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### Wired for pain, shaped by the mind

*Interactions between pain and psychopathology in pediatric and adult patient populations*

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# CHAPTER 7

A MULTIDISCIPLINARY ASSESSMENT OF PAIN IN JUVENILE  
IDIOPATHIC ARTHRITIS

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# A MULTIDISCIPLINARY ASSESSMENT OF PAIN IN JUVENILE IDIOPATHIC ARTHRITIS

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SEMINARS IN  
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## **Abstract**

**Introduction:** Pain is prevalent in juvenile idiopathic arthritis (JIA). Unknowns regarding the biological drivers of pain complicate therapeutic targeting. We employed neuroimaging to define pain-related neurobiological features altered in JIA.

**Methods:** 16 male and female JIA patients ( $12.7 \pm 2.8$  years of age) on active treatment were enrolled, together with age- and sex-matched controls. Patients were assessed using physical examination, clinical questionnaires, musculoskeletal MRI, and structural neuroimaging. In addition, functional magnetic resonance imaging (fMRI) data were collected during the resting-state, hand-motor task performance, and cold stimulation of the hand and knee.

**Results:** Patients with and without pain and with and without inflammation (joint and systemic) were evaluated. Pain severity was associated with more physical stress and poorer cognitive function. Corrected for multiple comparisons, morphological analysis revealed decreased cortical thickness within the insula cortex and a negative correlation between caudate nucleus volume and pain severity. Functional neuroimaging findings suggested alteration within neurocircuitry structures regulating emotional pain processing (anterior insula) in addition to the default-mode and sensorimotor networks.

**Conclusions:** Patients with JIA may exhibit changes in neurobiological circuits related to pain. These preliminary findings suggest mechanisms by which pain could potentially become dissociated from detectable joint pathology and persist independently of inflammation or treatment status.

### **Key words:**

Juvenile idiopathic arthritis, Pain, Inflammation, Voxel-based morphometry, Functional magnetic resonance imaging, Musculoskeletal, Anterior Insula, Caudate

## Introduction

Juvenile idiopathic arthritis (JIA) is a cluster of inflammatory articular diseases affecting children and adolescents 16 years of age or younger<sup>1,2</sup>. The cardinal features of JIA, which are often the focus of treatment, include joint swelling, stiffness, and tenderness. Other detrimental elements of the disease frequently experienced by patients, such as malaise, fatigue and, importantly, pain, are more difficult to quantify and treat. Such intangible symptoms may not be amenable to the clinical attention necessary for optimal treatment<sup>3</sup>. Indeed, despite the broad range of available therapeutic approaches, including disease-modifying anti-rheumatic drugs (DMARDs) and a rapidly expanding list of biologic response modifiers (BRMs)<sup>4-6</sup>, JIA pain remains a complex, multifaceted and often poorly treated process that adversely impacts numerous domains of the child's well-being (e.g., physical functioning and emotional health)<sup>7-11</sup>. Moreover, pain in JIA may not only negatively impact the health related- quality of life (HR-QoL) during childhood years, but pain may have negative implications into and throughout adulthood<sup>12-17</sup>. Such data point to the long-lasting impact that JIA, specifically JIA pain, may have on a developing and perhaps vulnerable nervous system, and stress the importance of an aggressive focus on mitigation of JIA pain early in its presentation<sup>18</sup>. This task, unfortunately, remains challenging as many unknowns regarding the clinical, behavioral, and biological drivers of arthritis-related pain confound optimal therapeutic approaches.

No single marker can encapsulate the status of a patient with JIA, and so several domains make up the American College of Rheumatology (ACR) JIA core set<sup>19</sup>. Factors quantified in this measure include the number of actively affected joints, the number of joints with decreased motion, humoral measures of inflammation (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)), patient global assessment, and physician global assessment. Pain, as experienced by children with arthritis, may indeed

impact several domains of the ACR JIA core set. Moreover, since the core set does not have a separate measure of pain, the effect that pain has on a patient is artificially subsumed within, for example, joint inflammation and acute phase reactants. Per force, therapeutic strategies which improve CRP levels or inflamed joints will seem to effectively treat pain as well. However, in JIA patients for whom pain is not correlated with core set domains, even a minimal amount of joint pathology may coincide with a robust pain phenotype that is resistant to DMARDs, BRMs, or poly-therapeutic approaches.

Additionally, just as uncontrolled joint inflammation in arthritis may result in irreversible damage to bone and cartilage, festering pain can lead to altered nociceptive processing, peripheral or central sensitization, and intractable amplified pain<sup>18, 20</sup>. This latter phenomenon of a 'primed system' is supported by recent observations of high pain sensitivity in JIA relating to a prior history of active arthritis rather than the sole presence of joint inflammation<sup>16, 21-23</sup>. Thus, a better understanding of the biological, clinical and pathophysiological aspects of pain in various JIA states is necessary to improve recognition, monitoring and targeting of pain, ultimately leading to more effective treatment strategies.

Considering the imperfect association between pain and joint pathology in JIA, our goal in this hypothesis generating study is to evaluate patients' subjective and objective experience with arthritis and pain, in order to gain insights into components of pain. To elucidate pain mechanisms in JIA, we performed a multidisciplinary, pilot investigation of JIA patients on active treatment. The cornerstone of our strategy consisted of a novel probing of central nervous system (CNS) pain circuitry with structural and functional magnetic resonance imaging (fMRI). Scans were performed in JIA patients during resting- and evoked- (hand motor task performance and cold pain stimulation) states. The study design also consisted of an evaluation of musculoskeletal joints using physical examination and non-contrast MRI. In addition, the subject and parent or guardian completed questionnaires primarily from the Patient-Reported Outcomes Measurement Information System (PROMIS) database<sup>24</sup>. This approach allowed us to test our hypothesis

that pain in JIA patients, independent of inflammatory status, will be underpinned by altered neurocircuitry regulating affective and sensorimotor elements of pain. Here, in addition to reporting imaging-based findings, we describe individual JIA cases with a focus on pain symptomatology reported during the patients' clinical course.

## **Material and Methods**

### Study participants

This investigation was approved by the Boston Children's Hospital (BCH) Institutional Review Board and met the Helsinki criteria for the study of human subjects. JIA patients were recruited from the Rheumatology Program, Division of Immunology, at BCH. Prior to participation, each participant and a parent or legal guardian were given a detailed overview of study procedures before providing informed written assent and/or consent. The study enrolled 16 patients between 8 - 16 years of age (11 females; 5 males) with a diagnosis of JIA (**Table 1**). All patients were on active treatment at the time of enrollment and had prior or ongoing symptoms in hand and wrist joints. The majority of patients also reported symptoms outside of the hand or wrist, usually knee or ankle joints.

### Clinical questionnaires

A battery of pediatric clinical questionnaires derived from the PROMIS database (<http://www.healthmeasures.net>) was utilized to capture patient reported levels of:

- (i.) pain intensity (0-10 numerical rating scale), where 0 is no pain and 10 is the worst pain imaginable,

- (ii.) pain behavior (external manifestations of pain),
- (iii.) quality of pain (i.e., sensory & affective elements),
- (iv.) anxiety,
- (v.) depressive mood,
- (vi.) psychological stress,
- (vii.) cognitive function,
- (viii.) physical activity,
- (ix.) physical stress, and
- (x.) strength impact.

Each PROMIS questionnaire assessed pain and other symptoms in the past seven days. Parents or guardians of JIA patients also completed the Adult Response to Children's Symptoms (ARCS) questionnaire<sup>25</sup>. The 29 items of ARCS were used to determine the parent's or guardian's behaviors in response to the child's pain. Study participants also provided demographic data (age and gender). Each ARCS question was scored on a five-point Likert scale (Never: 0 to Always: 4). Parents or guardians also completed the Childhood Health Assessment Questionnaire (CHAQ), which informed on the child's physical limitations, disability, pain severity and quality of life.

#### Imaging Data Acquisition

Nine of the 16 enrolled JIA patients, as well as 13 healthy controls (HCs) matched for age, gender and handedness underwent MRI procedures. Each JIA patient (N=9) completed both neuroimaging (~45 minutes) and non-contrast musculoskeletal MRI (~30 minutes), while HCs solely underwent neuroimaging. JIA patients were taken out of the scanner and given a 10-minute break between non-

contrast, musculoskeletal MRI and neuroimaging procedures. Eight JIA patients (N=8) underwent non-contrast, musculoskeletal MRI of the hand and wrist joint, while one patient (Patient 12) completed parallel imaging procedures of the knee as well as radiographic imaging of the back. Patient 12 noted experiencing more pain and other symptoms in the knee and back during her study evaluation, and therefore those regions were probed with musculoskeletal imaging. All MRI procedures were performed on a Siemens 3T TRIO scanners (Siemens, Erlangen, Germany) and using a 4-channel flex coil for hand-wrist MRI, 15-channel coil for knee MRI and 32-channel head coil for neuroimaging.

*Musculoskeletal MRI:* Multiplanar Musculoskeletal MRI data was performed to identify potential bone erosion, cartilage degradation, joint space narrowing, bone marrow edema, soft tissue edema, joint fluid, synovitis and tenosynovitis. The following sequences were performed in each scan session.

*Turbo spin-echo T1-weighted MRI:* TR/TE = 575ms/14ms; Coronal plane

*Fast spin-echo (FSE) T2-weighted MRI:* Time of Repetition/Echo Time (TR/TE) = 5500ms/50ms; Axial plane

*Short-TI Inversion Recovery (STIR) MRI:* TR = 4500ms/27ms; TI = 220ms; Axial and coronal planes

*3D Double Echo Steady State (DESS) MRI:* TR/TE = 14ms/5ms; Flip angle = 25°; Coronal plane

*Fast spin-echo (FSE) Proton Density MRI:* TR/TE = 2200ms/35ms; Axial and sagittal planes

*Neuroimaging:* A combination of structural and functional neuroimaging was performed. High-resolution anatomical MRI data was collected using a multi-echo magnetization-prepared rapid acquisition with gradient echo (MPRAGE) using the following parameters: 1 mm isotropic, TR/TE1/TE2/TE3/TE4 = 2.53s/1.69ms/3.55ms/5.41ms/7.27ms, BW=650Hz/Px, 160 slices. Total scan time = 5:23 min. fMRI data

were collected during the resting-state (eyes-open) as well as during task-based and evoked stimulation conditions (JIA patients only). Resting-state fMRI data were collected using a gradient echo-echo planar pulse sequence with  $3.0 \times 3.0 \times 3.0 \text{ mm}^3$  resolution. fMRI scan parameters: TR = 1100 ms, TE = 30 ms, field of view (FOV) =  $228 \times 228$ , FA =  $70^\circ$ , Axial Slices = 51. Parallel fMRI scan parameters were used for task-based and evoked stimulation fMRI; however, a TR of 2000 ms was implemented.

To probe movement-evoked, CNS responses in JIA patients alone, fMRI data were collected during a unilateral hand-motor task. Individuals first completed a training session outside of the MRI environment, where the task was explained and performed by the subject. While in the scanner, study participants were visually cued to open and close the symptomatic hand in a 30/10 sec off/on manner for five cycles. The task was performed using the left hand as patients had previous or ongoing symptoms in both hands or the left hand. Cold stimuli or environments can often trigger pain and other symptoms in JIA patients. In prior work involving quantitative sensory testing (QST), we observed that JIA patients may demonstrate pain hypersensitivity to cold stimuli within a symptomatic joint and in disease-free anatomical locations (e.g., thenar eminence)<sup>23</sup>. Thus, during fMRI acquisition, cold stimuli ( $10^\circ\text{C}$ ) were applied to hand-wrist and knee joints in a 30/10 sec off/on manner (Medoc LTD, Israel). Stimuli were delivered using a  $1.6 \times 1.6 \text{ cm}^2$  thermode and applied to the dorsum of the hand-wrist joints and in a region where patients reported pain. For JIA patients in remission, cold stimuli were applied to hand-wrist regions with prior symptom presentation. In order to explore if differences in CNS responses to cold stimuli are specific to the hand or if they expand to other parts of the body, we applied the same cold stimuli to the knee joint (ipsilateral to the stimulated hand-wrist joint). At the end of each cold stimulation fMRI scan, a verbal pain rating was obtained.

### Questionnaire Analyses

For each JIA patient, the summed raw scores obtained from PROMIS-based questionnaires were converted to a T-scores. Higher scores indicated worse symptom severity (i.e., affective pain quality) or greater capability (i.e., cognitive function). During the assessment of clinical questionnaire data, JIA patients (N=6) were sub-divided into low (Pain Level: 0 - 3/10) and high (Pain Level:  $\geq 4$ ) pain groups. Statistical comparisons between low and high pain patients were performed using a two-tailed t-test ( $\alpha = 0.05$ ). Spearman's rank correlation coefficients were also calculated to explore the association between self-reported pain intensities and each PROMIS-based measure.

#### Imaging Data Analyses

*Musculoskeletal MRI:* Each musculoskeletal MRI dataset was clinically evaluated by a board-certified pediatric radiologist with musculoskeletal imaging expertise at BCH (KE). The presence or absence of bone marrow edema, osseous erosions, joint space narrowing, synovitis/joint fluid, and tenosynovitis was determined on a binary scale. Joint fluid/synovitis was evaluated as a combined entity given that contrast was not administered during data acquisition.

*Neuroimaging:* Using FreeSurfer, we performed a volumetric analysis in order to determine inter-group differences in cortical thickness and sub-cortical volume. Processing steps included (a.) motion correction, (b.) removal of non-brain tissue, (c.) automated Talairach transformation, (d.) segmentation of the subcortical white matter and deep grey matter volumetric structures, (e.) intensity normalization, (f.) tessellation of the grey matter/white matter boundary, (g.) automated topology correction, (h.) surface deformation, (i.) registration of the subjects' brains to a common atlas and (j.) cortical parcellation to set atlas<sup>26,27</sup>. To determine cortical thickness difference within the insula cortex subdivision, the Destrieux Atlas was utilized<sup>28</sup>. The subdivisions included the long insular gyrus and central sulcus of the insula, short

insular gyri, anterior segment of the circular sulcus of the insula, inferior segment of the circular sulcus of the insula, and superior segment of the circular sulcus of the insula. Individual structural maps were resampled into MNI space, followed by fitting higher-level general linear model (GLM) with a Monte Carlo simulation cluster analysis (10,000 iterations) to achieve a cluster-corrected threshold of  $p < 0.05$ . Subsequently, for the cortical thickness and sub-cortical volumes that are calculated and normalized to the whole brain volumes, statistically significant differences between the study groups are assessed.

A whole-brain region-of-interest (ROI)-to-ROI resting-state functional connectivity analysis was performed with the CONN-fMRI toolbox v18.b in conjunction with Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). Preprocessing included: functional realignment, slice-time corrected, spatially normalized to the Montreal Neurological Institute (MNI) space using the normalized echo planar image (EPI) template image in SPM, and spatially smoothed with a 5-mm full-width half-maximum Gaussian kernel. Motion parameters from realignment were evaluated, and a motion artefact threshold (translation  $> 0.9$  mm, rotation  $> 1^\circ$ ) was employed for exclusion<sup>29</sup>. No participants displayed gross movements to require exclusion. Blood-oxygen-level-dependent (BOLD) data were bandpass filtered (0.008–0.09 Hz) to reduce low-frequency drift and noise effects. Individual correlation maps were generated in the CONN toolbox by extracting the mean resting-state BOLD time course from each seed ROI and calculating correlation coefficients with the BOLD time course of each voxel throughout the whole brain. The resulting coefficients were converted to normally distributed scores using Fisher's transformation to give maps of voxel-wise functional connectivity for each seed ROI for each subject. All regions of interest were extracted as part of the pre-loaded CONN toolbox and represent regions outlined in the FSL Harvard-Oxford Atlas and AAL atlas for cerebellar regions. A statistical comparison ( $p < 0.001$ , uncorrected) of resting-state functional connectivity at the ROI and network level among JIA patients and healthy controls was then performed.

FSL version 6.0.1 FEAT was used to apply a hierarchical fMRI general linear model (GLM) to evoked fMRI data to assess CNS functionality during hand-motor task performance and cold stimulation. Preprocessing steps followed those described for resting-state fMRI data. For first-level analysis, a voxel-wise GLM analysis was used to characterize the BOLD response. The BOLD response corresponding to the stimulation paradigm (off-on, boxcar function) will be modeled using explanatory variables (EVs) convolved with a gamma function (3 secs standard deviation and 6 secs hemodynamic lag). In group-level, fixed-effects comparisons, t-test results for each voxel were converted to Z scores and thresholded to  $Z > 3.1$  ( $p < 0.001$ ) and a cluster significance threshold of  $p = 0.05$ . Statistical maps denoting significant activation were superimposed on the MNI152 template brain. ROI level assessments were also performed in order to further inform on activation at the single patient level or determine associations between fMRI and other study measures. Here, subject-specific, parameter estimate values were extracted and averaged across study cohorts or conditions. ROIs were defined using the Harvard-Oxford subcortical & cortical structural atlases.

## Results

### Patient Overview

The present study enrolled and evaluated 16 JIA patients (mean age  $\pm$  SD:  $12.7 \pm 2.8$  years) experiencing a range of clinical pain severity (mean pain severity  $\pm$  SD (0-10 scale):  $3.19 \pm 2.59$ ) (**Table 1**). The majority of patients were female (N=11) and diagnosed with polyarticular JIA. Patients varied based on their inflammatory status (ESR and CRP) and disease severity (see clinical Juvenile Disease Activity Score (cJADAS) score<sup>30</sup>). The cJADAS consisted of a physician visual analog scale (VAS), patient VAS and total joint count with each max at 10, yielding a total maximum score of 30. No significant correlations among pain, ESR or JADAS scores were observed ( $R = -0.12$  to  $0.49$ ). A trend in correlation between clinical pain

severity and ESR levels (N=13; R = 0.49, P = 0.09) was calculated. With exception to one polyarticular JIA case (Patient 16), all patients were treated with a DMARD (methotrexate or leflunomide), BRM (adalimumab, infliximab or secukinumab) or combination therapy (e.g., methotrexate + adalimumab) at the time of enrollment. Patient 16 was treated with naproxen.

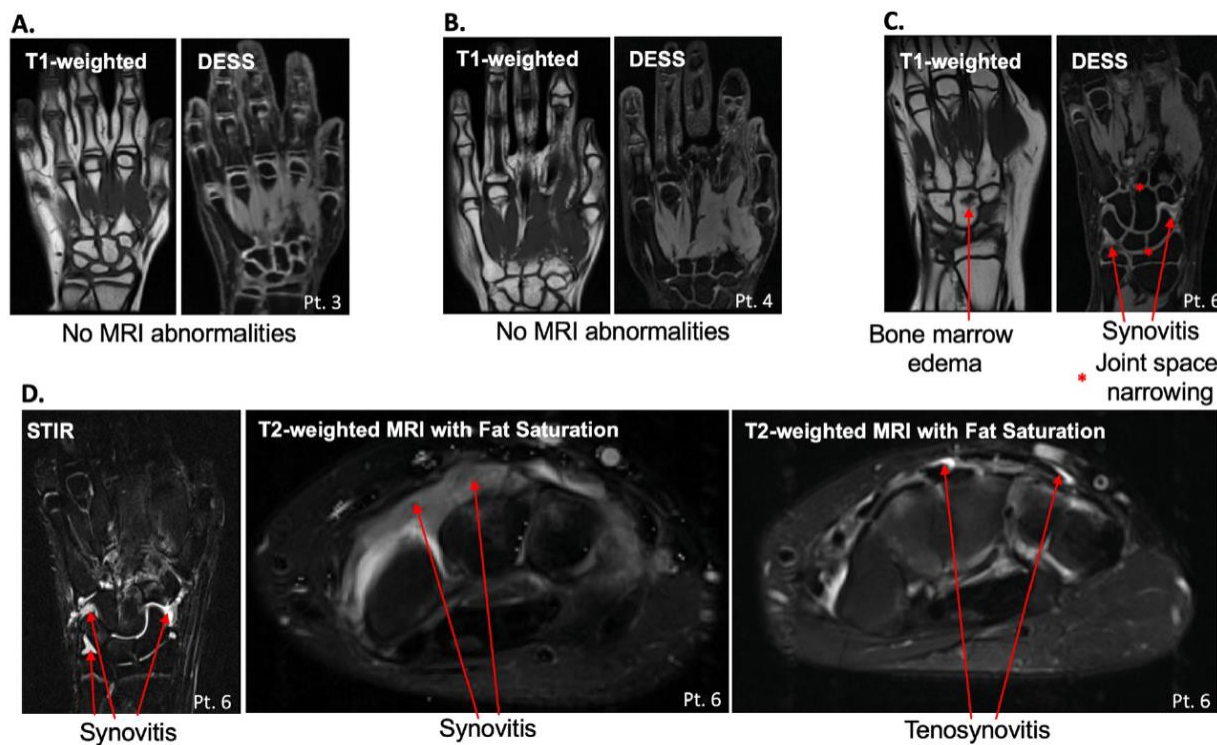
In the majority of patients (N=7), multiplanar and multisequence MRI scan revealed normally appearing soft tissue and healthy extensor and flexor tendons. In **Figure 1**, MRI data from Patients 3 and 4 are provided as examples of JIA patients presenting with no MRI abnormalities. Presence of fluid in tendon sheaths was not detected. These patients also demonstrated a lack of definite joint space narrowing, joint effusion, or synovitis. Alignment of the hand, wrist or knee joint (Patient 12, data not shown) was similarly preserved.

#### Clinical Vignettes

Below, clinical courses for four JIA patients are highlighted with a focus on pain, joint stiffness, and inflammation.

*JIA Patient 3 (Remission):* Patient 3 (9-year-old female; **Table 1**) presented in 2012 at 2 years of age with bilateral knee arthritis. At the time, she would often limp and walk with a stiff gait, especially in the morning or after a nap. She was seen in the BCH Rheumatology Clinic in February of 2012 and diagnosed with ANA positive oligoarticular JIA. She was initially treated with intra-articular steroid injections of the knees. Unfortunately, her arthritis extended to involve her wrists, elbows, knees, left hip, and ankles. She was started on methotrexate and then etanercept was added. By 2015, the patient's pain and arthritis were well-controlled, and her medications were decreased. In the setting of the medication wean, her arthritis flared, and recapturing remission was difficult. She was trialed on multiple medications including

etanercept and leflunomide and then leflunomide, methotrexate, and adalimumab. She required an intra-articular hip injection in 2017. By 2019, she entered remission again. The patient remains on leflunomide and adalimumab and did not experience any pain, stiffness or other symptoms during the study evaluation. MRI of the hand revealed no signs of joint pathology (**Figure 1A**).



**Figure 1: Hand and wrist musculoskeletal MRI.** At the time of neuroimaging evaluation, multiplanar musculoskeletal MRI revealed that while Patients 3 and 4 had no MRI abnormalities (**A-B**), Patient 6 (**C-D**) displayed multiple pathological features. Patient 6 showed synovitis, tenosynovitis, bone marrow edema, and joint-space narrowing in hand and wrist joints. As reported in **Table 1**, CRP and ESR levels were normal for Patients 3 and 4 but elevated in Patient 6 (CRP: 0.09 mg/dL & ESR: 24 mm/hr), further confirming non-inflammatory vs. inflammatory status.

*JIA Patient 4 (Pain + No Inflammation):* Patient 4 (15-year-old female; **Table 1**) initially presented to BCH Rheumatology Clinic in June 2018 with joint pain, joint swelling and morning stiffness in her hands and knees. Symptoms were present since December 2017. At this time, the patient was also diagnosed with ulcerative colitis. She was being treated with infliximab and 6-mercaptopurine when she was initially seen

in the BCH Rheumatology Clinic. She reported improvement on infliximab treatment but still had swelling, decreased range of motion and tenderness particularly in her right hand and right knee. She had normal inflammatory markers, namely ESR and CRP, as well as negative rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody. Given the distribution of her joint involvement, she was diagnosed with seronegative polyarticular JIA. Her treatment was switched from 6-mercaptopurine to methotrexate. In October 2018, she had resolution of her arthritis except for persistent pain and arthritis of the third metacarpophalangeal (MCP) joint. She received an intraarticular steroid injection in her third MCP by interventional radiology, but did not experience improvement. In February 2019, as she was still symptomatic, her methotrexate was switched to injection form and the dose was increased. In June 2019, she had swelling and tenderness in multiple joints of her right hand, her infliximab dose was increased, and she was recommended to start doing aerobic exercises to decrease the overall pain sensation. In September 2019, she still had pain and tenderness in her hand that did not resolve despite another intraarticular steroid injection by interventional radiology and switching from weekly methotrexate injections to daily leflunomide. During the time of study evaluation, the patient was treated with a combination of methotrexate and infliximab. While there was tenderness to palpation over the (MCP) and proximal interphalangeal (PIP) joints, MRI of the hand revealed no signs of joint pathology (**Figure 1B**).

*JIA Patient 6 (Pain + Inflammation):* Patient 6 (12-year-old male; **Table 1**) initially presented in June 2018 with morning stiffness and pain in his knees, shoulders, feet, hands, wrists, and fingers. The joint pain caused him to have difficulty using staircases and opening bottles. He was first seen in the BCH Rheumatology Clinic in December 2018, where he was noted to have arthritis of his shoulders, wrists, knees, left hip, and temporomandibular joint (TMJ). His labs were notable for elevated ESR and CRP, along with positive RF and anti-CCP antibody. He was diagnosed with seropositive polyarticular JIA and was

started on methotrexate and prednisone but did not achieve complete disease remission and required intra-articular steroid injections of both knees. He was started on etanercept in March 2019 but still had evidence of active arthritis at multiple metatarsophalangeal (MTP), MCP, and distal interphalangeal (DIP) joints. Because he did not improve, he was switched to adalimumab every two weeks. At a follow-up visit in April 2019, he was noted to have some improvement on adalimumab but still had active arthritis and pain in his wrists and MCPs. During the time of study evaluation, the patient was treated with a combination of methotrexate and adalimumab.

Hand/wrist MRI in patient 6 revealed synovitis/joint fluid, tenosynovitis, bone marrow edema, and joint space narrowing (**Figure 1C-D**). Subchondral bone marrow edema was evident in carpal and metacarpal bones of the left hand. Mild narrowing of the carpal-metacarpal joint spaces, alongside synovial hypertrophy of intercarpal joints, carpal-metacarpal joints, and dorsal recesses were observed. Fluid/synovial thickening were detected in multiple extensor tendon compartments. Soft-tissue structures remained preserved.

*JIA Patient 12 (Pain + Inflammation):* Patient 12 (16-year-old female; **Table 1**) initially presented to BCH Rheumatology Clinic in September 2007 at 4 years of age for evaluation of left knee arthritis that was first noted in June 2007. After negative Lyme disease tests, she received intermittent courses of naproxen and ibuprofen without resolution of her arthritis. Patient 12 was later diagnosed with polyarticular JIA with enthesitis. She was started on sulfasalazine, which did provide some improvement in her knee synovitis. She had no arthritis by November 2008 and her sulfasalazine was discontinued. However, by November 2009, she was noted to have a return of her morning stiffness, as well as evidence of a small left knee effusion. She was prescribed meloxicam, which had limited therapeutic benefit. Her symptoms continued to worsen and by January 2010, she was experiencing more diffuse morning stiffness, and she was

restarted on sulfasalazine. This did provide some relief, and the patient was later tapered off sulfasalazine. By March 2012, she was again experiencing morning stiffness and pain. She was prescribed topical diclofenac and celecoxib for use as needed. The patient did achieve remission between 2012 and 2015; however, her symptoms worsened and by April 2015, she was noted to have right ankle arthritis and was prescribed naproxen. Her symptoms continued to worsen with involvement of her left ankle and left TMJ by July 2015. She was started on oral methotrexate and prednisolone that provided limited relief. Patient 12 was completely tapered off methotrexate by February 2016. However, by December 2018, her arthritis was worsening with evidence of decreased interincisal opening of her jaw and flexion contracture of both elbows with some left elbow tenderness and was prescribed naproxen and topical diclofenac. The latter treatment approach did not provide enough relief and by January 2019, she had evidence of TMJ arthritis with persistent decreased interincisal opening, along with synovitis at her left elbow, left sacroiliac joint, bilateral ankles, and bilateral Achilles tendonitis. Starting in February 2019, Patient 12 received adalimumab treatment every 2 weeks. In September of 2019, the patient remained symptomatic as she experienced relief from joint discomfort and pain shortly after adalimumab administration, but the therapeutic effects waned over the course of a 10-day period. She reported pain in her jaw, back, elbow, hands, knees, and ankles, which worsened after activity (e.g., writing, chewing, standing or walking). She continued to require intermittent use of ibuprofen to alleviate joint pain. During the time of study enrollment and neuroimaging evaluation, the patient reported moderate to high levels of pain in the sacroiliac joints and paravertebral muscles of the spine. However, there was no definite radiographic sclerosis or subchondral erosion along the sacroiliac joints. Upon physical examination, Patient 12 appeared to have some evidence of synovitis at her TMJ, knees, and sacroiliac joint along with Achilles tendonitis and enthesitis at the insertion of the Achilles tendons into the calcaneus. Her adalimumab

dosing regimen was increased from bi-weekly to weekly prior to study evaluation. MRI of the knee revealed no signs of joint pathology (data not shown).

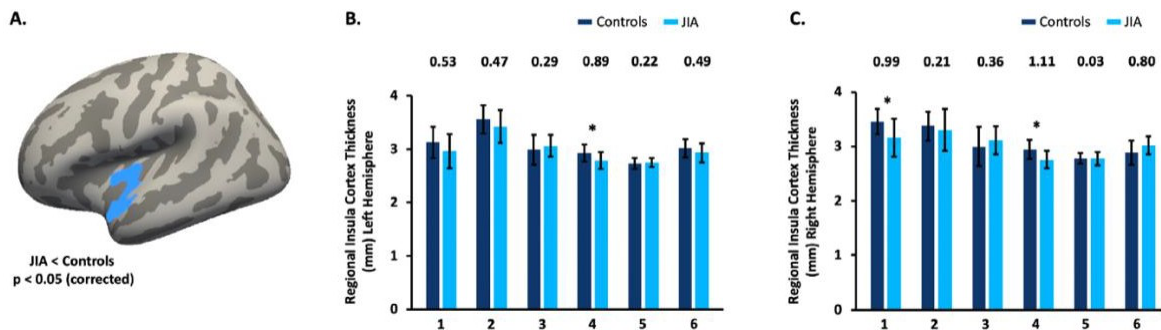
### Pain, Mental Health, Physical Health and Disability in JIA

Across all study participants, PROMIS-based questionnaire ratings of Pain Behavior, Pain Quality, Anxiety, Depressive Symptoms, Psychological Stress, Cognitive Function, and Physical Activity were within normal limits (**Table 2**). As a group, mild impairment was noted on Physical Stress and Strength Impact. Data were also examined separately for patients with a low (0-3/10) and high (4-10/10) self-reported pain intensity. Children with high pain intensity reported more Pain Quality (Sensory) and at a level consistent with children who have chronic pain. Children with high pain intensity also reported less strength than the low pain group. Children reported that pain intensity was associated with measures of engaged pain behavior, the affective (e.g., uncomfortable) and sensory qualities of pain (e.g., throbbing) (**Table 3**). JIA patients with higher ratings of pain also reported more difficulty with cognitive functioning. Parent or guardian account of disability, pain severity and quality of life were assessed using the CHAQ and ARCS (**Table 4**). At the group-level and across the three CHAQ domains, JIA patients were characterized with low levels of symptoms and disability (*CHAQ Disability Index (mean ± standard deviation): 0.32 ± 0.48; CHAQ Pain Severity Score: 0.47 ± 0.50; CHAQ Quality of Life Score: 0.45 ± 0.62*). Low to moderate ARCS scores (*mean ± standard deviation: 1.57 ± 0.49*) likely arose from multiple JIA patients in remission or experiencing low levels of disability.

### CNS Morphological Properties

To determine how neurobiological properties are altered in JIA patients as a whole, gray matter morphological properties (i.e., cortical thickness and subcortical volume) was compared between patient

and healthy control datasets. Voxel-wise morphological analysis revealed a significant ( $p < 0.05$ , corrected) decrease in cortical thickness in the left insula cortex in JIA patient relative to control subjects (**Figure 2**). The insula, particularly its anterior segment, is frequently activated by noxious somatosensory stimulation and plays a key role in mediating emotional aspects of pain<sup>31,32</sup>. However, an assessment of cortical thickness in subdivisions of the insula, as defined by the Destrieux Atlas, demonstrated reduced thickness in both left and right hemispheres. A significant correlation was not observed between patient-reported clinical pain severity and insula cortex thicknesses, either for the whole insula or its subdivisions. However, higher ESR values corresponded with lower cortical thickness values – an effect more dominant in the left relative to the right hemisphere (Left insula:  $R = -0.80$ ,  $p = 0.03$ ; Right insula:  $R = -0.60$ ;  $p = 0.15$ ;  $N = 7$ ). Furthermore, the volume of the caudate nuclei showed significant negative correlations with pain severity (Left Caudate:  $R = -0.70$ ,  $P = 0.04$ ; Right Caudate:  $R = -0.71$ ,  $P = 0.03$ ;  $N = 9$ ).

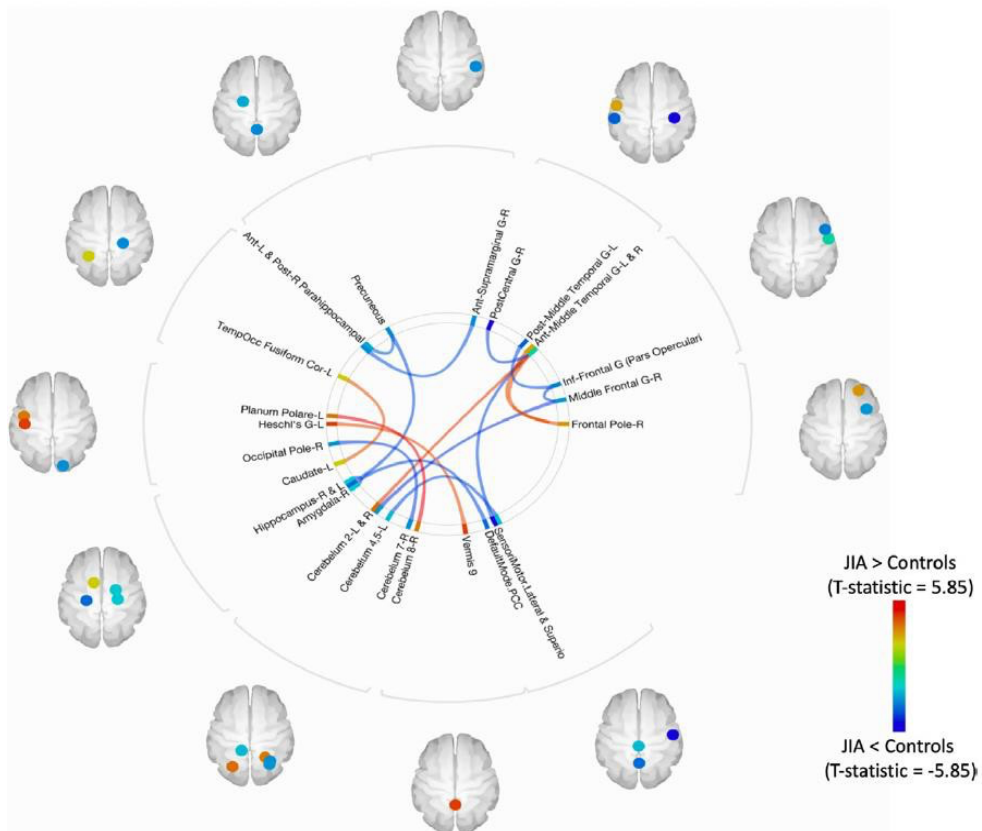


**Figure 2: Decreased insula cortical thickness in JIA patients.** **A.** Insular cortex region (blue cluster) showing a significant decrease in cortical thickness in JIA patients vs. healthy controls. Only the left-hemisphere insular cluster remain significant after correction for multiple comparisons. Left (**B.**) and right (**C.**) hemisphere group-level comparisons of insula cortex sub-regions defined using the Destrieux atlas. Cohen's  $d$  effects sizes are noted in the top row of each bar graph. Bar graphs depict mean and standard deviations. \* $p < 0.05$  1: the long insular gyrus and central sulcus of the insula; 2: short insular gyri; 3: anterior segment of the circular sulcus of the insula; 4: inferior segment of the circular sulcus of the insula; 5: superior segment of the circular sulcus of the insula; 6: whole insula.

### Functional Connectivity

In the absence of any task performance or evoked stimulation, CNS functional connectivity was significantly different among JIA patients and healthy controls (**Figure 3**). JIA patients showed a significant

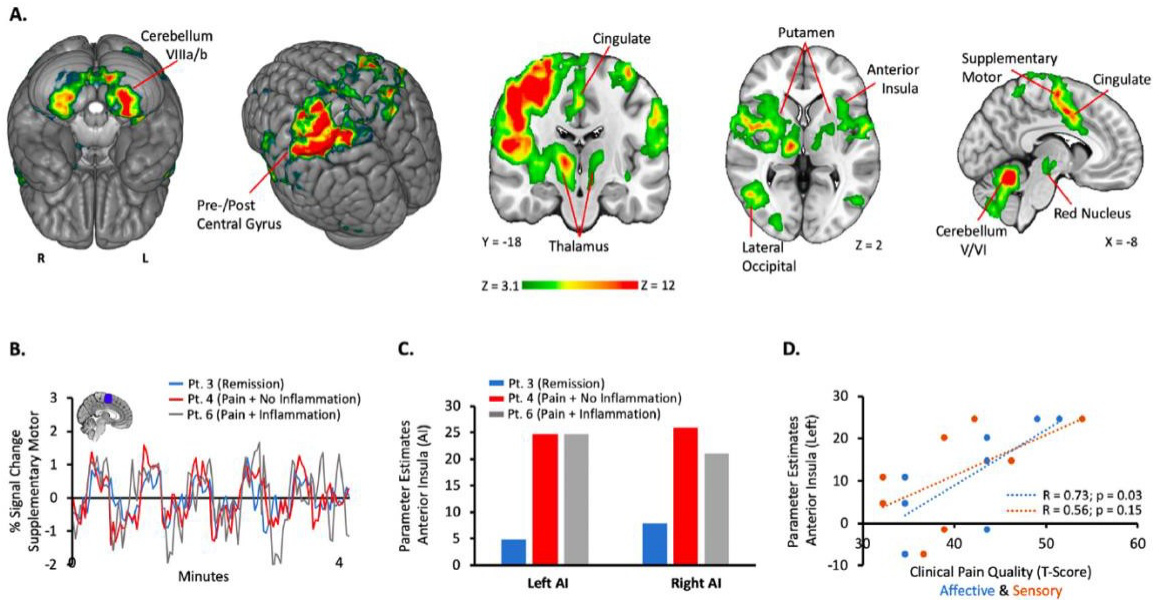
( $p < 0.001$ ) loss of coherence among brain regions that regulate emotional aspects of pain (amygdala, hippocampus, and parahippocampal gyri) as well as sensorimotor regions (post central gyri and lateral and superior aspects of the sensorimotor network)<sup>33</sup>. The default mode network (DMN), specifically the posterior cingulate cortex (PCC) subdivision showed a loss of connectivity with the amygdala (JIA patients:  $-0.13 \pm 0.074$ ; healthy controls:  $0.069 \pm 0.21$ ; Cohen's  $d$  effect size = 1.23). For regions such as the caudate and frontal pole, an increase in connectivity was measured in JIA patients relative to healthy controls. Cerebellar lobules showed both decreases (Crus IV, V, and VII) and increases (Crus II and VIII) in connectivity with multiple cortical structures. Interestingly, a decrease in functional connectivity among the medial prefrontal aspects of the DMN and anterior insula (AI) corresponded with greater clinical pain intensity (medial prefrontal DMN-left AI:  $R = -0.73$ ;  $P = 0.03$ ; medial prefrontal DMN-right AI:  $R = -0.53$ ;  $P = 0.14$ ).



**Figure 3: Resting-state functional connectivity alterations in JIA patients.** Blue-light blue and red-orange connections respectively represent significant ( $p < 0.001$ , uncorrected) connectivity decreases and increases in JIA patients vs. controls. Group-level, functional connectivity decreases were observed among subcortical salience system nodes (amygdala), the default mode network (DMN) and sensorimotor structures (post central gyri), while connectivity increases were quantified among dorsal striatal nuclei (caudate), multiple cerebellar subdivisions, and temporal cortex sub-regions.

#### CNS Activity During Hand-Motor Task in JIA Patients

The fMRI data were collected as JIA patients performed a motor task of the affected hand, which consisted of a visually guided, open-close exercise. As expected, robust responses were detected within sensorimotor network structures such as the cerebellum, red nucleus, thalamus, putamen, and pre-post central gyrus (**Figure 4**). Significant activation was also present along the anterior and mid cingulate as well as the AI. Subject-specific time courses extracted from the supplementary motor area confirmed that each participant performed the task and across all 5 cycles of the paradigm. Evoked responses specific to the AI suggest greater activation in this region in symptomatic patients versus those in a quiescent stage of their clinical course. Moreover, the left AI showed a significant association ( $R = 0.73$ ;  $P = 0.03$ ) with self-reports of an affective pain quality, while the correlation with sensory aspects of pain was not significant ( $R = 0.56$ ;  $P = 0.15$ ). The extent of affective and sensory clinical pain quality was assessed using the Pediatric Pain Quality-Affective and Pediatric Pain Quality-Sensory short forms, respectively.

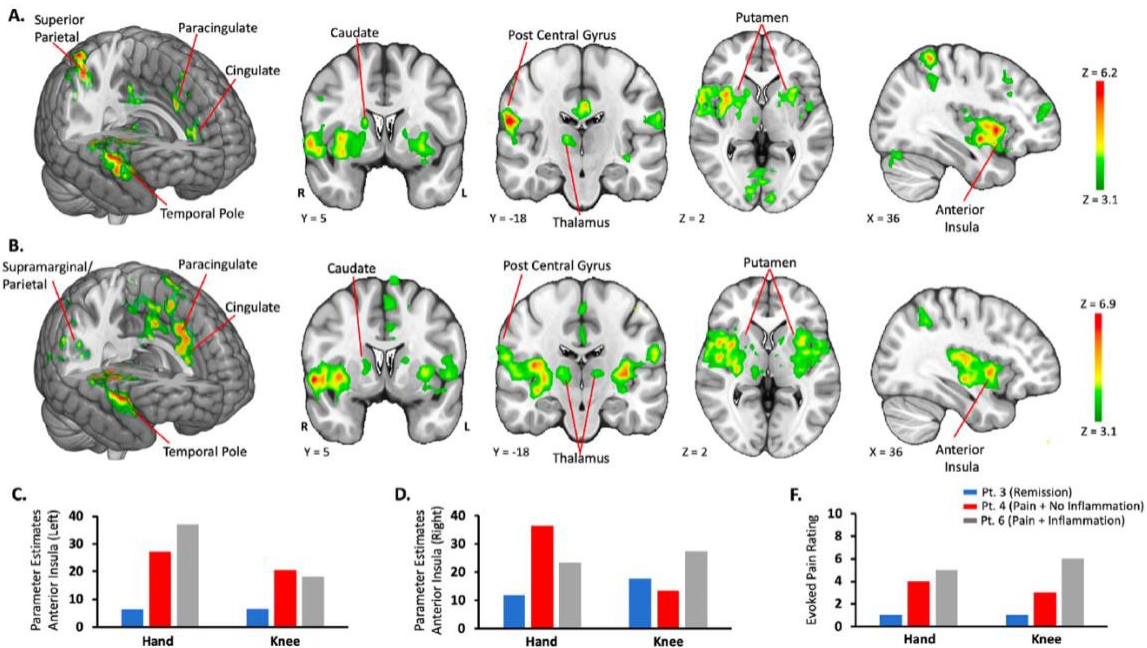


**Figure 4: Hand-motor task activation.** (A.) Group-level activation maps elicited by the hand-motor task superimposed on the Montreal Neurological Institute (MNI) template brain. Significant activation was observed across brain stem (red nucleus), subcortical structures (thalamus, putamen, pallidum), cortical structures (pre-/post central gyrus, cingulate and insula) and cerebellar lobules. One patient (Patient 1) demonstrated significant head motion during data acquisition and was not included in group-level analyses. (B.) Patient-specific time courses extracted from the supplementary motor cortex demonstrate the ability of Patients 3 (blue), 4 (red), and 6 (gray) to complete the hand-motor task across the full four-minute fMRI sequence. (C.) Individual fMRI responses extracted from the left anterior insula (AI) differentiate a state of remission (Patient 3) vs. pain state (Patients 4 and 6) stronger than that observed in the right AI. (D.) Correlation of left AI fMRI responses with clinical pain quality in JIA show a significant relationship between activity in the left AI and affective pain quality (light blue), but not sensory pain quality (orange).

#### CNS Responses to Cold Stimulation (Hand and Knee) in JIA Patients

Following the hand-motor task, JIA patients were administered cold stimuli (10°C) on the dorsum of the hand followed by the knee. At the knee site, the thermal stimulation device was placed in a region where the patient described ongoing or prior clinical pain. The mean  $\pm$  standard deviation evoked pain ratings (0- 10 pain scale) for cold stimulation at the hand and knee were  $2.44 \pm 1.92$  and  $1.88 \pm 2.03$ , respectively. Evoked cold stimulation fMRI responses in subcortical (thalamus and putamen) and cortical (cingulate and temporal cortex) regions for the hand and knee stimulation largely overlapped and significant ( $p < 0.05$ ) differences were not detected when comparing the two datasets (Figure 5). However, similar to the

hand-motor task, greater activation localized to the anterior insula was suggested for symptomatic JIA patients relative to individuals in remission. Across all JIA patients, evoked cold stimulation fMRI responses (hand + knee) in the left AI and cold stimulation pain ratings (hand + knee) showed a positive, yet insignificant trend ( $R = 0.50$ ,  $P = 0.08$ ).



**Figure 5: Central evoked cold stimulation responses.** Group-level activation evoked by (A.) cold stimuli ( $10^{\circ}\text{C}$ ) applied to the dorsum of the left hand largely parallel responses arisen from (B.) cold stimulation ( $10^{\circ}\text{C}$ ) applied to the left knee. During cold stimulation, anterior insula (AI) activity differentiated patients in remission (Patient 3; blue) vs. those with pain, with (Patient 6; gray) or without (Patient 4; red) inflammation. The effect was clearer in the (C.) left AI compared to (D.) right AI. (E.) Verbal pain ratings following cold stimulation at the hand and knee were also lower for the patient in remission vs. the two patients reporting clinical pain.

## Discussion

In addition to the stiffness and limited mobility of arthritis, children and adolescents diagnosed with JIA also must cope with potentially debilitating pain<sup>1, 2, 4</sup>. Although the prevalence and consequences of pain in JIA have been underscored in multiple natural history studies<sup>12, 13</sup>; pain in children remains less clearly understood, compared, for example, with adults diagnosed with painful rheumatic diseases. This is likely

due to several factors, including fewer studies, difficulties children may have in communicating abstract sensations<sup>34, 35</sup>, and the tendency of care providers to focus more on objective measures of the disease<sup>36</sup>. Recently, there has been a greater clinical focus on JIA pain and its treatment. For example, the overall impact of pain in JIA, and the importance of providing effective analgesic treatment to patients, were highlighted in the 2019 American College of Rheumatology treatment guidelines for JIA<sup>37</sup>. In fact, "*Pain was selected as an important outcome*" alongside disease activity, quality of life, joint damage, and serious adverse events<sup>37</sup>. It is projected that a firmer understanding of the clinical and biological driver(s) of JIA pain can lead to more focused treatment and improved outcomes in one of the most prevalent inflammatory disorders of children. In the present study, we carried out a multidisciplinary characterization of JIA patients and sought a better understanding of the clinical, emotional, and biological aspects of pain in JIA patients. Here, we also sought to understand how this common symptom of the disease associates with other facets of life such as physical activity or cognitive health. Furthermore, the current study provides the essential building blocks necessary for expanding our understanding of pain neurobiology in JIA as well as more accurate categorization of patients based on pain and inflammation profiles.

The presentation of pain or objective features of JIA such as synovitis can vary greatly across JIA patients as well as during each individual's clinical course. From the 4 cases described here, it can be appreciated that while some patients may achieve sustained remission with standard therapeutic approaches (i.e., methotrexate and adalimumab), for others, pain alone or pain with inflammation may persist despite receiving similar treatment regimens. Moreover, an examination of the clinical cases in conjunction with assessment of serologic markers of inflammation and musculoskeletal imaging observations further confirm the discordance often observed between subjective reports of pain and objective measures of joint inflammation and pathology<sup>38-40</sup>. At the group-level, a weak association ( $R =$

0.49) among ESR values and clinical pain severity was observed, which may also reflect the fact that most JIA patients did not have widespread joint inflammation at the time of study evaluation. However, only in a limited number of patients did physical examinations or a comprehensive assessment with musculoskeletal imaging demonstrate clear signs of joint inflammation or pathology, which could be expected to induce pain. The prevalent disconnect between the experience of pain and the presence of measurable inflammation in JIA points to the need to comprehend active pain mechanisms outside of the immediate musculoskeletal compartment. Thus, we performed a neuroimaging-based evaluation of JIA patients in order to determine whether and how central features associate with clinical pain.

Resting-state fMRI identified both increases and decreases in functional connectivity in JIA patients relative to controls. Of note, connectivity changes spanned both sensorimotor and affective nodes of the pain processing pathways, which is in accord with pain intensity scores significantly correlating with both sensory and affective pain quality (**Table 3**). In JIA patients, a decrease in functional connectivity among the medial prefrontal component of the DMN and AI corresponded with greater clinical pain intensity. This suggests that in higher JIA pain states, a decoupling of CNS functionality among networks facilitates subjective accounts of pain<sup>32, 41, 42</sup>. A key pain processing center engaged in the interception or self-referential thinking with a major pain processing center, is the AI. It mediates emotional or bodily self-awareness, among many functions, integrates sensory signals, and modulates the intensity of pain. The AI, together with the ACC, amygdala, ventral striatum, and ventral tegmental area, comprise a salience network<sup>43</sup>. Implication of the AI in JIA was further realized in hand-motor task and evoked cold stimulation fMRI findings. JIA patients with pain, arguably independent of inflammatory status, demonstrated enhanced activity within the left AI (ipsilateral to the stimulation site). Of note, AI fMRI responses during the hand motor task were more correlated with the extent of affective pain quality compared to sensory clinical pain quality, which is in accord with involvement of the AI in emotional

regulation of pain. A significant correlation was not observed between evoked thermal stimulation fMRI responses and evoked thermal pain ratings (see study limitations below).

To our knowledge, prior neuroimaging studies in JIA have not been performed. Moreover, a young and developing CNS, along with the childhood experience of pain, may differ from that of adults. This suggests that extrapolating conclusions from adult studies to juvenile patients might not be possible. Nonetheless, some additional insights into central pain processing in JIA may be further garnered from studies performed in rheumatoid arthritis (RA) patients<sup>44</sup>. Efforts to characterize central mechanisms that underlie pain in RA were first based on positron emission tomography studies. A reduction in regional cerebral blood flow (CBF) was observed within the prefrontal cortex and anterior cingulate cortex (ACC) during heat stimulation, which correlated with depressive symptoms<sup>45</sup>. In work by Yee and colleagues, an opposite trend was observed where CBF within medial frontal cortex and dorsolateral prefrontal cortex increased during low or high pressure stimulation<sup>46</sup>. In other efforts, volumetric changes within the basal ganglia were noted and pointed to a mesocorticolimbic component of pain perception in RA in addition to somatosensory circuitry<sup>47, 48</sup>. Flodin et al. implemented resting-state fMRI in order to compare functional CNS interactions between RA patients and healthy controls<sup>49</sup>. Arthritis patients demonstrated increases in functional connectivity between affective pain processing regions (mid-cingulate and mid-frontal cortices) and sensorimotor circuitry. This may relate to modulations in motor function or physical activity that RA patients commonly experience. Evaluation of evoked pain fMRI responses during joint compression implicated regions such as the ACC, insula, and prefrontal cortex<sup>50-53</sup>. Importantly, a sustained suppression of CNS activity could also be detected within three days of initiating treatment with certolizumab pegol, or 24 hours with infliximab. The findings by Schett and colleagues suggest that early treatment responses can be detected with fMRI at the single-subject and group levels. More recent work by Basu and colleagues<sup>54-56</sup> have probed structural and functional properties in not only RA patients, but

also those diagnosed with RA-fibromyalgia comorbidity. Notably, higher levels of inflammation as measured by ESR levels were correlated with greater connectivity between, for example, parietal and medial prefrontal cortices. A greater connectivity strength predicted not only measures of pain, but also fatigue and cognitive dysfunction. Similarly, in patients with RA-fibromyalgia comorbidity, an increase in functional connectivity involving the insula, parietal, cingulate, and medial prefrontal cortices was associated with higher ESR levels, arguably pointing to peripherally driven pain mechanisms.

A number of behavioral and neurobiological parallels can be observed between the current set of results derived from JIA patients and those reported earlier in RA. Pain in both populations may not only impact or associate with the physical aspects of patients' quality of life, but also their mental health. In the current JIA sample, we observed that greater pain severity corresponded with experiencing more patient-reported cognitive difficulties. Disruption of functional connectivity between the DMN and insula and in the context of clinical pain severity also commonly appears in JIA and RA. A potentially important similarity between JIA and RA patients is the negative association between cortical thickness and ESR levels, yet the regions showing this relationship differed (i.e., insula in JIA vs. inferior parietal lobule in RA)<sup>56</sup>. Interestingly, functional connectivity between the DMN and AI has also been implicated in other adult clinical pain conditions such as fibromyalgia<sup>57</sup>. However, in fibromyalgia an increase in DMN-AI connectivity was associated with pain severity. The observed inter-study differences may stem from a number of factors including differences in study cohort age, duration of disease, specific disease, active treatments, or anatomical definitions of the DMN and AI. With respect to JIA, further work is needed to dissect the functionality of DMN or salience network during inflammatory and pain states.

The current investigation provides a first assessment of neurobiological properties in JIA patients, with a focus on pain. These findings were put in the context of clinical status for individual patients as well as more standard measures utilized to monitor JIA pathophysiology or disease severity (i.e.,

musculoskeletal MRI or systemic inflammatory markers). However, limitations are indeed noted for this pilot investigation. All JIA patients evaluated in this study were on active treatment, yet the specific treatment plans differed between patients with some participants using a single immune modulatory agent (i.e., methotrexate *or* adalimumab), while others received combination therapy (i.e., methotrexate *and* adalimumab). Patients also varied according to which joints or the number of joints presented with pain and arthritis prior to or during study enrollment. Such clinical factors likely contributed to study variability. This investigation was also limited in sample size. However, the current dataset may facilitate power analyses of multiple study endpoints derived from neuroimaging and behavioral methods. The latter will prove critical for appropriately designing future work probing similar study measures and pain neurobiology in JIA. While novel mechanistic insights were elucidated in the current study, much remains unknown regarding the pain-inflammation disconnect, which can be better understood using larger cohorts of JIA patients with and without pain and simultaneously, JIA patients with and without inflammation. The work also employed a combination of resting-state, hand-motor tasks, and evoked cold (10°C) stimulation paradigms during fMRI acquisition. Considering that patients as young as 8 years of age were enrolled in this study and evaluated in a novel MRI environment, a more conservative approach was taken in terms of tasks completed by patients or magnitude of cold stimuli. The hand-motor task was easily performed by all patients and induced robust CNS activation that showed correlation with behavioral pain measures. In future work, a hand-grip exercise performed with a pressure device and adapted for children may be utilized during fMRI acquisition<sup>52</sup>. With respect to thermal pain fMRI, a 10°C stimulus was associated with inducing a very low level of pain by some patients. Cold stimulation corresponding to a pre-determined subject-specific pain threshold temperature may be more informative for characterizing thermal pain processing in JIA. Furthermore, pressure stimulation similar to earlier pain fMRI studies performed in adult population should be considered<sup>50, 51, 58</sup>.

## **Conclusions**

In summary, our study demonstrates a multidisciplinary approach to better understand pain in JIA. From a clinical or behavioral perspective, we observed that pain may not only affect physical aspects of life, but concomitantly, a patient's cognitive health. Additionally, pain in JIA, apparently independent of inflammatory status of the JIA patient, ultimately had a robust sensory and affective quality. Such findings point to the potential of neuroimaging as an additional tool to complement clinical, serologic, and musculoskeletal MRI for elucidating pain mechanisms in JIA, and the underlying cause for the dissociation between perceived pain and detectable joint pathology in JIA.

**Table 1.** Patient characteristics.

Patient	Age (y)	Gender	JIA Subtype	Medication Usage	Pain Level (Patient Reported)	ESR, mm/h	CRP, mg/dL	cJADAS
1	10	M	oJIA, ANA-	Methotrexate	6	3	0.03	12
2*	13	M	JPsA, ANA-	Methotrexate, Secukinumab	1	17	0.09	2
3*	9	F	pJIA, ANA+	Methotrexate, Adalimumab	0	—	—	5
4*	15	F	pJIA, ANA+, RF-	Methotrexate, Infliximab	2	6	<0.03	16
5	16	F	pJIA, RF+	Adalimumab	8	20	0.13	12
6*	12	M	pJIA, RF+	Methotrexate, Adalimumab	6	23	0.19	1
7*	16	F	pJIA, RF-, ANA+	Methotrexate, Infliximab	0	8	<0.03	1
8	8	M	pJIA, RF-	Methotrexate, Adalimumab	4	14	<0.03	0
9	13	F	pJIA, RF-	Methotrexate, Adalimumab	2	2	<0.03	—
10*	12	F	pJIA, ANA+, RF-	Leflunomide	3	2	0.04	1
11*	9	F	oJIA, ANA-	Methotrexate, Adalimumab	1	7	0.53	0
12*	16	F	pJIA, ANA+, RF-	Adalimumab	6	13	<0.03	10
13*	10	F	pJIA, RF+	Methotrexate, Adalimumab	2	—	—	4
14	13	F	pJIA, RF-	Methotrexate	0	1	<0.03	0
15	15	F	pJIA, RF-ANA+	Methotrexate	4	26	0.2	0
16	16	F	pJIA, ANA-RF-	Naproxen	6	—	—	—

\* Denotes JIA patients who underwent combined neuroimaging and musculoskeletal MRI procedures. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. cJADAS: clinical Juvenile Disease Activity Score. JIA-juvenile idiopathic arthritis. oJIA- oligoarticular juvenile idiopathic arthritis. JPsA- juvenile psoriatic arthritis. pJIA- polyarticular JIA. ANA: antinuclear antibody. psJIA- psoriatic. RF: rheumatoid factor.

**Table 2.** Group-level PROMIS scores. Low (Pain Level: 0-3) vs. High (Pain Level: 4-10) pain cohorts.

PROMIS Scale	All Patients Mean ± SD (N = 16)	Pain: 0–3 Mean ± SD (N = 9)	Pain: 4–10 Mean ± SD (N = 7)	P-value
<b>Pain Intensity Rating</b>	3.19 ± 2.59	1.22 ± 1.09	5.71 ± 1.38	<b>0.0000</b>
<b>Pain Behavior</b>	41.63 ± 13.10	34.79 ± 12.27	50.41 ± 8.25	<b>0.012</b>
<b>Pain Quality (Affective)</b>	42.45 ± 6.09	40.42 ± 7.23	45.06 ± 2.98	0.14
<b>Pain Quality (Sensory)</b>	44.12 ± 8.88	40.18 ± 7.55	49.17 ± 8.26	<b>0.040</b>
<b>Anxiety</b>	47.26 ± 7.37	46.6 ± 7.80	48.11 ± 7.29	0.70
<b>Depressive Symptoms</b>	46.76 ± 9.40	49.33 ± 9.48	43.44 ± 8.86	0.23
<b>Psychological Stress</b>	50.96 ± 7.83	50.79 ± 8.51	51.19 ± 7.53	0.92
<b>Cognitive Function</b>	50.47 ± 7.53	53.27 ± 6.45	46.87 ± 7.72	0.092
<b>Physical Activity</b>	51.35 ± 8.51	48.82 ± 5.24	54.60 ± 11.08	0.16
<b>Physical Stress</b>	57.34 ± 9.83	53.6 ± 9.71	61.61 ± 8.70	0.12
<b>Strength Impact</b>	43.10 ± 8.58	46.91 ± 7.39	38.20 ± 7.82	<b>0.04</b>

SD: Standard Deviation.

**Table 3.** Association between patient reported pain intensities and PROMIS scores.

PROMIS Score	R	P-value
<b>Pain Behavior</b>	0.79	<b>0.00037</b>
<b>Pain Quality-Affective</b>	0.58	<b>0.019</b>
<b>Pain Quality-Sensory</b>	0.72	<b>0.0016</b>
<b>Anxiety</b>	0.19	0.49
<b>Depressive Symptoms</b>	-0.36	0.17
<b>Psychological Stress</b>	0.089	0.74
<b>Cognitive Function</b>	-0.61	<b>0.011</b>
<b>Physical Activity</b>	0.28	0.30
<b>Physical Stress</b>	0.50	<b>0.049</b>
<b>Strength Impact</b>	-0.75	<b>0.00089</b>

**Table 4.** Parent-based questionnaires.

Patient	CHAQ Disability Index (0–3)	CHAQ Pain Severity Score (0–3)	CHAQ Quality of Life Score (0–3)	ARCS Average Score (0–4)
1	0.25	0.6	0.5	2
2	0	0.1	0.3	1.3
3	0	0	0	1.7
4	0.38	0.6	1.3	1.6
5	1.6	1.9	2.1	2.5
6	1	1	1.2	1.7
7	0	0.1	0.1	0.6
8	0.25	0.6	0	1.5
9	0.88	0.7	0.5	2.1
10	0.38	0.6	0	1.6
11	0	0.2	0.1	1.9
12	0	0.2	0.2	0.9
13	0	0.2	0.1	1.8
14	0	0	0	1.2
15	0	0.2	0.3	1.1
16	0.75	1.2	1.6	1.7

CHAQ: Childhood Health Assessment Questionnaire.

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