PSYCHOLOGY, PSYCHIATRY, IMAGING & BRAIN NEUROSCIENCE SECTION

Structural MRI Analysis of Chronic Pain Patients Following Interdisciplinary Treatment Shows Changes in Brain Volume and Opiate-Dependent Reorganization of the Amygdala and Hippocampus

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Abstract

Objective. The present study examined pre- to post-treatment changes in volumes for brain structures known to be associated with pain processing (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens) following an interdisciplinary pain management program. **Design.** Twenty-one patients participating in a four-week interdisciplinary pain management program completed the study. The program consisted of individual and group therapies with the following disciplines: physical therapy, occupational therapy, pain psychology, biofeedback/relaxation training, nursing lectures, and medical management. All patients underwent functional magnetic resonance imaging of the brain before the start and at completion of the program. They also completed standard outcome measures assessing pain, symptoms of central sensitization, disability, mood, coping, pain acceptance, and impressions of change. **Results.** Our results showed a significant increase in total brain volume, as well as increased volumes in the thalamus, hippocampus, and amygdala. As expected, we also found significant improvements in our standard outcome measures. The majority of patients rated themselves as much or very much improved. The increase in volume in the hippocampus was significantly associated with patient perceptions of change. However, the correlations were in the unexpected direction, such that greater increases in hippocampal volume were associated with perceptions of less improvement. Further exploratory analyses comparing patients by their opioid use status (use vs no use) showed differential program effects on volume increases in the hippocampus and amygdala. **Conclusions.** These findings show that a four-week interdisciplinary pain management program resulted in changes in the brain, which adds objective findings further demonstrating program efficacy.

Key Words: MRI; Chronic Pain; Interdisciplinary Pain Management

Introduction

Chronic pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. It affects >100 million US citizens [2]

with >\$500 billion in costs annually [2, 3]. Given that chronic pain encompasses both physical and emotional components, including depression, anxiety, catastrophizing, and passive coping, that interact with life stressors and social and financial reinforcement of pain behaviors to influence perceived pain and

disability [4], it presents a highly complex treatment target.

Effective treatment of such a complex target requires a comprehensive approach. Several recent national guidelines including the National Institutes of Health's National Pain Strategy and the Centers for Disease Control's opioid prescribing guidelines recognize the value of utilizing an "integrated, patient-centered plan of coordinated care managed by an interdisciplinary team" [5] to address the emotional and physical components of pain as these plans are effective [6–17], low-risk [11], and cost-effective [4, 7, 11, 18–20] means of improving pain [8–10, 14, 16, 17, 21], affective distress [9, 16, 22], and function [8–10, 14–16, 22] in the immediate and long-term [10, 23].

Treatment recommendations to address chronic pain using a biopsychosocial approach have been driven, in part, by recent advances in neuroimaging that have demonstrated the importance of central mechanisms of nociception, modulation, and neuroplasticity in patients with pain [24]. Research has helped elucidate changes in brain structure and function associated with chronic pain [25–28]. Taylor et al. [29] were among the first to show neuroplasticity related to neuropathic pain; they showed reductions in both gray and white matter in humans approximately one and a half years following surgical repair of upper limb peripheral nerve transection. Most often chronic pain is associated with global and local changes in gray matter properties involving volume, density, and thickness [25–27, 29–32]. Changes are localized to subcortical regions including the thalamus, amygdala, hippocampus, nucleus accumbens, caudate, putamen, and globus pallidus [30, 31, 33–37]. Furthermore, structural abnormalities have been found to correspond to poorer performance on indices of sensory recovery as well as other behavioral outcomes [29, 32].

Increases in gray matter volume have been observed in normal adults following only 45 minutes of repetitive sensory stimulation, demonstrating how rapidly neuroplasticity can occur [38]. This neuroplasticity can be leveraged through appropriate therapeutic interventions to improve alterations in brain structure and connectivity that have occurred in patients with chronic pain. Treatments of chronic pain, including surgery and injections for low back pain [39, 40], botulinum toxin for migraines [41], and acupuncture for fibromyalgia [42], have improved or partially normalized the brain abnormalities seen in chronic pain. Pediatric patients undergoing interdisciplinary and multidisciplinary treatment for complex regional pain syndrome have also demonstrated favorable changes in brain structure and function in direct response to this intervention [43, 44]. However, no similar studies have been conducted in adult patients undergoing interdisciplinary pain management treatment programs. This treatment approach focuses on therapeutic exercise, cognitive behavioral therapy, medication management, and development of effective coping

strategies to improve function by addressing the biological, physical, cognitive, affective, and behavioral components of pain [45]. Given this comprehensive approach targeting chronic pain at the central nervous system level, it is reasonable to expect at least a partial reversal of the characteristic brain changes observed in this population.

Not only is chronic pain a complex target to treat, but measuring success of an intervention can also be challenging. There is no widely accepted objective metric by which improvements in interdisciplinary pain management treatment programs can be quantified. The current standard is to collect patient self-reported measures and performance-based testing of physical function; however, these fail to provide a full understanding of the mechanisms underlying changes in response to treatment and do not capture the global impact of the intervention on the intended target in these programs—the brain. Although brain neuroimaging is not intended to replace self-reporting of pain, it can complement it by improving understanding of neural mechanisms of treatment, potentially leading to more targeted treatment approaches, and can help validate and provide insight into conclusions drawn from self-report [24, 46].

The purpose of this study was to examine changes in volumes for subcortical brain structures known to be associated with pain processing and show morphological reorganization with chronic pain (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens) following a four-week interdisciplinary pain management program and correlate these changes with patient-reported impression of change to explore how these two approaches may complement each other to generate a global assessment of treatment effects. It was hypothesized that gray matter brain volume would increase as a result of neuronal plasticity in response to treatment in a four-week interdisciplinary pain management program and that these changes would correlate with traditionally reported outcomes. Additionally, exploratory analyses were done to determine if results differed in subjects taking opioid medications.

Methods

Subjects

Twenty-five subjects were recruited from an outpatient pain management center at an academic standalone rehabilitation center (Figure 1). Potential subjects were a heterogeneous group of chronic pain patients who were scheduled to begin a four-week (8 h/d, M–F) intensive interdisciplinary pain management program. The program included group and individual pain psychology (e.g., pain cycles, cognitive restructuring), relaxation/biofeedback (e.g., diaphragmatic breathing), physical therapy (PT; conditioning), occupational therapy (OT; pacing), and medical management. Treatment sessions were scheduled for seven hours each day. Patients in the

program receive on average 100–110 hours of treatment over the four weeks, which is typically divided equally among PT, OT, and psychology (including biofeedback). We always try to make the ratio of group-to-individual treatments 1:1 (50% of each). Inclusion criteria included English speaking, stable health, between the ages of 18 and 75, and pain intensity rating $>5/10$. Exclusion criteria included potential for secondary gain (active litigation related to pain, disability claim, or worker's compensation) that could result in less patient engagement and effort put into the program, neurological disorder (e.g., seizures, Parkinson's disease, stroke, etc.), unstable medical condition (diabetes mellitus, congestive heart failure, malignancy), history of or current substance abuse/dependence (including alcohol and opioids), intra-axial implants (e.g., spinal cord stimulators or pumps), exclusion for magnetic resonance (MR) safety (any metallic implants, brain or skull abnormalities, tattoos on large body parts, and claustrophobia), and pregnancy or inability to use an effective form of contraception in women of child-bearing age.

There was a 16% (four subjects) dropout rate (two withdrew from the treatment program and two were discharged early). The final sample ($N=21$) was predominantly female (76%), with a mean age (SD) of 49.3 (15.2) years and mean pain duration (SD) of 8.5 (11.0) years. The most frequent primary pain diagnosis was chronic low back pain (38%). Thirty-eight percent of the final sample ($N=8$) were actively using opioid pain medications. Compared with non-opioid users, they had been in pain for a significantly longer period ($t_{19} = 2.532$, $P = 0.020$). Participant characteristics are presented in Table 1. This study was reviewed and approved by the local university's institutional review board (IRB), and all data collection and management were conducted according to the IRB-approved protocol, the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996.

Figure 1. Flow diagram of the patient sample.

Measures

Pain

Numeric Rating Scale (NRS). This is an 11-point pain intensity rating scale. The scale ranges from 0 (no pain) to 10 (worst pain imaginable). The NRS is a well-validated measure of pain intensity [47, 48].

Patient Impression of Change

Multidimensional Patient Impression of Change (MPIC) [22]. The MPIC is a measure designed to assess patient impressions of change over seven clinical domains in addition to overall status. The seven clinical domains include overall pain, sleep, mood, physical functioning, ability to cope with pain, ability to manage pain flare-ups, and effectiveness of medication. Each item is rated on a scale from 1 to 7 (with 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse). The internal consistency for the MPIC in the current study was good, at $\alpha = 0.91$.

Depression

Center for Epidemiologic Studies Depression Scale (CES-D 10) [49]. The CES-D 10 consists of 10 nonsomatic symptoms of depression. Each item is rated on a scale ranging from 0 (rarely or none of the time/less than one day) to 3 (most or all of the time/five to seven days) for the past week. The measure has adequate reliability (test-retest, $r = 0.71$) and good predictive validity among those with chronic pain [49, 50]. The internal consistency for the CES-D in the current study was $\alpha = 0.87$.

Pain-Related Anxiety

Pain Anxiety Symptoms Scale (PASS-20) [51]. The PASS-20 assesses pain-related anxiety and yields four subscale scores (cognitive, escape, fear, physiological). Items are assessed on a six-point scale ranging from 0 (never) to 5 (always). The measure has good internal consistency (mean $\alpha = 0.81$), construct validity, and predictive validity [51]. The internal consistency for the current study was good (mean $\alpha = 0.82$, range = 0.74–0.90).

Pain-Related Symptoms (Central Sensitization)

Central Sensitization Inventory (CSI) [52]. The CSI assesses health-related symptoms associated with central sensitivity syndrome-related disorders. The measure includes 25 somatic (e.g., headaches, muscle stiffness, digestive problems) and emotional symptoms (e.g., depression, anxiety, stress), which are rated on a five-point scale ranging from 0 (never) to 4 (always). The CSI has good psychometric properties (test-retest $r = 0.82$ and internal consistency $\alpha = 0.88$). The internal consistency for the CSI in the current study was $\alpha = 0.80$.

Table 1. Patient characteristics

Variables	Completers (N = 21)	Nonopioid (N = 13)	Opioid User (N = 8)
Age, mean $\pm$ SD, y	49.33 (15.2)	50.92 (17.2)	46.75 (11.97)
Pain duration, mean $\pm$ SD, y	8.5 (11.0)	4.2 (3.73)	15.3 (15.3)*
Sex (F), No. (%) female	16 (76.2)	9 (69.2)	7 (87.5)
Primary diagnosis (F), No. (%)			
Chronic low back pain	8 (38.1)	3 (23.1)	5 (62.5)
Rheumatological	6 (28.6)	4 (30.8)	2 (25.0)
Chronic neck pain	3 (14.3)	3 (23.1)	0 (0)
Lower extremity	2 (9.6)	1 (7.7)	1 (12.5)
Neuropathic	1 (4.8)	1 (7.7)	0 (0)
Pelvic	1 (4.8)	1 (7.7)	0 (0)

* $P < 0.05$.

Pain Acceptance

Chronic Pain Acceptance Questionnaire (CPAQ) [53]. The CPAQ assesses the degree to which a patient is accepting of their chronic pain. The scale includes 20 items assessed on a seven-point scale ranging from 0 (never true) to 6 (always true). It yields a total score and two subscale scores (activity engagement and willingness) with distinct contributions [54]. The measure has adequate reliability ($\alpha = 0.78$ – 0.82). The internal consistency for the current study was good (activity engagement $\alpha = 0.85$, willingness $\alpha = 0.85$).

Coping with Pain

Coping Strategies Questionnaire–Revised (CSQ-R) [55]. The CSQ-R assess the frequency at which patients use a variety of coping strategies. The measure consists of 27 items that are rated along a seven-item scale, ranging from 0 (never do that) to 6 (always do that), yielding six subscale scores (distraction, catastrophizing, ignoring, distancing, cognitive coping, praying). The CSQ-R scores have adequate reliability ($\alpha = 0.74$ – 0.88). Two subscales were used in the current study (cognitive coping and catastrophizing), representing adaptive and maladaptive coping strategies. The internal consistency for the subscales in the current study was good (cognitive coping $\alpha = 0.79$ and catastrophizing $\alpha = 0.97$).

Pain-Related Disability

Pain Disability Index (PDI) [56]. The PDI assesses perceived disability among seven areas of patient functioning (family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activity). Each item is rated along a 0 (no disability) to 10 (total disability) scale and then summed to yield a total score. The measure has good internal consistency ($\alpha = 0.87$) and is a reliable and valid measure of pain-related disability [57, 58]. The internal consistency for the PDI in the current study was $\alpha = 0.84$.

Scan and Anatomical Data Acquisition

High-resolution T1-weighted brain images were collected using integrated parallel imaging techniques (PAT;

GRAPPA) representing receiver coil-based data acceleration methods. The acquisition parameters were isometric voxel size = $1 \times 1 \times 1$ mm, TR = 2,300 ms, TE = 2.40 ms, flip angle = 9° , acceleration factor of 2, base resolution 256, slices = 176, and field of view (FoV) = 256 mm. The encoding directions were from anterior to posterior, and the time of acquisition was five minutes 21 seconds.

Image Processing

Volumetric analyses of T1-weighted images were performed through automated processes using FSL (version 5.0.8). We investigated volume differences in all subcortical nuclei including thalamus, putamen, pallidum, caudate, amygdala, and hippocampus. After using FSL's brain extraction tool (BET) to remove the skull from all images, FSL's integrated registration and segmentation tool (FIRST) was utilized to segment these specific subcortical regions and extract their volume measurement [59]. Due to the small sample size, subcortical region sizes were summed for both the right and left hemisphere. All subcortical regions were manually checked for aberrant segmentations. In addition, we checked for outliers for each subcortical region using Tukey's fences method [60]. Outliers were identified as any observation outside the range of $(Q_1 - k(Q_3 - Q_1), Q_3 + k(Q_3 - Q_1))$, where Q_1 is the lower quartile, Q_3 is the upper quartile, and $k = 1.5$. There were no outliers in our data.

Changes in total gray volume following treatment were assessed using SIENA in FSL (version 5.0.8). SIENA computes subject-wise percent brain volume change (PBVC) between two input images at different points in time. It utilizes a series of FSL routines to strip the non-brain tissue from the two images (BET), register the two brains under the constraint that the skulls are used to hold the scaling constant during the registration, and estimate the brain change between the two time points (two-time-point percent brain volume change was estimated with SIENA [61], part of FSL [62]).

Statistical Analyses

Before analyses, all variables were inspected for outliers, which were defined as $z = \pm 3.29$. There were no

outliers detected for any of the psychometric variables. Using Tukey's fences method (described above), no outliers were detected for changes in brain volumes. However, using the criteria of $z = \pm 3.29$, one outlier was detected, which was for percent change in volume in the thalamus. Therefore, analysis on this variable was conducted with and without the outlier. Descriptive statistics were used to describe the results of the MPIC. One-sample t tests were conducted to assess average percent change (pretreatment to post-treatment) in total brain volume as well as for each anatomical structure. Then zero-order Pearson correlations were used to assess the relationships between patients' impressions of change, with anatomical structures shown to have changes in brain volume following program completion. The statistical significance level was set at $P < 0.05$ for all analyses. However, due to the large number of correlational analyses, significance was also reported utilizing two commonly used multiple-comparisons corrections: the conservative Bonferroni and the more lenient false discovery rate (FDR) corrections. Exploratory mixed-model analyses of variance were used to examine for difference between opioid users and nonusers by treatment time. Due to the significant difference in pain duration between the two groups, pain duration was entered as a covariate in the analyses. Statistical analyses for behavioral measures, including t tests, Pearson correlations, and mixed-model analyses of covariance, were conducted using PASW Statistics 18.0.

Results

Psychometric Outcomes

Following the program, patients showed significant physical improvements with statistically significant reductions in pain (NRS), disability (PDI), and pain-related symptoms associated with central sensitization (CSI). Emotionally, patients endorsed significantly fewer symptoms of depression (CES-D 10) and pain-related anxiety (PASS-20) following program completion. Patients reported a statistically significant reduction in the use of a maladaptive coping strategy (CSQ-R catastrophizing) but no increase in the use of an adaptive coping technique (CSQ-R coping, $P = 0.426$). They did show significant improvements in their acceptance of chronic pain, with increases in both their activity engagement and willingness to experience pain. Please see Table 2 for outcome details.

Summary of MPIC

Examination of responses per each MPIC domain (Table 3) shows that some improvement (minimally improved to very much improved) was perceived by the majority of the patients, ranging from 67% to 100% among all domains. Furthermore, more than half ($\geq 52\%$) of the patients perceived themselves as much improved or very

much improved in all but two of the clinical domains, with greatest frequencies occurring for cope with pain and overall status (both 76%). The two exceptions were for medication effectiveness (43%) and pain (48%). Correlations among the MPIC domains ranged from $r = 0.23$ to $r = 0.89$.

Associations of Outcome Measures with MPIC

The correlations between the outcome measures and the MPIC domains were all in the expected directions (Table 4). That is, reductions in distress were associated with greater levels of perceived improvements (negative correlations), and increases in pain acceptance and adaptive coping were associated with greater levels of perceived improvements (positive correlations). There were several statistically significant correlations. Seven of the eight MPIC domains (all but sleep) significantly correlated with at least one outcome measure. MPIC-pain correlated with pain intensity, MPIC-physical functioning correlated with pain intensity and disability, MPIC-mood correlated with willingness to experience pain, MPIC-cope with pain correlated with central sensitization, MPIC-manage flare-ups correlated with central sensitization, MPIC-medication effectiveness correlated with pain-related anxiety, and MPIC-overall status correlated with pain intensity and central sensitization.

Volume Changes in Brain and Anatomical Structure

Average volumes for all right and left subcortical regions before (visit 1) and after (visit 2) treatment are displayed in Table 5. Due to the small sample size, subcortical region sizes were summed for both the right and left hemispheres, and changes in subcortical volume were computed as percent changes, $100 * (\text{volume 2} - \text{volume 1}) / \text{volume 1}$, with positive numbers indicating increased volume following treatment, while negative numbers indicated decreased volume. We observed significant increases in volume for several of the anatomical structures: thalamus (with the outlier, $t [20] = 2.099$, $P = 0.049$; without the outlier, $t [19] = 1.980$, $P = 0.062$), hippocampus ($t [20] = 2.601$, $P = 0.017$), and amygdala ($t [20] = 2.937$, $P = 0.008$). There was trend toward a significant increase for the pallidum ($t [20] = 1.891$, $P = 0.073$), and the remaining structures (caudate, putamen, and accumbens) did not show significant changes in volume (all $t \leq 1.248$, all $P \geq 0.226$) (Figure 2). In addition, there were statistically significant increases in total brain volume (average percent change) following treatment ($t [20] = 4.779$, $P \leq 0.001$). We also explored laterality effects and laterality treatment interaction for each subregion using a repeated-measures analysis of variance. Overall, there were no laterality effects (all $P > 0.31$) or laterality treatment interaction (all $P > 0.25$). Therefore, these results justify averaging volumes across hemispheres.

Table 2. Program outcome descriptions (means and standard errors) and statistics

Outcome	Initial	Discharge	Δ Score	T Score
Pain intensity (NRS)	6.71 (0.40)	4.76 (0.49)	−1.95 (0.51)	3.799**
Disability	41.47 (2.99)	25.62 (3.29)	−15.91 (1.82)	8.756**
Central sensitization	50.81 (2.63)	41.04 (2.83)	−10.76 (1.65)	6.527**
Depression	15.62 (1.47)	8.90 (1.17)	−6.71 (1.25)	5.363**
Pain-related anxiety	52.33 (4.33)	29.14 (3.07)	−23.19 (4.69)	4.944**
Catastrophizing	13.50 (1.54)	6.93 (1.20)	−6.56 (1.22)	5.384**
Cognitive coping	12.45 (0.78)	13.34 (0.72)	+0.89 (0.75)	−1.191
Activity engagement	31.57 (2.23)	42.90 (1.88)	+11.33 (2.14)	−5.292**
Pain willingness	17.24 (1.79)	23.43 (1.74)	+6.19 (2.17)	−2.852*

NRS = numeric rating scale.

* $P < 0.05$;** $P < 0.01$.**Table 3.** MPIC response rates

MPIC Rating	Overall Status, %	Pain, %	Sleep, %	Mood, %	Physical Function, %	Cope with Pain, %	Manage Flare-ups, %	Med. Effect, %
1 = very much improved	33.3	19.0	19.0	23.8	19.0	23.8	28.6	19.0
2 = much improved	42.9	28.6	42.9	38.1	33.3	52.4	41.1	23.8
3 = minimally improved	19.0	33.3	14.3	28.6	42.9	23.8	28.6	23.8
4 = no change	4.8	14.3	23.8	9.5	4.8	0	0	23.6
5 = minimally worse	0	4.8	0	0	0	0	0	4.9
6 = much worse	0	0	0	0	0	0	0	0
7 = very much worse	0	0	0	0	0	0	0	0

Table 4. Pearson correlations of MPIC domains with psychometric outcomes

Outcome	Overall Status	Pain	Sleep	Mood	Physical Function	Cope with Pain	Manage Flare-ups	Med. Effect
Reductions								
Pain	−0.44*	−0.52*	−0.39	−0.15	−0.44*	−0.21	−0.41	−0.23
Sensitization	−0.53*	−0.34	−0.39	−0.24	−0.27	−0.48*	−0.46*	−0.23
Disability	−0.21	−0.18	−0.34	−0.18	−0.63**†‡	−0.20	−0.30	−0.37
Depression	−0.11	−0.10	−0.34	−0.12	−0.07	−0.20	−0.16	−0.27
Pain anxiety	−0.35	−0.37	−0.43	−0.39	−0.19	−0.09	−0.29	−0.49*
Catastrophize	−0.33	−0.24	−0.28	−0.31	−0.20	−0.12	−0.35	−0.26
Increases								
Act. engagement	0.42	0.41	0.41	0.41	0.22	0.31	0.43	0.37
Willingness	0.33	0.20	0.21	0.46*	0.33	0.22	0.36	0.34
Cognitive cope	0.18	−0.05	0.30	0.40	0.14	0.22	0.25	0.14

MPIC = Multidimensional Patient Impression of Change.

* $P < 0.05$;** $P < 0.01$.†False discovery rate correction ($Q < 0.05$).‡Bonferroni correction ($P < 0.00625$).

Associations of Volume Changes with Patients' Impressions of Change

The relationships of the anatomical structures (including whole brain) that showed significant increases in volume following treatment with patient impressions of change were examined. The hippocampus was significantly correlated with responses on all eight domains of the MPIC (all $r = 0.47$ – 0.66 , all $P < 0.05$) (Figure 3). Greater levels of perceived improvement were associated with smaller increases in hippocampal volume. MPIC domains did not significantly correlate with volume changes in the amygdala (all $r = -0.14$ to -0.40 , all $P > 0.05$), thalamus (all r

$= 0.10$ to 0.42 , all $P > 0.05$), or whole brain (all $r = -0.14$ to 0.12 , all $P > 0.05$).

Psychometric Outcomes by Opioid Use Status

Both groups (opioid users and nonusers) showed significant reductions in pain ($t [7] = 3.987$, $P = 0.005$; $t [12] = 2.243$, $P = 0.045$), disability ($t [7] = 4.822$, $P = 0.002$; $t [12] = 7.184$, $P < 0.001$), symptoms of central sensitization ($t [7] = 5.877$, $P = 0.001$; $t [12] = 4.618$, $P = 0.001$), depression ($t [7] = 3.137$, $P = 0.016$; $t [12] = 4.211$, $P = 0.001$), pain-related anxiety ($t [7] = 3.280$, $P \leq 0.013$; $t [12] = 3.589$, $P = 0.004$), and catastrophic

Figure 2. Mean percent change in brain volumes. Following participation in an intensive four-week interdisciplinary pain management program, subjects showed a significant increase in whole-brain volume ($M = 0.39$, $P < 0.001$). Subjects had significantly increased volumes in the amygdala ($M = 4.17$, $P < 0.01$), hippocampus ($M = 2.78$, $P < 0.05$), and thalamus ($M = 0.79$, $P < 0.05$). Error bars represent ± 1 standard error.

Table 5. Subcortical volumes (c.c.) before (visit 1) and after (visit 2) treatment

Region	Visit 1, Mean $\pm$ SEM	Visit 2, Mean $\pm$ SEM
Right thalamus	7.356 $\pm$ 0.211	7.416 $\pm$ 0.215
Left thalamus	7.305 $\pm$ 0.162	7.365 $\pm$ 0.169
Right caudate	3.409 $\pm$ 0.101	3.406 $\pm$ 0.101
Left caudate	3.382 $\pm$ 0.069	3.382 $\pm$ 0.076
Right putamen	4.693 $\pm$ 0.162	4.698 $\pm$ 0.156
Left putamen	4.653 $\pm$ 0.125	4.661 $\pm$ 0.122
Right pallidum	1.752 $\pm$ 0.068	1.776 $\pm$ 0.071
Left pallidum	1.741 $\pm$ 0.059	1.763 $\pm$ 0.060
Right hippocampus	3.840 $\pm$ 0.145	3.949 $\pm$ 0.156
Left hippocampus	3.805 $\pm$ 0.112	3.912 $\pm$ 0.121
Right amygdala	1.283 $\pm$ 0.056	1.329 $\pm$ 0.052
Left amygdala	1.278 $\pm$ 0.058	1.324 $\pm$ 0.053
Right accumbens	0.481 $\pm$ 0.023	0.494 $\pm$ 0.026
Left accumbens	0.476 $\pm$ 0.020	0.489 $\pm$ 0.023

SEM = standard error of the mean.

thinking (t [7] = 3.329, $P \leq 0.013$; t [12] = 4.062, $P = 0.002$). Both groups showed increased activity engagement (t [7] = -4.242, $P = 0.004$; t [12] = -3.485, $P = 0.005$). Opioid users did not show increased willingness to experience pain (t [7] = -1.478, $P = 0.183$), whereas the nonopioid users did (t [12] = -2.379, $P \leq 0.035$). The pre- to post-treatment change scores were similar between the two groups for all but one of the outcomes. Opioid users showed a greater reduction in symptoms of central sensitization than nonopioid users ($M = -15.75$ vs -7.69). Please see Table 6 for descriptions and group statistics.

MPIC Ratings by Opioid Use Status

Opioid users perceived themselves to have had greater levels of improvement on all MPIC domains compared with nonopioid users (Figure 4). However, only the difference for the sleep domain met statistical significance (t [19] = 2.564, $P = 0.019$), whereas pain, mood, and

overall status trended toward significance (all $P = 0.65$ – 0.180).

Volume Changes in Whole-Brain and Anatomical Structures by Opioid Use Status

The average percent increase in total brain volume was greater for nonopioid users ($M = 0.51$) compared with opioid users ($M = 0.21$), which trended toward statistical significance (t [19] = 1.855, $P = 0.079$). Examination of pre- vs post-treatment volumes in the thalamus by opioid use status showed neither a significant interaction (F [1, 18] = 0.003, $P = 0.956$, partial $\eta^2 = 0.000$) nor a significant treatment main effect (F [1, 18] = 3.838, $P = 0.066$, partial $\eta^2 = 0.176$). However, there was a significant group main effect, with the opioid users having overall greater volume in the thalamus than the nonopioid users (F [1, 18] = 8.054, $P = 0.011$, partial $\eta^2 = 0.309$). For the amygdala, there was a significant treatment main effect (F [1, 18] = 9.716, $P = 0.006$, partial $\eta^2 = 0.351$) with increased volume following treatment. Furthermore, there was a significant interaction whereby those taking opioids showed a greater increase in volume for the amygdala than nonopioid users (F [1, 18] = 6.151, $P = 0.023$, partial $\eta^2 = 0.255$). The group main effect was nonsignificant (F [1, 18] = 0.053, $P = 0.821$, partial $\eta^2 = 0.003$) (Figure 5). For the hippocampus, the group main effect was not significant (F [1, 18] = 0.604, $P = 0.447$, partial $\eta^2 = 0.032$), and there was a trend for the treatment main effect (F [1, 18] = 4.119, $P = 0.057$, partial $\eta^2 = 0.186$). The interaction was statistically significant, with nonopioid users showing a greater increase than opioid users (F [1, 18] = 5.332, $P = 0.033$, partial $\eta^2 = 0.229$) (Figure 6).

Morphine Equivalence

Although not a primary outcome in the study, we compared pre- and postprogram morphine equivalences

Figure 3. Scatter plots of correlations of percent change in hippocampal volume with postprogram ratings on the Multidimensional Patient Impression of Change. *Significance with and without false discovery rate correction ($P < 0.05$, $Q < 0.05$). †Significance with Bonferroni correction ($P < 0.00625$).

Table 6. Program outcome change scores by opioid use status

Outcome	Opioid Users (N = 8), Mean (SE)	Nonusers (N = 13), Mean (SE)	T Score
Pain intensity (NRS)	-2.38 (0.60)**	-1.69 (0.75)*	-0.635
Disability	-16.38 (3.40)**	-15.62 (2.17)**	-0.219
Central sensitization	-15.75 (2.63)**	-7.69 (1.67)**	-0.230*
Depression	-7.13 (2.27)*	-6.46 (1.53)**	-0.251
Pain-related anxiety	-24.00 (7.32)*	-22.69 (6.32)**	-0.132
Catastrophizing	-6.94 (2.08)*	-6.33 (1.56)**	-0.235
Activity engagement	+13.00 (3.07)**	+10.31 (2.96)**	0.601
Pain willingness	-5.13 (3.47)	-6.85 (2.88)*	-0.377

NRS = numeric rating scale; SE = standard error.

* $P < 0.05$;

** $P < 0.01$.

(MEQs) for the opioid use group. The postprogram mean MEQ ($M = 34.75$, $SE = 10.65$) was significantly lower than the preprogram MEQ score ($M = 76.94$, $SE = 14.51$; $t [7] = 2.981$, $P = 0.020$). The mean change in MEQ scores was not significantly correlated with any of the psychometric outcomes (all $r = 0.107$ – 0.657 , all $P \geq 0.077$), MPIC ratings (all $r = 0.043$ – 0.448 , all $P \geq 0.238$), or volumetric changes (all $r = 0.025$ – 0.108 , all $P \geq 0.799$).

Discussion

To our knowledge, this is the first study to examine the impact of an interdisciplinary pain management program on volumetric brain changes in adults with chronic pain. We found significant changes in brain morphology following participation in an interdisciplinary pain

management program in our adult population. More specifically, we found significant volumetric increases in the whole brain as well as in several anatomical structures (amygdala, hippocampus, and thalamus). There is only one other study that has explored the effects of interdisciplinary pain management on the brain; it was conducted on pediatric pain patients. Comparisons of the brain networks in a sample of pediatric patients with complex regional pain syndrome (CRPS) with those of matched controls detected several differences (increases and decreases) in connectivity within the salience, central executive, right and left fronto-parietal, sensorimotor, and default mode networks before treatment [43]. The age-matched controls displayed no changes in brain networks from the first to second scan; however, many of the

Figure 4. Mean ratings on the Multidimensional Patient Impression of Change by opioid use status. Lower values represent greater levels of perceived improvement. Participants taking opioid medications had average postprogram ratings ranging from 1.63 to 2.38, while the ratings of participants not taking opioids ranged from 2.15 to 3.0. The opioid patients perceived their level of improvement on the sleep domain ($M = 1.75 \pm 0.37$) to be significantly better ($*P < 0.05$) than those not taking opioid medications ($M = 2.85 \pm 0.25$). Error bar = ± 1 standard error.

Figure 5. Amygdala volume change by opioid use. A) The average increase in percent volume change was greater for patients on opioids ($M = 7.75\%$, $SE = 2.68$) compared with those not on opioids ($M = 1.96\%$, $SE = 1.33$). Error bar = ± 1 standard error. B) Significant interaction shows the differential treatment effect.

Figure 6. Hippocampus volume change by opioid use. A) The opioid group demonstrated a small reduction in hippocampal volume ($M = -0.55\%$, $SE = 0.67$), whereas the nonopioid group showed a significantly greater increase in volume ($M = 4.83\%$, $SE = 1.41$). Error bar = ± 1 standard error. B) Significant interaction shows the differential treatment effect.

pretreatment differences between the CRPS patients and controls subsided following an intensive interdisciplinary pain management program. We added to these findings by showing the impact of interdisciplinary pain management on the brains of adult pain patients.

Previous studies have consistently observed morphological changes in the central nervous system across several types of chronic pain (for a review, see [63]). Originally, these changes were thought to be primarily associated with age-related gray matter atrophy [64]. However, as gray matter changes can exhibit partial reversal following effective therapy, this theory has been challenged [39]. Although the cellular mechanisms underlying morphological changes remain unclear, it has been suggested that changes in the number of glial cells might account for gray matter volume changes in the basal ganglia [65]. Furthermore, it has been hypothesized that neuro-inflammation, especially microglial activation, may play a critical role in abnormal gray matter changes and maintenance of gray matter volume [66, 67]. Perhaps the most accepted hypothesis is that the brain morphological changes observed in chronic pain patients might represent neuronal plasticity [68]. We think that the volumetric changes observed in the current study may reflect neuronal plasticity in response to a myriad of changes within nociceptive and pain-modulatory brain circuitry stimulated through participation in the interdisciplinary treatment program.

Changes in brain volumes differed significantly by opioid use status. In the pediatric population, significant differences in neuroanatomical brain volumes have been found in children with prenatal opioid exposure compared with age-matched controls [69]. Children with

prenatal opioid exposure had significantly smaller basal ganglia, thalamus, and cerebellar white matter. In the present study, our sample of adult opioid users had an overall larger volume in the thalamus compared with nonopioid users. These conflicting findings could possibly be due to age-related and neuroanatomical developmental differences in the cohorts used in the two studies. Previous adult population studies have shown opioid use to be associated with smaller amygdala volumes [70, 71]. In one of these studies, non-chronic pain patients who were classified with opioid dependency had significantly smaller amygdala volumes than did a matched sample of healthy controls [70]. In another study, Younger et al. [71] compared the effects of morphine on the brains of opioid-naïve chronic low back patients compared with CLBP patients receiving a placebo. One month after the initiation of morphine, six weeks after the pretreatment scan, follow-up imaging showed several regions with increased gray matter, and there were significant volumetric reductions in both the amygdala and the hippocampus. Greater morphine doses correlated with larger reductions in volumes in the amygdala, but not in the hippocampus. Although morphine use did not continue beyond the one-month protocol, the effects of morphine on the brain volumes were maintained at follow-up nearly five months later. There were no pre to post significant differences in imaging for the patients who received placebo. In our study, we showed that patients on opioids had a significant increase in amygdala volume following one month of interdisciplinary pain management, which was not associated with reduction in MEQ. This rapid change in volume following such a short period in opioid users demonstrates the robust impact of interdisciplinary treatment on the brain.

The impact of interdisciplinary pain management appears, at least in this study, to have differential effects on the brain based on current opioid use status. While opioid users showed significant volumetric increases in the amygdala, nonopioid users showed a significant increase in the hippocampus. Although not statistically significant, the hippocampal volumes were greater for the opioid users pre- and post-treatment. This finding contradicts Younger et al.'s finding that chronic pain patients administered an opioid had decreased hippocampal volume compared with a matched sample of pain patients on placebo. Even if the nonopioid users in the current study had prior opioid experience and maintained a decreased hippocampal volume from prior use, we would not expect it to be lower than for those actively taking opioids during the study. Furthermore, even if the doses from possible prior use in nonopioid patients had been greater than what was being taken by the opioid users in the current study, Younger et al. showed that morphine doses did not correlate with changes in volume. Thus, it is unclear why the interdisciplinary pain management program had differential effects on brain volume in opioid users vs nonusers, especially since both anatomical

structures are part of the drive-reward learning process. Additional, well-controlled studies are needed to further clarify this.

Consistent with our previous studies examining program outcomes, the patients in the current study showed improvements on all but one outcome, and they reported improvements among multiple clinical domains of the MPIC, including pain, sleep, mood, physical functioning, coping with pain, managing pain flare-ups, and the effectiveness of their medications [22, 72, 73]. Opioid users showed a greater reduction in symptoms of central sensitization than nonopioid users, and they also tended to rate themselves higher in terms of levels of improvement than did the nonopioid users, but only the rating for sleep significantly differed by opioid usage. The patient-reported improvements assessed by the MPIC were correlated in the expected directions with behavioral outcome measures. However, all the domains on the MPIC correlated negatively with changes in hippocampal brain volume, such that higher levels of perceived improvements were associated with smaller increases in volume. This finding is opposite to what we expected. This could perhaps be supported by the findings that the nonopioid users showed a greater increase in hippocampal volume, but somewhat lower overall ratings of improvement on the MPIC.

Limitations

There are some limitations to the current study. First, there was no randomization, as the patients recruited into the study were patients who had enrolled in the interdisciplinary pain management program based on clinical evaluation, need, and recommendation. Second, the sample was diagnostically heterogeneous, and use of medications including both opioids and nonopioids (e.g., antidepressant and antiseizure medications) was not controlled for. Lastly, the sample size was small; however, both the overall and subgroup samples in the current study are comparable to those reported in the Younger et al. and Upadhyay et al. studies [70, 71].

Conclusions

Despite these limitations, this study adds to the current literature by showing significant increases in brain volumes following participation in a four-week interdisciplinary pain management program in an adult chronic pain population. At least some of these changes were associated, albeit in the opposite direction to that expected, with perceived patient improvements. Furthermore, this study shows differential effects based on opioid use status, and thus we suggest that future brain imaging studies specifically focus on opioid use and response to interdisciplinary pain management. Moreover, the findings of this study lend objective support to program effectiveness

beyond improvements that have been traditionally demonstrated via subjective self-report measures.

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