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Is There an Association Between Lateralization of Chronic Pain in the Body and Depression?

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Abstract: **Depression commonly co-occurs with chronic pain and can worsen pain outcomes. Recent theoretical work has hypothesized that pain localized to the left hemibody is a risk factor for worse depression due to overlap in underlying neural substrates. This hypothesis has not been tested a priori. Using a large sample of treatment-seeking adults with mixed-etiology chronic pain (N = 1,185), our cross-sectional study tested whether patients with left-sided pain endorse worse depressive symptoms. We also examined differences in other pain-related functioning measures. We tested 4 comparisons based on painful body areas using the CHOIR body map: 1) only left-sided (OL) versus any right-sided pain; 2) only right-sided (OR) versus any left-sided pain; 3) OL versus OR versus bilateral pain; and 4) more left-sided versus more right-sided versus equal-sided pain. Analysis of variance models showed OL pain was not associated with worse depression (F = 5.50, P = .019). Any left-sided pain was associated with worse depression, though the effect was small (F = 8.58, P = .003, Cohens d = .29). Bilateral pain was associated with worse depression (F = 8.05, P < .001, Cohens d = .24–.33). Regardless of pain location, more body areas endorsed was associated with greater depression. Although a more rigorous assessment of pain laterality is needed, our findings do not support the hypothesis that left-lateralized pain is associated with worse depression.**

Perspective: ***Pain lateralized to the left side of the body has been hypothesized as a risk factor for worse depression in chronic pain, despite never being tested in a large, real-world sample of patients with chronic pain. Findings showed that more widespread pain, not pain laterality, was associated with worse depression.***

Key Words: *Chronic pain, depression, negative affect, laterality, CHOIR body map*

Mental health is an essential component of the biopsychosocial model of chronic pain.[1] Depression, in particular, frequently co-occurs with chronic pain.[2] Patients with chronic pain are nearly three times more likely to have a diagnosis of major depression compared to patients without chronic pain,[3] and half of all patients seeking pain treatment have elevated depressive symptoms.[2,3] Likewise, over 60% of patients seeking outpatient treatment for depression report having chronic pain.[4–7] Worse depression is associated with greater pain intensity, pain interference, pain-related disability, and health care costs.[6,8–13] Prior longitudinal research has also demonstrated a bidirectional relationship between pain and depression, such that worsening pain predicted worsening depression, and vice versa, over the course of 12 months.[14] Co-occurring chronic pain and depression are associated with less benefit from medical treatment, including epidural steroid injections,[15] lumbar spine surgery,[16] spinal cord stimulation,[17] and antidepressant medications.[5,18,19]

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Recently, the side of the body pain localizes, referred to as pain laterality, has been hypothesized as a potential risk factor for worse depression in individuals with chronic pain. Maallo and colleagues[20] reviewed the literature and proposed that chronic pain and depression may frequently co-occur due to overlap in their underlaying neural substrates, primarily in the forebrain. Specifically, their literature review indicated that the right-sided thalamus, insula, and anterior cingulate cortex were responsive to pain and demonstrated strong associations with depressive symptoms, though there was no preference for activation of one side or the other. Thus, in their review, they put forth a lateralized pain and depression model, which posits that left-sided body pain, processed in the right hemisphere, is associated with more severe depression. The review identified 11 clinical studies in humans supporting that left-sided chronic pain is associated with worse measures of psychological distress.[21–30] Of these 11 studies, however, only 5 utilized depression severity scales,[22,24–26,30] and only 4 made a comparison between patients with left-sided versus right-sided pain.[22,24–26] Nevertheless, Maallo and colleagues[20] concluded that chronic left-sided body pain is more likely to present with greater psychological distress and that the lateralized pain and depression model may provide a framework for identifying those at risk of depression with chronic pain. This hypothesis is contradictory to findings in the literature that suggest patients with multiple pain conditions or widespread pain (regardless of lateralization) have higher odds of comorbid depression, compared to patients with a single pain area or no pain at all.[31–33]

If a substantial link between left-sided pain and depression can be confirmed in a large, real-world population, then clinicians can be alerted to this risk factor and offer mental health resources at an earlier stage of treatment—potentially enhancing treatment success and reducing health care utilization.[34] Yet, to date, the lateralized pain and depression model has yet to be examined a priori with preregistered datasets and outcomes. Additionally, there is a paucity of studies that examine depression severity associated with left-sided versus right-sided pain in a mixed population of patients with varying chronic pain disorders.[35]

Based on these considerations, our current study aims to determine whether patients with left-sided chronic pain have more severe symptoms of depression in a real-world, clinical population of adults with chronic pain of varying etiologies. Using rigorous methods of preregistered datasets and outcomes, we tested the following prespecified hypotheses with and without average pain intensity and pain interference as a covariate: 1) having any left-sided chronic pain (as opposed to exclusively right-sided pain) is associated with more severe depression symptoms and 2) having more left-sided body regions affected by chronic pain (as opposed to more right-sided regions) is associated with more severe depression symptoms. As an exploratory aim, we will also examine if having any left-sided chronic pain is associated with worse severity of several other pain-related functioning measures (pain catastrophizing, pain interference, pain behavior, fatigue, anxiety, sleep disturbance, anger, emotional support, social satisfaction, social isolation, and mobility).

Methods

Study Design

The Stanford University institutional review board approved this study under a retrospective chart review protocol. The requirement for written patient consent was waived as this project uses existing deidentified data in a retrospective study design. We employed a prespecified cross-sectional study design that examined 2 factors: depression severity by pain laterality, without stratification. An exploratory dataset was first analyzed to calculate the minimum sample size needed in the confirmatory analysis using a separate, independent dataset (see Sample Size Rationale). This study's aims, hypotheses, and statistical analysis plan were preregistered and posted on the Open Science Framework website on March 14, 2022 (https://osf.io/sycvg/). Exploratory data analyses occurred prior to the preregistration in September 2021, and the confirmatory data analyses occurred following preregistration in July 2022.

Data Collection

We extracted data from the Stanford University learning health system, the Collaborative Health Outcomes Information Registry (CHOIR; http://choir.stanford.edu), which contains detailed demographic information and patient-reported outcomes from treatment-seeking individuals with chronic pain.[36] All data for this study were obtained via secure, online surveys completed voluntarily, without financial compensation, before a patient's initial appointment at the Stanford Pain Management Clinic. CHOIR uses both traditional long-form assessments and item response theory-based assessments from the Patient-Reported Outcomes Measurement Information System (PROMIS) item banks developed by the National Institutes of Health.

Participants

For the exploratory dataset (n = 1,717), we used a convenience sample of all patients who completed a CHOIR survey at their initial visit between July 1, 2018 and December 31, 2018. Patients in the confirmatory dataset (n = 1,635) completed a CHOIR survey at their initial visit between January 1, 2019 and June 30, 2019. Patients were eligible for inclusion if they 1) completed the CHOIR survey at their initial clinical visit at Stanford Pain Management Center, 2) selected at least 1 affected body area on the CHOIR body map, and 3) completed the PROMIS depression assessment. Exclusion criteria included pain duration < 3 months (since chronic pain is typically defined as pain lasting ≥3 months[37]) and average pain intensity < 3 out of 10 on the numerical rating scale (NRS). Participants were also excluded if their pain was limited to the face, head and neck, since sensory afferents from these areas have both contralateral and ipsilateral projections to both hemispheres.[38] Of the 1,635 patients in the confirmatory dataset, we excluded 81 patients for a pain duration of < 3 months, 299 patients were excluded for pain limited to the head and neck, and 70 patients were excluded for

reporting an average pain intensity of < 3 out of 10 on the NRS. Data from 1,185 patients were retained for analysis.

Measures

Demographics

Participants reported demographic information, including age, sex (male, female), race, ethnicity (Hispanic/Latino or Not Hispanic/Latino), marital status, and education level. Pain duration reported in months and years was also collected. Patients could also select "unknown" or "prefer not to respond" for each demographic question besides age.

Pain Location Groups

The CHOIR body map is a validated, electronic, visual representation of the human body that allows participants to indicate their location(s) of pain.[39,40] Using a computer mouse or touch screen device, participants select the body areas affected by pain in response to the instructions (see Fig 1 for the body map and instructions). If the participant does not have any pain, they can select the response, "I have no pain." There are 74 numbered areas on the CHOIR body map, adapted from previously published body maps and designed to reflect areas commonly described in chronic pain disorders. The CHOIR body map has demonstrated validity and reliability in several published studies of chronic pain outcomes.[33,40–44] Since not all patients have pain that is restricted to only one side of the body, we tested our hypotheses using four pain location groups. Pain location groups were assigned based on the endorsement of pain areas on the body map, such that participants were assigned to 1 of 2 or 3 groups for each comparison: 1) only left-sided (OL) pain versus any right-sided pain; 2) only right-sided (OR) pain versus any left-sided pain; 3) OL pain versus OR pain versus bilateral pain; and 4) more left-sided pain versus more right-sided pain versus equal numbers of pain areas on both sides.

Depression Severity

CHOIR uses computerized adaptive testing instruments from the PROMIS. Depression severity was measured by the PROMIS depression assessment, which has demonstrated validity and reliability across diverse clinical populations, including individuals with chronic pain.[45–47] Items in the PROMIS depression assessment use a 7-day time frame and a 5-point rating scale that ranges from 1 ("Never") to 5 ("Always"); the questions focus on affective and cognitive symptoms of

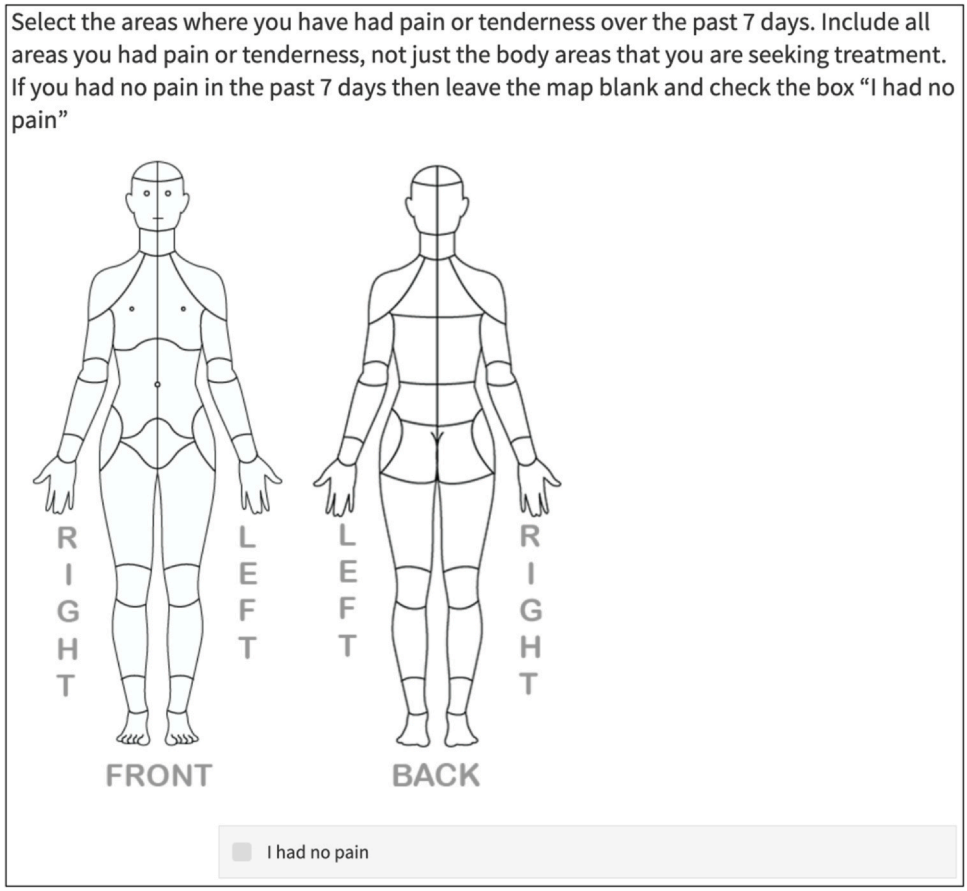

Figure 1. CHOIR body map. This digital body figure has 36 anterior segments and 38 posterior segments for patients to indicate areas of pain. Patients can also indicate that they have no pain. There are 2 versions of the body map representing male and female anatomy. Participants who identified as male or female were shown the corresponding body map, while those who chose "other" or preferred not to answer were provided the female body map.

depression rather than somatic symptoms such as fatigue and appetite changes. The PROMIS depression assessment generates a T-score, where a score of 50 indicates the mean (standard deviation [SD] 10), and higher scores indicate more severe depression symptoms.

Pain Intensity

Pain intensity was measured in CHOIR by using an 11-point NRS ranging from 0 ("no pain") to 10 ("pain as bad as it can be"). Participants were asked to rate their average pain intensity over the past 7 days, and this measure was used as a prespecified covariate in the analysis. NRS measures have been extensively used and demonstrate validity and reliability in chronic pain populations.[48]

Exploratory Pain-Related Functioning Measures

For exploratory analyses, the following PROMIS measures were included for their relevance to the pain experience: pain interference, pain behavior, fatigue, anxiety, sleep disturbance, anger, emotional support, social satisfaction, social isolation, and mobility. Computer Adaptive Testing administration was used to administer the PROMIS measures. This strategy utilizes the Computer Adaptive Testing item banks for each measure and uses information from prior questions to select future ones, which reduces administration time while increasing reliability and validity. T-scores are calculated and normed based on the U.S. population (M = 50, SD = 10). Higher scores indicate worse functioning, except for mobility and satisfaction with social roles, in which lower scores indicate worse functioning. All PROMIS item banks have been tested extensively in several chronic pain samples.[49–56] The Pain Catastrophizing Scale (PCS) was also included for exploratory analyses; the PCS is a 13-item self-report measure of pain catastrophizing, which refers to the tendency to magnify, ruminate over, and feel helpless in response to pain sensations.[57] Higher scores on the PCS indicate more pain catastrophizing. The PCS has demonstrated sound psychometric properties in chronic pain samples.[52,57,58]

Statistical Analysis

Descriptive analyses were conducted using SPSS (version 26.0; IBM Corp, Armonk, NY)[59] and all other analyses were conducted using RStudio (version 4.0.3; Posit, Boston, MA).[60] First, because the CHOIR body map automatically defaults to a female body map when the patient's sex is missing or reported as "unknown" or "prefer not to answer," we examined whether this feature may have influenced any key study variables. We used chi-square and analysis of variance (ANOVA) tests to determine if missingness, selecting unknown, or preferring not to respond was associated with differences in depression, average pain intensity, or pain location group. Significance tests were Bonferroni-corrected for multiple comparisons ($P = .008$). As a post hoc analysis, we also examined potential differences in demographic factors by pain laterality group to determine if there may be additional demographic confounders using ANOVA and chi-square tests, and significance tests were Bonferroni-corrected for multiple comparisons ($P = .0125$). Any demographic factors that are significant will be included as a covariate in the sensitivity analyses.

To examine whether depression varied as a function of pain location, a 2-way (Pain location group × PROMIS depression score) fixed ANOVA was used. Assumptions were assessed, including testing for variance homogeneity using Levene's test. Post hoc tests were used when examining > 2 groups. Cohen's *d* was calculated to measure the effect size (small = .2, medium = .5, large = .8).[61] An analysis of covariance (Pain location group × PROMIS depression score) with average pain intensity, pain interference, and any significant demographic factors as covariates to examine their potentially confounding impact on pain laterality and depression. Partial eta-squared was calculated as a measure of effect size (small = .01, medium = .09, large = .25).[62] A Bonferroni-corrected *P*-value of .00625 (.05/8) was used to determine statistical significance for the ANOVA and analysis of covariance. Next, within each pain location group, Pearson *r* correlations were conducted between the number of body regions endorsed on the CHOIR body map and the PROMIS depression score. A Bonferroni-corrected *P*-value of .00625 was used for Pearson's *r*.

For exploratory purposes, we ran four 11-way (Pain location group × 11 pain-related measures) multivariate analysis of variance to see if pain laterality may vary by other important physical, psychological, or social functioning measures. Partial eta-squared was used to measure of effect size. The Bonferroni-corrected $P = .0015$ (.05/33).

Sample Size Rationale

We justified the sample size for the confirmatory analysis based on the variance in the exploratory dataset. The SD of the PROMIS depression score in the exploratory dataset was 9.9 points, consistent with the SD of 10 in the general population for which this instrument is scaled on. In the exploratory dataset, 121 patients (10%) had pain restricted to the left side of the body, and 140 patients (12%) had pain restricted to the right side of the body. Using an allocation ratio of 1:10, a SD of 9.9 points for the outcome, a minimally important difference of 3 points,[46] and a 2-sided significance level of .05, we estimated that a minimum sample size of 950 is needed to achieve 80% power for the confirmatory analysis.

Results

Sample Characteristics

Sensitivity analyses showed no differences in study variables between those who had missing sex or selected unknown or prefer not to respond (and were thus automatically assigned the female body map; n = 57) compared to those who had selected male or female (χ^2's < .22, *P*'s > .80). The sample was primarily middle-aged (M = 52.5, SD = 17.1 years), female (65%),

Table 1. Full Sample Demographic Characteristics

MEASURE	N	MEAN (SD) OR %
Age	1,185	52.5 (17.1)
Sex		
Male	355	30%
Female	770	65%
Refused/Unknown*	60	5%
Race		
White	674	57%
Asian	103	9%
Black/African American	57	5%
Native Hawaiian/Pacific Islander	4	< 1%
Native American/Alaska Native	5	< 1%
Other	168	14%
Refused/Unknown*	174	15%
Ethnicity		
Hispanic/Latino	130	11%
Non-Hispanic/Latino	876	74%
Refused/Unknown*	179	15%
Marital status		
Never married/Living together	300	26%
Married	621	52%
Separated/Divorced/Widowed	250	21%
Refused/Unknown*	14	1%
Education		
Grade 11 or lower	70	6%
High school diploma/GED	98	8%
Some college, no degree	250	21%
Vocational/Associate degree	142	12%
Bachelors degree	313	26%
Masters or higher degree	293	25%
Refused/Unknown*	19	2%

GED, General Educational Diploma.
*Includes those who selected "prefer not to answer," "unknown," or had missing data.

White (57%), non-Hispanic (74%), married or living together (58%), and well-educated (51% had a Bachelor's degree or higher). See Table 1 for the demographic characteristics of the full sample. There were no significant differences in demographic characteristics by pain location group (all χ^2's > 15.55, all P's > .016, see Supplementary Table 1) except for age. Those with OL pain (M = 56.19, SD = 17.17) were older than those with any right-sided pain (M = 52.03, SD = 17.09; $F = 6.97$, $P = .008$). Those with OL pain were also older than those with bilateral pain (M = 51.49, SD = 16.95; $F = 7.40$, $P < .001$). Lastly, those with more right-sided pain and those with more left-sided pain were older than those with equivalent sides of pain (M = 48.40, SD = 17.59; $F = 20.03$, $P < .001$). There were no significant differences in age between those with OR pain and any left-sided pain ($F = 5.94$, $P = .015$).

Means and SDs of all study variables by pain location groups are in Table 2. Across the entire sample, depression scores were in the mild range (M = 53.0, SD = 10.1), average pain intensity in the moderate range (M = 5.9, SD = 1.9), and participants endorsed 12 painful body locations on average (excluding the head and neck regions; M = 11.7, SD = 11.5).

Table 2. Means and Standard Deviations of Study Variables by Pain Location Group

		COMPARISON 1		COMPARISON 2		COMPARISON 3			COMPARISON 4		
VARIABLE	ENTIRE SAMPLE	ONLY LEFT	ANY RIGHT	ONLY RIGHT	ANY LEFT	ONLY LEFT	ONLY RIGHT	BILATERAL	MORE LEFT	MORE RIGHT	EQUIVALENT SIDES
N	1,185	133	1,052	125	1,060	133	125	927	364	391	430
Depression	53.0 ± 10.1	51.1 ± 11.6	53.3 ± 9.8	50.6 ± 9.1	53.3 ± 10.1	51.1 ± 11.6	50.6 ± 9.1	53.7 ± 9.9	52.9 ± 10.1	53.0 ± 10.0	53.2 ± 10.0
Average pain	5.9 ± 1.9	5.7 ± 2.0	5.9 ± 1.8	5.7 ± 2.0	5.9 ± 1.8	5.7 ± 2.0	5.7 ± 2.0	6.0 ± 1.8	5.8 ± 1.8	6.1 ± 1.9	5.8 ± 1.8
Pain catastrophizing	21.7 ± 12.5	19.2 ± 13.4	22.0 ± 12.3	20.3 ± 12.1	21.8 ± 12.5	19.2 ± 13.4	20.3 ± 12.1	22.2 ± 12.4	20.7 ± 12.8	21.5 ± 12.4	22.6 ± 12.3
Number of pain locations	11.7 ± 11.5	4.3 ± 3.8	12.7 ± 11.8	4.2 ± 3.7	12.6 ± 11.8	4.3 ± 3.8	4.2 ± 3.7	13.8 ± 12.1	11.3 ± 10.3	11.5 ± 10.4	12.3 ± 13.4
Pain interference	64.6 ± 6.7	63.4 ± 6.9	64.7 ± 6.7	62.2 ± 6.9	64.8 ± 6.7	63.4 ± 6.9	62.2 ± 6.9	65.0 ± 6.6	64.7 ± 6.5	64.5 ± 6.8	64.5 ± 6.9
Pain behavior	59.0 ± 3.5	58.3 ± 3.8	59.1 ± 3.5	58.1 ± 3.4	59.1 ± 3.5	58.3 ± 3.8	58.1 ± 3.4	59.2 ± 3.5	59.0 ± 3.4	59.0 ± 3.4	59.0 ± 3.8
Fatigue	58.0 ± 10.3	54.3 ± 10.9	58.4 ± 10.2	53.1 ± 9.7	58.5 ± 10.2	54.3 ± 10.9	53.1 ± 9.7	59.1 ± 10.0	57.6 ± 10.1	57.9 ± 10.1	58.2 ± 10.8
Anxiety	54.1 ± 9.9	52.5 ± 11.4	54.3 ± 9.7	51.7 ± 8.5	54.3 ± 10.1	52.5 ± 11.4	51.7 ± 8.5	54.6 ± 9.8	54.1 ± 10.1	54.1 ± 9.9	54.1 ± 9.9
Sleep disturbance	56.6 ± 9.6	54.1 ± 8.8	56.9 ± 9.6	52.7 ± 9.3	57.0 ± 9.5	54.1 ± 8.8	52.7 ± 9.3	57.4 ± 9.5	56.9 ± 9.4	56.7 ± 9.6	56.2 ± 9.7
Anger	48.3 ± 10.3	47.8 ± 11.1	48.3 ± 10.2	46.0 ± 9.0	48.5 ± 10.4	47.8 ± 11.1	46.0 ± 9.0	48.6 ± 10.3	48.4 ± 10.0	48.3 ± 9.9	48.1 ± 10.8
Emotional support	51.8 ± 9.7	52.9 ± 9.4	51.6 ± 9.7	52.1 ± 9.8	51.7 ± 9.7	52.9 ± 9.4	52.1 ± 9.8	51.6 ± 9.7	51.7 ± 9.5	51.3 ± 9.9	52.3 ± 9.6
Satisfaction w/ social roles	42.0 ± 9.6	43.9 ± 10.0	41.8 ± 9.5	43.6 ± 9.7	41.8 ± 9.6	43.9 ± 10.0	43.6 ± 9.7	41.5 ± 9.5	41.8 ± 9.3	41.8 ± 9.3	42.4 ± 10.2
Social isolation	46.7 ± 9.5	45.7 ± 9.9	46.8 ± 9.3	44.0 ± 8.9	47.0 ± 9.5	45.7 ± 9.9	44.0 ± 8.9	47.2 ± 9.4	46.8 ± 9.6	46.6 ± 9.3	46.7 ± 9.5
Mobility	39.6 ± 8.8	40.5 ± 9.5	39.4 ± 8.7	41.0 ± 10.0	39.4 ± 8.6	40.5 ± 9.5	41.0 ± 10.0	39.2 ± 8.5	39.0 ± 8.2	38.7 ± 8.7	40.8 ± 9.2

NOTE. Data are presented as mean ± standard deviation. w/ = with

Differences in Depression by Pain Location

Results examining depression by pain location group are presented in Table 3, and the same models controlling for age, average pain intensity, and pain interference are presented in Supplementary Table 2. All Levene's tests were nonsignificant indicating homogeneity of variance across pain location groups. In comparison 1, we found no significant difference in depression scores between those with any right-sided pain (M = 53.3, SD = 9.8) and OL pain (M = 51.1, SD = 11.6). The effect size of this mean difference was small (Cohen's $d = .20$). When controlling for age, average pain intensity and pain interference, the pattern of results remained the same, and greater pain interference was associated with greater depression. Pearson r correlations indicated that a greater number of pain regions was associated with significantly greater depression scores among those with OL pain ($r = .27$, $P = .002$) and those with any right-sided pain ($r = .21$, $P < .001$).

In comparison 2, we found that those with any left-sided pain (M = 53.3, SD = 10.1) had significantly worse depression than those with OR pain (M = 50.6, SD = 9.1). The effect size of this mean difference was small (Cohen's $d = 29$). When controlling for age, average pain intensity, and pain interference, there was no longer a significant difference between the groups, and greater pain interference was associated with greater depression. Pearson r correlations indicated that a greater number of pain regions was associated with significantly greater depression scores among those with any left-sided pain ($r = .21$, $P < .001$), though it was not significant among those with OR pain ($r = .06$, $P = .48$).

In comparison 3, those with bilateral pain (M = 53.7, SD = 9.9) had significantly higher depression scores than those with OR pain (M = 50.6, SD = 9.1, $P = .004$). The difference between those with OL pain did not survive the Bonferroni correction (M = 51.1, SD = 11.6, $P = .02$). There were no significant differences in depression score between those with OL or OR pain ($P = .99$, Cohen's $d = .05$). The overall effect size was small ($\eta_p^2 = .02$). There was a small effect between bilateral pain and OR pain groups (Cohen's $d = .33$) and between bilateral pain and OL pain (Cohen's $d = .24$). When controlling for age, average pain intensity, and pain interference, there was no longer a significant difference between groups and greater pain interference was associated with greater depression. Pearson r correlations indicated that a greater number of pain regions was associated with significantly greater depression scores among those with bilateral pain ($r = .20$, $P < .001$).

In comparison 4, there were no differences in depression scores between those with more left-sided pain, more right-sided pain, and equal numbers of pain regions on both sides. The overall effect size of this difference was negligible ($\eta_p^2 < .01$). When controlling for age, average pain intensity, and pain interference, the pattern of results remained the same, and greater pain interference was associated with greater depression. Pearson r correlations indicated that greater number of pain regions was associated with significantly greater depression scores among those with more left-sided pain ($r = .22$, $P < .001$), more right-sided pain ($r = .25$, $P < .001$), and equal number of pain regions on both sides ($r = .19$, $P < .001$).

Differences in Other Pain-Related Functioning Outcomes

To assess whether pain laterality was associated with other important physical, psychological, or social factors, we conducted 4 11-way multivariate analysis of variances (Table 4). In comparison 1, we found that those with any right-sided pain had greater fatigue and sleep disturbance than those with OL pain. No significant differences in the other 9 functioning measures. In comparison 2, we found that those with any left-sided pain had greater fatigue, anxiety, sleep disturbance, and social isolation than those with OR pain. No significant differences in the other 6 functioning measures.

In comparison 3, we found the overall models for pain interference, pain behavior, fatigue, anxiety, sleep disturbance, and social isolation were significant. Post hoc

Table 3. Results of ANOVA Between Pain Location Groups and Depression Score

COMPARISON		SUM OF SQUARES	DF	MEAN SQUARE	F	P	EFFECT SIZE†
Comparison 1: Only left vs Any right	Between	553.85	1	553.85	5.50	.019	$d = .20$
	Within	119,052.95	1,183	100.64			
	Total	119,606.81	1,184				
Comparison 2: Only right vs Any left	Between	861.57	1	861.57	8.58	.003*	$d = .29$
	Within	118,745.24	1,183	100.38			
	Total	119,606.81	1,184				
Comparison 3: Only left vs Only right vs Mixed	Between	1,608.09	1	804.04	8.05	< .001*	$\eta_p^2 = .01$
	Within	117,998.72	1,183	99.83			
	Total	119,606.81	1,184				
Comparison 4: More left vs More right vs Equivalent sides	Between	25.36	1	12.68	.13	.88	$\eta_p^2 < .01$
	Within	119,581.45	1,183	101.17			
	Total	119,606.81	1,184				

*Significance based on $P < .00625$.
†Small effect size is $d > .2$ or $\eta_2^b > .01$, and medium effect size is $d > .5$ or $\eta_2^b > .09$.

Table 4. Results of MANOVA Between Pain Location Groups and 11 Pain-related Functioning Measures

	COMPARISON 1: ONLY LEFT VS ANY RIGHT			*COMPARISON 2: ONLY RIGHT VS ANY LEFT*			*COMPARISON 3: ONLY LEFT VS ONLY RIGHT VS BILATERAL*			*COMPARISON 4: MORE LEFT VS MORE RIGHT VS EQUIVALENT SIDES*		
VARIABLE	*F (DF)*	*P*	$H_p^{2\dagger}$	*F (DF)*	*P*	$H_p^{2\dagger}$	*F (DF)*	*P*	$H_p^{2\dagger}$	*F (DF)*	*P*	$H_p^{2\dagger}$
Pain Catastrophizing	5.74 (1)	.02	< .01	1.63 (1)	.20	< .01	4.11 (1)	.02	< .01	2.34 (1)	.10	< .01
Pain Interference	4.34 (1)	.04	< .01	17.78 (1)	< .001*	.02	12.41 (1)	< .001*	.02	.12 (1)	.89	< .01
Pain Behavior	6.69 (1)	.01	< .01	8.89 (1)	.003	< .01	8.93 (1)	< .001*	.02	.03 (1)	.97	< .01
Fatigue	18.98 (1)	< .001*	.02	31.35 (1)	< .001*	.03	29.31 (1)	< .001*	.05	.30 (1)	.74	< .01
Anxiety	3.86 (1)	.005	< .01	7.74 (1)	< .001*	< .01	6.59 (1)	.001*	.01	.001 (1)	.99	< .01
Sleep Disturbance	10.31 (1)	.001*	< .01	23.60 (1)	< .001*	.02	19.45 (1)	< .001*	.03	.45 (1)	.64	< .01
Anger	.30 (1)	.59	< .01	6.66 (1)	.10	< .01	3.71 (1)	.03	.01	.06 (1)	.93	< .01
Emotional Support	2.08 (1)	.15	< .01	.19 (1)	.66	< .01	1.23 (1)	.29	< .01	1.03 (1)	.36	< .01
Satisfaction w/ Social Roles	5.70 (1)	.02	< .01	3.65 (1)	.06	< .01	5.33 (1)	.005	.01	.40 (1)	.67	< .01
Social Isolation	1.77 (1)	.18	< .01	11.61 (1)	.001*	.01	7.38 (1)	.001*	.01	.03 (1)	.97	< .01
Physical function	1.60 (1)	.21	< .01	3.99 (1)	.05	< .01	3.15 (1)	.04	< .01	6.40 (1)	.002	.01

Abbreviations: MANOVA, multivariate analysis of variance; w/, with.
*Significance based on $P < .0015$.
†Small effect size is $\eta_p^2 > .01$, and medium effect size is $\eta_p^2 > .09$.

tests revealed that those with bilateral pain had greater pain interference than those with OR pain ($P < .001$), but did not survive Bonferroni correction when compared to OL pain ($P = .03$). OL and OR pain did not differ in pain interference levels ($P = .41$). The same pattern emerged for social isolation. Those with bilateral pain had worse fatigue and sleep disturbance than those with OR pain and OL pain (P's < .001). OL and OR pain did not differ in sleep disturbance or fatigue levels (P's > .71). Post hoc tests for anxiety and pain behavior did not survive correction indicating no significant mean differences between groups. Lastly, in comparison 4, there were no significant differences in any functioning measures between groups. Effect sizes across all group comparisons ranged from negligible to small (η_p^2 ranged < .01–.05).

Discussion

This study aimed to determine whether patients with left-sided chronic pain have more severe symptoms of depression in a real-world, clinical sample of adults with mixed-etiology chronic pain. Several comparisons were conducted to assess different iterations of pain laterality and ensure methodological rigor. Overall, none of the pain location groups resulted in significant differences in depression symptoms except for comparison 2 (any left vs OR pain), which was no longer significant after controlling for age, average pain intensity, and pain interference. Moreover, again except for the OR pain group, all other groupings demonstrated a positive correlation between the number of pain regions and depression scores, all of which demonstrated a consistently small effect size. Our results thus suggest that the intensity of depression does not depend on the laterality of pain and, therefore, does not support Maallo's lateralized pain-depression dyad model.[20] Instead, our findings show that the number of pain regions (regardless of laterality) was correlated with worse depression scores, consistent with previous findings that widespread pain is associated with worse outcomes, and specifically worse depression.[33,41–44]

To rigorously test the first hypothesis, that having left-sided pain will have more severe depression symptoms, we conducted 4 comparisons. The laterality model was partially supported in 1 of 4 comparisons, which showed that people with any left-sided pain (as compared to OR pain) had higher average depression scores, although this association was no longer significant after controlling for age, average pain intensity, and pain interference. The effect size of this difference was small, indicating limited clinical value. The laterality model was not supported when we examined the other comparisons, namely OL pain (as compared to any right-sided pain or bilateral pain) did not have significantly higher depression scores. Rather, we found that bilateral pain evidenced greater depression scores, suggesting that widespread pain may be more of an important risk factor for higher depression. Notably, much of the study sample (78%) reported bilateral pain

and exploratory analyses showed that bilateral pain was associated with several worse pain-related functioning measures, including pain interference, social isolation, fatigue, and sleep.

Noting the results of the first 3 comparisons were potentially affected by the differences in the number of patients in each group, comparing those with more left-sided body regions versus more right-sided versus equivalent-sided pain generated fairly equal size groups (n = 364, n = 391, n = 430, respectively). Consistent with prior study findings, depression scores did not differ between these groups, nor were there significant differences in any other pain-related functioning measures. Together, these findings do not support the pain and depression laterality model proposed by Maallo and colleagues,[20] and instead suggest that having widespread, bilateral pain may contribute to worse depression.

To test the second hypothesis, that more left-sided body regions affected by chronic pain are associated with more severe depression symptoms, we conducted correlation analyses within the various groupings between the number of regions in pain and depression scores. Across all analyses, the number of pain regions was associated with worse depression symptoms (r's = .19–.27), except among those with exclusively right-sided pain (r = .06, P = .48). Apart from this group, the correlation coefficients were fairly stable (averaging at r = .22). These results refute the proposition made by Maallo and colleagues[20] that left-lateralized pain would be associated with more depression. Again, this is in line with evidence in the literature that a more widespread pain distribution over the body is associated with a more severe clinical picture and worse prognosis.[33,41–44]

Overall, results do not reveal a consistent pattern to support the lateralized pain-depression dyad model[20] and contribute further evidence to the mixed literature on laterality. Prior work on pain conditions that involve lateralized symptom presentation shows equal frequency of pain occurring on either side, such as in migraine[7] and chronic regional pain syndrome.[8–10] These findings, in concert with the current work, suggest that pain in either the left or right side of the body can occur at the same rate and without significant differences in mental health symptoms. Finally, as cited by Maallo and colleagues, a literature review of "psychogenic pain"[11] (ie, pain without an identifiable medical cause) revealed the frequency of left-sided functional and motor symptoms was higher only in studies where references to laterality were featured in the title, and otherwise, laterality was not supported.

When we examined differences in other pain-related symptoms, including physical, psychological, and social factors, the findings were variable and did not evidence a consistent pattern with respect to laterality. Overall, bilateral pain evidenced worse pain interference, social isolation, fatigue, and sleep, although left-sided pain did not differ significantly on depression, pain interference, and social isolation. Patients with exclusively right-sided pain appeared to have the least functioning impairments, as evidenced by lower pain interference scores than those with only left or bilateral pain. However, all effect sizes across these comparisons and variables were negligible to small suggesting spurious results with very low clinical relevance. In our sensitivity analyses, across all pain location groups, higher pain interference was associated with worse depression consistent with prior work.[63] Although differences in age emerged by pain location group, age was not a significant predictor of depression scores.

Despite evidence from the experimental neuroimaging literature supporting potential shared laterality in the context of pain and depression,[1] clinical and experimental pain do not always share the same neural substrates,[15,16] and the same could be true of lateralization. This may be due in part to the emotional and autonomic reactions that are salient in pain conditions, which complicate the clinical presentation, and may also be associated with relatively small sample sizes in experimental and clinical studies. In addition, this heterogeneity may result from individual differences in the manifestations of pathology, in contrast to the controlled conditions of an experiment.

Our study has several limitations. First, the CHOIR body map may not accurately capture pain laterality. Prior examination of the body map psychometric properties[39] demonstrated excellent interclass correlations with other body map measurements and patient self-report, and excellent 1-week test-retest reliability (r = .93). While right and left labels were included (see Fig 1), it is possible that participants may have mislabeled right and left-sided pain locations contributing to potential measurement error. Additionally, the CHOIR body map does not assess pain severity in each location, which may be an important consideration when determining pain laterality. Future research using a more rigorous assessment of pain laterality that integrates pain frequency, intensity, and duration of each location is needed to confirm the current findings. Depression scores were self-reported and ranged mostly from minimal to moderate, suggesting a restricted range of scores potentially limiting the ability to detect differences between groups. However, a recent study found ≥53 on the PROMIS measure had good sensitivity and specificity in identifying those with a depressive disorder diagnosis as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[64] The current sample had an average PROMIS depression score of 53 (SD = 10.1), and despite scores being in the mild range, this suggests that, on average, participants had a probable presence of depressive disorder diagnosis. The collection of objective measures and clinical diagnostic interviews should be considered in future studies. Additionally, while not examined in the current study, it is possible that pain laterality may be associated with specific depression symptom clusters, and should be explored in future research.

Regarding generalizability, the study sample consisted predominantly of well-educated White women, limiting the findings applicability to other diverse patient groups and geographic locations. The current study also utilized cross-sectional data. It is possible that longitudinal associations between pain laterality, depression, and other functioning measures may exist and were not captured in our findings. Finally, while we did not find differences in pain

laterality assignment and sex, which is its own topic in the pain literature,[17–19] future studies should further explore the role of sex in pain laterality.[26]

Conclusions

In sum, the present work is the first study to examine the potential associations between pain laterality and depression within a large sample of real-world, treatment-seeking, mixed-etiology patients. A rigorous study design was used, which included preregistered hypotheses and analysis plan, replicating findings in exploratory and confirmatory datasets, and comprehensively grouping patients based on their individualized pattern of body regions in pain. Findings clearly indicate that the severity of depression and other pain-related outcomes is not dependent or associated with pain laterality, but rather, is more closely associated with a widespread distribution of pain across the body.

Disclosures

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Dr. Darnall is Chief Science Advisor at AppliedVR and she receives consulting fees for this role. Dr. Darnall receives royalties for 4 pain treatment books she has authored or coauthored. She is the principal investigator for 2 pain research awards from the Patient-Centered Outcomes Research Institute. Dr. Darnall is principal investigator for 2 NIH grants. Dr. Darnall serves on the Board of Directors for the American Academy of Pain Medicine, is on the Board of Directors for the Institute for Brain Potential, and is on the Medical Advisory Board for the Facial Pain Association. Dr. Darnall is a scientific member of the NIH Interagency Pain Research Coordinating Committee, a former member of the Centers for Disease Control and Prevention Opioid Workgroup (2020–2021), and a current member of the Pain Advisory Group of the American Psychological Association. All other authors have no conflicts of interest to disclose.

Appendix A. Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2024.02.004.

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