbox Fear-Affect Survey; Stress = NIH Toolbox Perceived Stress Survey; Sadness = NIH Toolbox Sadness Survey.

3. Results

3.1. Descriptive statistics

Sample characteristics for the final sample (n = 228) can be viewed in Table 1. Descriptive statistics for all measures included in the present study can be viewed in Table 2.

Table 1. Sample characteristics.

	n = 228
Age	
Mean (SD)	28.7 (3.78)
Median [Min, Max]	28.0 [22.0, 36.0]
Race	
Am. Indian/Alaskan Nat.	0 (0%)
Asian/Nat. Hawaiian/Other Pacific Is.	10 (4.4%)
Black or African Am.	34 (14.9%)
More than one	5 (2.2%)
Unknown or Not Reported	6 (2.6%)
White	173 (75.9%)
Ethnicity	
Hispanic/Latino	23 (10.1%)
Not Hispanic/Latino	203 (89.0%)
Unknown or Not Reported	2 (0.9%)
Gender	
Female	108 (47.4%)
Male	120 (52.6%)

Table 2. Descriptive statistics for measures included in structural equation models.

	Mean (SD)	Skewness	Kurtosis
Pain Intensity	2.41 (1.76)	1.59	5.36
2-back Task Accuracy	83.5 (9.87)	-0.77	3.16

NIH Toolbox Anger-Affect	49.3 (8.48)	0.35	4.55
NIH Toolbox Perceived Stress	49.6 (8.68)	0.21	3.76
NIH Toolbox Sadness	47.6 (7.84)	0.65	4.13
NIH Toolbox Fear-Affect	51.3 (8.10)	0.29	4.43
aMCC Activity during 2-back Task	-0.011 (1.03)	-0.18	3.14
dMFC Activity during 2-back Task	0.398 (1.02)	-0.25	3.61
vmPFC Activity during 2-back Task	-0.684 (1.03)	-0.03	3.20

3.2. Zero-order correlations between pain, task-related brain activity, and 2-back task accuracy

Regarding the frequency of pain experience, 55% (228/416) of participants reported experiencing pain in the last 7 days. To understand the relationship between pain intensity and other variables of interest, we first examined zero-order correlations between variables of interest among the participants who reported non-zero pain intensity in the last 7 days (Fig. 1b; scatter plots depicted in Fig. 1c). Increased pain intensity was significantly associated with increases in the other measures of pain in the HCP dataset, namely pain interference, $r = .55$, $p_{corrected} < .001$, 95% CI[.46, .64], and the frequency of pain interfering with sleep (PSQI – Sleep Item), $r = .34$, $p_{corrected} < .001$, 95% CI[.22, .45]. Increased pain intensity was also significantly associated with increased self-reported anger, $r = .24$, $p_{corrected} < .001$, 95% CI[.12, .36], fear, $r = .26$, $p_{corrected} < .001$, 95% CI[.13, .38], perceived stress, $r = .25$, $p_{corrected} < .001$, 95% CI[.12, .37], and sadness, $r = .19$, $p_{corrected} = .01$, 95% CI[.06, .31].

To test whether the 2-back task was assessing WM as we hypothesized, we examined the relationship between participants' 2-back task performance and performance on the other HCP measure of WM, the List Sorting task. As predicted, higher 2-back task accuracy (% correct) was significantly associated with higher List Sorting scores, $r = .35$, $p_{corrected} < .001$, 95% CI[.23, .46].

Supporting the hypothesized relationships between our measures of interest, we found that increased pain intensity was significantly associated with lower accuracy on the 2-back task, r = -.28, $p_{corrected}$ < .001, 95% CI[-.39, -.15]. Increased task-related activity in the vmPFC was, in turn, significantly associated with lower 2-back task accuracy, r = -.25, $p_{corrected}$ < .001, 95% CI[-.37, -.12]. However, 2-back task performance was not associated with task-related activity in the aMCC, r = -.01, $p_{corrected}$ = .886, 95% CI[-.14, .12], or dMFC, r = .09, $p_{corrected}$ = .289, 95% CI[-.04, .22].

Together, our zero-order correlation findings indicate that individuals who reported non-zero pain intensity in the past 7 days also reported some degree of pain interference and sleep disruption due to pain, supporting the validity of the pain intensity measure as a general indicator of everyday pain. Supporting the validity of the 2-back task as a measure of WM, better 2-back task performance was significantly associated with better performance on the WM List Sorting task. Supporting our hypothesized relationships between our measures of interest, namely that pain intensity would be directly and indirectly associated with worse working memory task performance, we found that increased pain intensity and 2-back task-related activity in the vmPFC were both associated with worse 2-back task performance.

3.3. Increased pain intensity directly and indirectly associated with lower 2-back task accuracy in structural equation models.

The single factor measurement model of self-reported affective distress was identified and fit the data, $\chi^2(2, N = 228) = 2.39$, p = .300; CFI = 0.99, RMSEA = 0.03, SRMR = 0.01. All indicator loadings were significant (p < .001).

Next, we fit a structural model with a direct path from pain intensity to 2-back task accuracy and an indirect path via the self-reported affective distress latent construct. The

structural model was identified and fit the data, $\chi^2(8, N=225) = 9.51$, p = .302; CFI = 1.00, RMSEA = 0.029, SRMR = 0.02. Increased pain intensity was directly associated with lower 2-back task accuracy, b = -1.43, SE_b = 0.41, p = .001. Increased pain intensity was also associated with increased self-reported affective distress, b = 1.05, SE_b = 0.35, p = .002. However, self-reported affective distress was not associated with 2-back accuracy, b = -0.12, SE_b = 0.101, p = .242, and the indirect effect of pain intensity on 2-back task accuracy was not significant, b = -0.12, SE_b = 0.11, p = .268. The total relationship between pain intensity and 2-back task accuracy was significant, b = -1.55, SE_b = 0.39, p < .001.

We then added to the structural equation model the three ROIs of 2-back task-related activity (Fig. 3). We found that the structural model was identified and fit the data, $\chi^2(17, N=225) = 12.95$, p = .740; CFI = 1.00, RMSEA = 0.00, SRMR = 0.016. In this model, increased pain intensity was again directly associated with lower 2-back task accuracy, b = -1.26, SE_b = 0.39, p = .001, and with increased self-reported affective distress, b = 1.05, SE_b = 0.35, p = .002. Additionally, increased pain intensity was associated with increased task-related activity in the vmPFC, b = 0.11, SE_b = 0.04, p = .007. Increased vmPFC activity was in turn associated with lower 2-back task accuracy, b = -1.95, SE_b = 0.55, p < .001. Increased self-reported affective distress was significantly associated with lower task-related dMFC activity, b = -0.03, SE_b = 0.01, p = .034.

Testing indirect associations, we found a significant indirect association between pain intensity and 2-back task accuracy via task-related activity in the vmPFC, b = -0.22, SE_b = 0.10, p = .023. That is, increased pain intensity was associated with increased task-related activity in the vmPFC, which was in turn associated with lower 2-back task accuracy. The total relationship between pain intensity and 2-back task accuracy was significant, b = -1.43, SE_b = 0.41, p = .001.

In contrast, none of the other tested indirect associations between pain intensity and 2-back task accuracy were significant (all *p*-value's > .200). Full results from this model are available in Table 3.

To investigate whether the observed significant indirect association was due to other variables in our model, we specified a simplified model including only pain intensity, 2-back task-related vmPFC activity, and 2-back task accuracy. The indirect association between pain intensity and 2-back task accuracy via vmPFC activity remained significant in this simplified model, b = -0.19, SE_b = 0.08, p = .020, suggesting that the indirect association we observed in our full model was not merely due to the presence of other variables.

3.4. Participants reporting non-zero pain demonstrated attenuated vmPFC deactivation, but not lower 2-back task accuracy, compared to participants reporting zero pain

To further characterize the significant relationships observed in our final structural equation model, we compared participants who reported non-zero pain in the past 7 days to participants who reported zero pain in the past 7 days. Given prior findings that patients with chronic pain have worse WM task performance (see Berryman et al., 2013, for a review) and attenuated task-related deactivation of the default mode network (DMN) compared to healthy controls (Baliki et al., 2008), we conducted independent samples *t*-tests on measures of WM task performance and WM task-related activity in the vmPFC. WM task performance as measured by 2-back task accuracy did not significantly differ between the two groups, $t(373.26) = 0.22$, p = .828, 95% CI[-1.83, 2.29]. However, participants who reported non-zero pain (n = 228) in our sample had significantly greater 2-back task-related vmPFC activity than participants who reported zero pain (n = 186), $t(401.31) = 2.36$, p = .019, 95% CI[0.04, 0.47].

These findings suggest some similarity, at least in terms of 2-back task-related brain activity, between the healthy participants who reported non-zero pain in our sample and patients with chronic pain investigated in prior studies.

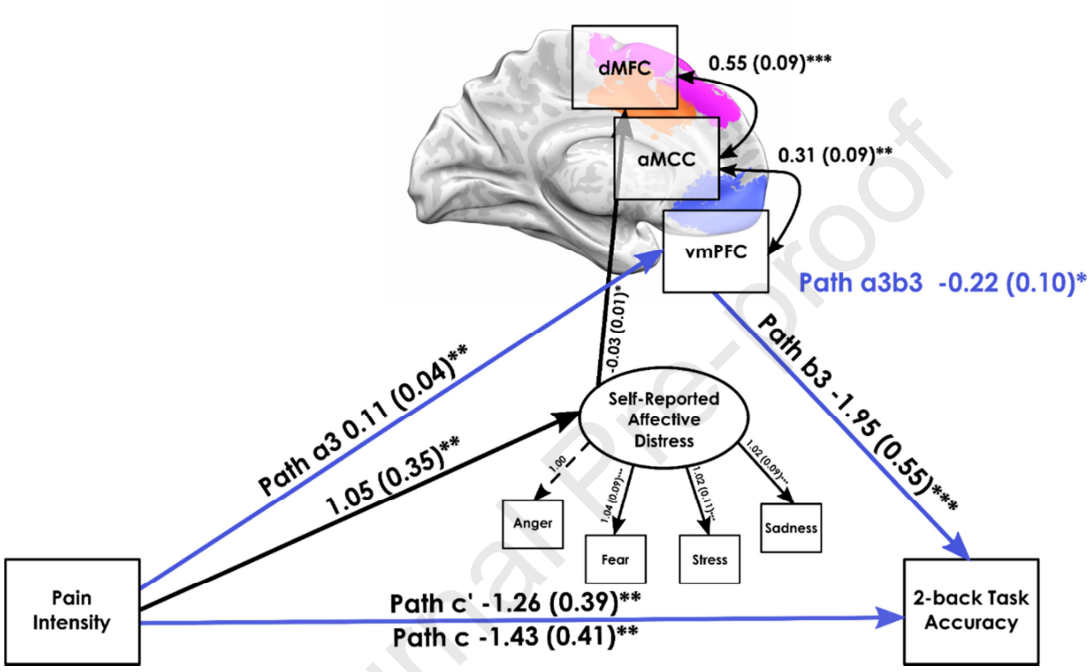

Figure. 3. Results of structural equation model testing the association between pain intensity and 2-back task accuracy. For display purposes, only significant ($p < .05$) paths are shown. Increased pain intensity was directly associated with lower 2-back task accuracy. In addition, increased pain intensity was indirectly associated with lower 2-back task accuracy via increased 2-back task-related activity in the vmPFC. Note: aMCC = anterior midcingulate cortex; dMFC = dorsal medial frontal cortex; vmPFC = ventromedial prefrontal cortex; Anger = NIH Toolbox Anger-Affect Survey; Fear = NIH Toolbox Fear-Affect Survey; Stress = NIH Toolbox Perceived Stress Survey; Sadness = NIH Toolbox Sadness Survey. *Note.* * $p < .05$, ** $p < .01$, ** $p < .001$.

Table 3. Results of structural equation model predicting 2-Back Accuracy.

	Estimate	SE	z	*p*
		Factor Loadings		
Self-Reported Affective Distress				
Anger	1.00[+]			
Stress	1.02***	0.11	9.01	.000
Sadness	1.02***	0.09	11.62	.000
Fear	1.04***	0.09	12.11	.000
		Regression Slopes		
2-back Task Accuracy				
Pain Intensity	-1.26**	0.38	-3.28	.001
aMCC Activity during 2-back	0.20	0.65	0.31	.754
dMFC Activity during 2-back	0.82	0.51	1.61	.108
vmPFC Activity during 2-back	-1.95***	0.55	-3.56	.000
Self-Reported Negative Affect	-0.11	0.10	-1.05	.293
aMCC Activity during 2-back				
Pain Intensity	0.06	0.04	1.45	.148
Self-Reported Affective Distress	-0.01	0.01	-0.64	.525
dMFC Activity during 2-back				
Pain Intensity	0.05	0.04	1.20	.230
Self-Reported Affective Distress	-0.03*	0.01	-2.11	.034
vmPFC Activity during 2-back				
Pain Intensity	0.11**	0.04	2.67	.007
Self-Reported Affective Distress	-0.01	0.01	-0.45	.651
Self-Reported Affective Distress				
Pain Intensity	1.05**	0.35	3.03	.002
		Residual Variances		
Anger	27.62***	3.97	6.96	.000
Stress	28.98***	3.73	7.76	.000
Sadness	15.79***	2.79	5.65	.000
Fear	17.68***	2.27	7.78	.000
2-back Task Accuracy	83.58***	7.74	10.80	.000
aMCC Activity during 2-back	1.06***	0.10	10.30	.000
dMFC Activity during 2-back	1.41***	0.14	10.25	.000
vmPFC Activity during 2-back	1.25***	0.12	10.61	.000
Pain Intensity	3.10[+]			
		Residual Covariances		
dMFC Activity during 2-back w/vmPFC Activity during 2-back	0.12	0.10	1.19	.234

aMCC Activity during 2-back w/vmPFC Activity during 2-back	0.31**	0.09	3.40	.001
aMCC Activity during 2-back w/dMFC Activity during 2-back	0.55***	0.09	5.91	.000
		Latent Variances		
Self-Reported Affective Distress	41.19***	7.41	5.56	.000
		Indirect Paths		
Pain -> aMCC -> 2-back	0.01	0.04	0.30	.763
Pain -> dMFC -> 2-back	0.04	0.04	0.98	.326
Pain -> vmPFC -> 2-back	-0.22*	0.10	-2.27	.023
Pain -> Affective Distress -> 2-back	-0.11	0.11	-1.03	.303
Pain -> Affective Distress -> aMCC -> 2-back	-0.00	0.01	-0.28	.779
Pain -> Affective Distress -> dMFC -> 2-back	-0.02	0.02	-1.20	.229
Pain -> Affective Distress -> vmPFC -> 2-back	0.01	0.02	0.46	.645
Total Effect	-1.43	0.41	-3.47	.001
		Fit Indices		
χ^2	12.95			
CFI	1.00			
TLI	1.01			
RMSEA	0.00			
Scaled χ^2	11.30(17)			

Note. Dependent variables are underlined with their respective predictors shown below, with the exception of the underlined Affective Distress latent variable where indicators are shown below. $^{+}$Fixed parameter; * $p < .05$, ** $p < .01$, ** $p < .001$

4. Discussion

In the present study, we (1) tested whether the negative relationship between non-experimental pain and working memory (WM) demonstrated in previous research extends to otherwise healthy individuals, and (2) examined whether self-reported affective distress or neurobiological factors related to pain, affective distress, and WM might account for this relationship. We found that pain intensity was negatively associated with accuracy on the 2-back task. We also found an indirect association between pain and 2-back task performance via neural

factors related to affective distress, specifically, increased self-reported pain intensity was related to worse 2-back task performance through increased activation in the ventromedial prefrontal cortex (vmPFC).

The direct negative association between everyday pain intensity and 2-back task accuracy that we observed is consistent with a previous online study which found pain-related increases in false alarms on a letter 2-back task (Attridge et al., 2015). Similarly, we found that as participants' pain intensity levels increased, their overall accuracy on the 2-back task decreased. Although the stimulus category types (places, tools, faces, body parts) used in the present study's 2-back task differed from the letter 2-back used by Attridge et al. (2015), the similarity of our findings to this prior study increases confidence in the replicability of the direct association.

While negative correlation between pain intensity and 2-back task accuracy that we report is weak (r = -.28, $p_{corrected} < .001$), it is comparable to the relationship between pain intensity measured outside the laboratory and WM task performance (number of correct rejections in 2-back task) reported by Attridge et al. (2015) (r = -0.16, $p < .001$). Other studies using similar tasks have found comparable significant (although weak) negative correlations, for example, Kuhajda et al. (2002) reported a negative correlation between headache pain intensity ratings and memory task performance, $r = -0.25$, $p = .024$. More broadly, our finding suggests, consistent with prior studies, that even relatively low levels of pain reported over the past 7 days, as observed in our healthy sample, may directly impact WM task performance.

The results of the current study suggest that the association between pain and WM performance may be partly explained by increased activation (i.e., attenuated deactivation) in the vmPFC. Laboratory-based studies of healthy individuals receiving experimentally induced pain have typically reported that increased vmPFC activity is associated with decreased pain (Atlas et

al., 2014). In contrast, studies with chronic pain patients have found that increased vmPFC activity is associated with increased pain (Apkarian et al., 2011). In the present study, we found that participants who reported non-zero pain in the past 7 days had significantly greater 2-back task-related vmPFC activity than participants reporting zero pain. Thus, it is possible that the participants reporting non-zero pain in our sample may, in certain aspects, more resemble patients with chronic pain than typically healthy participants. Further study is needed to compare WM-related vmPFC dysfunction in healthy individuals experiencing everyday pain outside of the laboratory with that experienced by patients with chronic pain.

Finally, although we found that participants who reported non-zero pain demonstrated significantly greater WM task-related vmPFC activity than participants who reported zero pain, we did not find that 2-back task performance itself significantly differed between the two groups. This suggests that differences between healthy individuals experiencing everyday pain and those not experiencing pain may be more sensitively characterized at the neural, rather than behavioral, level. Although there are consistently reported WM deficits in patients with chronic pain compared to healthy controls (Berryman et al., 2013), previous studies in healthy populations have shown mixed evidence that behavioral differences exist in pain vs. non-pain groups (e.g., behavioral differences were not consistently observed for all measures of an n-back task in Attridge et al., 2015). This may reflect the advantages of neuroimaging tools such as fMRI to provide additional information on the neurobiological impacts of pain. Relatedly, participants with non-zero pain may not have been experiencing sufficient pain intensity levels to impact WM performance compared to participants with zero pain, considering the mean pain intensity for the non-zero pain group was fairly low (M = 2.41). Importantly, however, we did observe a direct relationship between pain intensity and 2-back task accuracy in non-zero pain participants,

suggesting that participants experiencing increased pain intensity did demonstrate worse WM task performance.

4.1. Limitations

The results of our study should be interpreted in the context of certain limitations. First, while the use of HCP data allowed us to employ advanced statistical modeling to explore potential mediators in the relationship between pain and WM in a large and heterogeneous sample, the data collection procedures used in the HCP study and the lack of an experimentally induced pain stimulus necessitated that we draw observational rather than causal associations between our chosen variables. Second, because pain was not a primary focus of the HCP study, we lack data on the specific nature of the pain experienced by participants, or whether participants were in pain during the actual study procedures. However, it is notable that we report a direct and indirect association between pain and 2-back task accuracy despite the possibility that some participants may not have been experiencing pain during the 2-back task itself. Additionally, although participants were excluded if they reported using daily prescription medication for migraines in the past month, they were not explicitly excluded for the presence of chronic pain. As a result, it is possible that a small proportion of the participants in our sample may have been experiencing chronic pain. However, estimates for the prevalence of self-reported chronic pain in the United States range from 12.4-21.0% for participants aged 18-34 (Johannes et al., 2010), and is likely even lower in the HCP sample given that participants were excluded if taking daily prescription medication for migraines. Next, our measure of self-reported affective distress was a composite of several specific emotion items (i.e., fear, anger, stress, sadness). While each of these emotion items were highly correlated by virtue of being pain-related and negatively valenced, they are nevertheless theoretically discrete emotional states associated with

different levels of arousal and motivational tendencies. In the current study, affective distress, measured as a composite of negative pain-related emotions, was associated with pain reported over the past 7 days but was not associated with performance on the 2-back task. It is possible that the negative association between pain-related distress and WM performance is emotion-specific (i.e., present for fear but not for anger). Finally, despite our *a priori* interest in the variables included in our structural equation models, our results do not preclude the influence of other self-report or neural factors related to pain or WM.

4.2. Implications and future directions

The results of our study provide evidence for a negative relationship between levels of pain experienced over the past 7 days and WM in a large sample of healthy individuals, and point to a potential neurobiological mechanism of this relationship. Future studies will be needed to formally test whether the associations that we report in the present study are causal in nature. Our results, combining behavioral self-report and neurobiological measures into a single model, also help clarify the complex and often overlapping relationships between pain, emotion, and cognition (Gilam et al., 2020). Future studies could aim to use more complex methodologies, such as multivariate pattern analysis and machine learning algorithms (e.g., Kragel et al., 2018), to characterize patterns of brain activity that may comprise neural representations of these constructs. An important implication of this study is that even pain experienced outside of the laboratory (i.e., in everyday life) in otherwise healthy individuals can directly impact WM task performance. In consideration of this, we recommend that future studies examining pain and WM using ostensibly healthy populations consider measuring baseline pain prior to the induction of experimental pain stimuli, as individual variability in baseline pain levels could impact associated brain activity and WM task performance.

4.3. Conclusions

Together, our findings add to our understanding of the full impact of pain on cognitive functioning (Eccleston, 2013). In addition to demonstrating non-experimental pain-cognition associations in healthy individuals, our findings add to our understanding of the potential neural mechanisms that may contribute to this association. Our finding of a direct and indirect association between pain intensity and WM task performance in a large and publicly available dataset is consistent with prior literature that has separately identified pathways associated with the affective-motivational and self-regulatory aspects of pain among healthy volunteers and patients with chronic pain. Furthermore, our inclusion of multiple self-report measures of affective distress and task-related brain activity helps clarify the relative contributions of these factors on the relationship between pain and cognition. Our findings ideally will aid future efforts to understand the mechanisms underlying the relationship between pain experienced outside of the laboratory in healthy individuals and cognitive task performance. Our findings are clinically relevant in suggesting that even ostensibly healthy individuals who may not meet clinical criteria for pain disorders may nonetheless experience pain-related interference with other aspects of their cognition.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Open Practices Statement

The data used in the present study is publicly available through the Human Connectome Project (humanconnectome.org). Analyses conducted for the present study are available in an R Markdown file hosted on Open Science Framework (OSF): https://osf.io/x9eby/?view_only=04a81641cd5543179adbda9dd9231a18.

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Modeling neural and self-reported factors of affective distress in the relationship between pain and working memory in healthy individuals

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Highlights:

- Most studies examine pain in chronic pain patients and laboratory settings
- Few studies on pain in healthy individuals; affective distress may play a role
- Increased pain intensity directly associated with worse working memory performance
- Pain indirectly related to working memory via increased activity in vmPFC
- vmPFC may underlie pain-related deficits in working memory in healthy individuals