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TITLE: Defining the Role for Descending Pain Modulation and Reward-Aversion Processes Towards the Development of Chronic Pain in Endometriosis

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14. ABSTRACT

Purpose: Endometriosis, a condition in which uterine tissue grows outside the uterus, is a debilitating disease, affecting millions of women and which costs the United States approximately \$78 billion annually in pain- related disability. It has a deleterious impact on physical and emotional functioning, as well as quality of life, and is the leading cause of chronic pelvic pain (CPP). One study conducted on female Veterans utilizing the VA healthcare system found that the most frequent reproductive health diagnoses among those aged 18-44 were menstrual disorders and endometriosis. Compared with women without any reproductive health diagnoses, a higher proportion of female Veterans with such diagnoses had concomitant medical and mental health diagnoses and more VA outpatient encounters. **Scope:** We hypothesized that (1) intermittent or ongoing pain in patients with endometriosis, produces a sensitized peripheral and central nervous system (peripheral and central sensitization) that becomes maladaptive (centralization of pain) in patients who chronify vs. those that do not and (2) that there will be differences in brain circuit responsivity with age. The current grant utilized neuroimaging and pain psychophysics to investigate the impact of endometriosis on the brain in pre-menopausal women ages 12-44 years and investigated the comorbidity of endometriosis and migraine. **Findings:** Data analyses are underway but some significant findings include: (1) Functional brain changes found in adolescents with endometriosis-associated pain (EAP) compared to healthy, age-matched controls and in the EAP group, these brain changes were correlated with state anxiety and fear of pain. (2) Structural brain changes found between adolescents and adults with endometriosis, with older age associated with decreased cortical thickness of the right superior frontal gyrus, as well as decreased brain volumes in the fusiform gyrus (left hemisphere) and lateral occipital cortex (right hemisphere) in people with endometriosis compared to healthy controls. (3) In comparison to healthy, pain-free controls, people with menstrual related pain (endometriosis or dysmenorrhea) demonstrated weaker pain inhibition and less functional connectivity during an experimental task (offset analgesia). (4) When comparing patients with surgically confirmed endometriosis and dysmenorrhea to a pain-free control group, the pain-free group reported significantly lower pain catastrophizing scores compared to the endometriosis and dysmenorrhea groups. Adverse childhood experiences were significantly higher in the endometriosis-related pain group compared to the pain-free group, while recent adverse experiences were significantly higher in both the endometriosis-related pain and dysmenorrhea groups compared to the pain-free group. (5) When utilizing amplitude of low-frequency fluctuation (ALFF) in patients with endometriosis relative to controls, a significant ALFF increase was observed in three clusters within the orbitofrontal cortex. When comparing subgroups (endometriosis; endometriosis + migraine; healthy, pain-free controls), a significant decrease in ALFF was observed in the orbitofrontal cortex in patients with comorbid endometriosis and migraine relative to patients with endometriosis alone. In addition, increased functional connectivity was found between the right periaqueductal gray and right middle frontal gyrus in patients with the two comorbid pain conditions compared to the controls. **Significance:** Collectively, these results indicate that endometriosis and the associated pain confer central brain changes and significantly impact pain behavior and emotional functioning. The results from this grant enhance our understanding of the neurobiology of EAP, including age-related changes resulting from the disease, define an initial paradigm that may enhance the evaluation of patients in the clinic, and provide a step towards the use of objective measures for individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

15. SUBJECT TERMS Endometriosis; dysmenorrhea; chronic pelvic pain; fMRI; fNIRS; QST; offset analgesia; migraine; adolescents; pre-menopausal					
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1. INTRODUCTION:

Purpose: Endometriosis, a condition in which uterine tissue grows outside the uterus, is a debilitating disease, affecting millions of women and which costs the United States approximately \$78 billion annually in pain-related disability. It has a deleterious impact on physical and emotional functioning, as well as quality of life, and is the leading cause of chronic pelvic pain (CPP). One study conducted on female Veterans utilizing the VA healthcare system found that the most frequent reproductive health diagnoses among those aged 18-44 were menstrual disorders and endometriosis. Compared with women without any reproductive health diagnoses, a higher proportion of female Veterans with such diagnoses had concomitant medical and mental health diagnoses and more VA outpatient encounters. **Scope:** We hypothesized that (1) intermittent or ongoing pain in patients with endometriosis, produces a sensitized peripheral and central nervous system (peripheral and central sensitization) that becomes maladaptive (centralization of pain) in patients who chronify vs. those that do not and (2) that there will be differences in brain circuit responsivity with age. The current grant utilized neuroimaging and pain psychophysics to investigate the impact of endometriosis on the brain in pre-menopausal women ages 12-44 years and investigated the comorbidity of endometriosis and migraine. **Findings:** Data analyses are underway but some significant findings include: (1) Functional brain changes found in adolescents with endometriosis-associated pain (EAP) compared to healthy, age-matched controls and in the EAP group, these brain changes were correlated with state anxiety and fear of pain. (2) Structural brain changes found between adolescents and adults with endometriosis, with older age associated with decreased cortical thickness of the right superior frontal gyrus, as well as decreased brain volumes in the fusiform gyrus (left hemisphere) and lateral occipital cortex (right hemisphere) in people with endometriosis compared to healthy controls. (3) In comparison to healthy, pain-free controls, people with menstrual related pain (endometriosis or dysmenorrhea) demonstrated weaker pain inhibition and less functional connectivity during an experimental task (offset analgesia). (4) When comparing patients with surgically confirmed endometriosis and dysmenorrhea to a pain-free control group, the pain-free group reported significantly lower pain catastrophizing scores compared to the endometriosis and dysmenorrhea groups. Adverse childhood experiences were significantly higher in the endometriosis-related pain group compared to the pain-free group, while recent adverse experiences were significantly higher in both the endometriosis-related pain and dysmenorrhea groups compared to the pain-free group. (5) When utilizing amplitude of low-frequency fluctuation (ALFF) in patients with endometriosis relative to controls, a significant ALFF increase was observed in three clusters within the orbitofrontal cortex. When comparing subgroups (endometriosis; endometriosis + migraine; healthy, pain-free controls), a significant decrease in ALFF was observed in the orbitofrontal cortex in patients with comorbid endometriosis and migraine relative to patients with endometriosis alone. In addition, increased functional connectivity was found between the right periaqueductal gray and right middle frontal gyrus in patients with the two comorbid pain conditions compared to the controls. **Significance:** Collectively, these results indicate that endometriosis and the associated pain confer central brain changes and significantly impact pain behavior and emotional functioning. The results from this grant enhance our understanding of the neurobiology of EAP, including age-related changes resulting from the disease, define an initial paradigm that may enhance the evaluation of patients in the clinic, and provide a step towards the use of objective measures for individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

2. KEYWORDS:

Endometriosis; dysmenorrhea; chronic pelvic pain; fMRI; fNIRS; QST; offset analgesia; migraine; adolescents; pre-menopausal

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The project's specific aims included: (1) Defining changes in brain structure and function as a correlate of subjective measures of pain and psychophysical functioning in adolescent, young adult, and adult premenopausal people assigned female sex at birth who have a surgically confirmed endometriosis versus healthy, pain-free controls with a focus on an evoked pain task assessing descending pain inhibition (offset analgesia); (2) Longitudinally comparing brain metrics before and after surgery (structure and function) using functional Magnetic Resonance Imaging (fMRI) in people presenting for surgery for endometriosis; and (3) Comparing brain metrics of adolescents, young adults, and adult women with endometriosis with female patients ages 12 to 44 with migraines in our center's existing databases who have undergone structural and fMRIs.

We accomplished all of these goals during the grant period and no cost extension. Some of the work has been published (see Accomplishments) and some of the data has been analyzed with the manuscripts in preparation (see Results).

What was accomplished under these goals?

Data collection was completed during the NCE period. As the grant has concluded, data has been analyzed, some manuscripts have been published, and other manuscripts are in preparation. Some key findings from manuscripts that have been published or which are under review include:

(1) *Pelvic floor, abdominal and uterine tenderness in relation to pressure pain sensitivity among women with endometriosis and chronic pelvic pain*; PMID: 34340095

Objective: Pelvic floor pain, abdominal wall pain, and central nervous system pain amplification can be contributing factors in chronic pelvic pain (CPP), however; limited research has investigated the association of pelvic floor, abdominal, and uterine tenderness with central nervous system pain amplification. We assessed whether pressure pain thresholds on the non-dominant thumbnail, a marker of central nervous system pain amplification, were associated with pelvic floor, abdominal, and uterine tenderness among women with endometriosis or CPP.

Study Design: We conducted a cross-sectional study among 88 females with endometriosis and/or CPP. Abdominal (6 locations), pelvic floor (6 locations) and uterine (1 location) tenderness were assessed via a standardized physical exam. Participants reported their pain levels (0–10 scale) with application of 2 kg of pressure at each area, with a pain rating of ≥ 4 on the 0–10 scale considered moderate to severe pain. Pain sensitivity was measured on the non-dominant thumbnail by applying discrete pressure stimuli using a previously validated protocol.

Results: Overall, 50% (44/88), 42% (37/88), and 58% (51/88) of participants reported high pelvic floor, abdominal, and uterine tenderness, respectively. Pressure intensities needed to elicit ‘faint’ and ‘mild’ pain were lower for participants with high vs. low pelvic floor tenderness (median intensity for ‘faint’ pain=0.50 kgf/cm²(min-max:0.25–3.25) vs. 1.06(0.25–3.00), p-value=0.006; median intensity for ‘mild’ pain=2.00(0.63–4.88) vs. 2.63(0.75–6.00), p-value=0.03). No association was observed between pressure pain sensitivity and abdominal or uterine tenderness (p>0.11). Participants with endometriosis without pain were less likely to have high pelvic floor (22.2%), abdominal (11.1%), and uterine (25.9%) tenderness compared to participants with endometriosis with pain (63.0%, 50%, 65.2%, respectively) and participants with chronic pelvic pain (60%, 73.3%, 93.3%, respectively).

Conclusions: These results suggest that high pelvic floor tenderness among women with endometriosis/CPP may be a marker of heightened pain sensitivity suggestive of central nervous system pain amplification and may impact treatment response. Future research should examine whether this clinical phenotype predicts response to medical and behavioral treatments (e.g., anti-convulsants, behavioral therapy, Physical Therapy).

(2) *Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: Pilot resting-state fMRI study*; PMID: 36375399

Background: Endometriosis is the leading cause of chronic pelvic pain. Alterations in brain functional connectivity have been reported in adult women with endometriosis-associated pain (EAP), however, it is still unknown if similar patterns of changes exist in adolescents.

Methods: In this pilot study, resting-state fMRI scans were obtained from 11 adolescent and young women with EAP and 14 healthy female controls. Using a seed-to-voxel approach, we investigated functional connectivity between the anterior insula, medial prefrontal cortex, and the rest of the brain. Furthermore, we explored whether potential functional connectivity differences were correlated with clinical characteristics including disease duration, pain intensity, and different psychosocial factors (pain catastrophizing, fear of pain, functional disability, anxiety, and depression).

Results: Our findings revealed that patients with EAP demonstrated significantly decreased connectivity between the right anterior insula and two clusters: one in the right cerebellum, and one in the left middle frontal gyrus compared to controls. Additionally, functional connectivity between the right anterior insula and the right cerebellum was positively associated with pain intensity levels. In patients with EAP, brain changes were also correlated with state anxiety and fear of pain.

Conclusions: Our results are relevant not only for understanding the brain characteristics underlying EAP at a younger age, but also in enhancing future pain treatment efforts by supporting the involvement of the central nervous system in endometriosis.

Key Figure:

Main Effect of Group: Patients with EAP > Controls

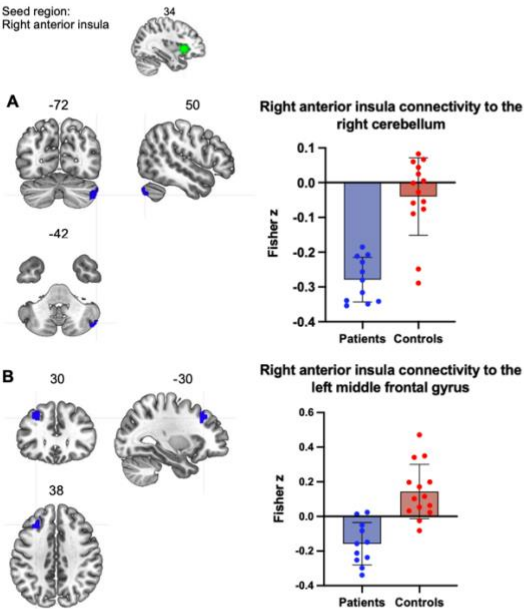


Figure 1. Altered resting-state functional connectivity between the right anterior insula and the rest of the brain in patients with endometriosis-associated pain (EAP) compared to healthy controls. The right anterior insula demonstrated significantly decreased functional connectivity to the right cerebellum (crus I and crus II) (A), and left middle frontal gyrus (B) in EAP patients. Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at $pFDR < 0.05$. Bar graphs indicate average and individual Fisher's z-transformed connectivity values. Error bars represent standard error of mean.

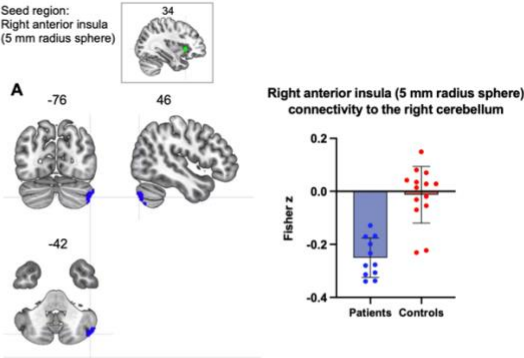
Results using 5 mm radius sphere: (new table and figure, not included in the manuscript)

Brain regions showing decreased functional connectivity with the right anterior insula (using 5 mm radius sphere) in patients with endometriosis-associated pain (EAP) compared to healthy controls.

Cluster	Cluster size	Peak MNI coordinates			Cluster p (FDR)	Cluster p -uncorr
		x	y	z		
Left middle frontal gyrus/ frontal pole	216	-30	30	38	0.003	0.000006
Right cerebellum	143	46	-76	-42	0.016	0.000014

Note. Clusters are significant at $pFDR < 0.05$ following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.

Main Effect of Group: Patients with EAP > Controls



(3) *Age-related changes in brain structure in persons with surgically confirmed endometriosis: A cross-sectional analysis integrating emotional functioning*; Manuscript draft completed; planned submission by 12/31/23

Background: The neurodevelopmental period during adolescence is highly vulnerable towards pain exposure and is poorly understood in women's health. Endometriosis is a highly prevalent and painful gynecological condition that can be observed in women prior to puberty and experienced throughout their lifetimes. No research to date elucidates the prolonged impact of endometriosis and associated pain (EAP) on the developing brain.

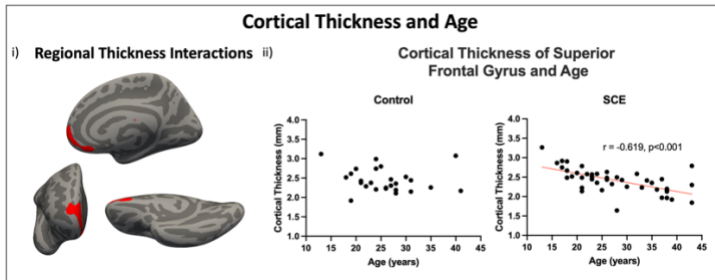
Methods: This cross-sectional investigation performed structural brain imaging and a battery of psychological and clinical tests on pre-menopausal people assigned female sex at birth (ages 12-44) with either surgically confirmed endometriosis (SCE; n=43) or no history of endometriosis (NHE; n=26) to understand the impact of EAP on the developing brain.

Results: We observed an interaction wherein decreased cortical thickness in the right superior frontal gyrus was negatively associated with age only in persons with SCE. A comparison of brain volumes demonstrated decreased volume in the in the SCE cohort in the fusiform gyrus (left hemisphere) and lateral occipital cortex

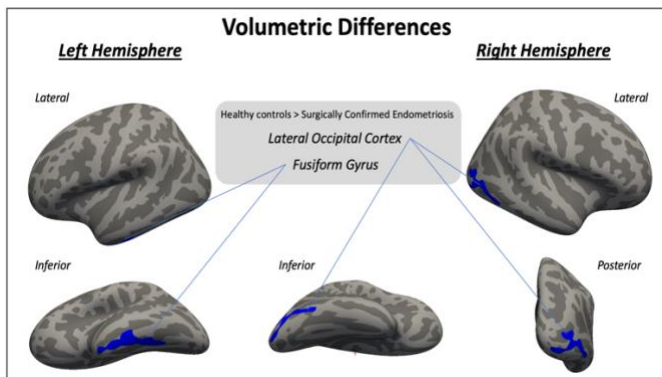
(right hemisphere). Affinity-based cluster analysis demonstrated sub-cohorts that support the relationship between central brain changes and pain behaviors.

Conclusion: Results provide evidence for a centralized impact of endometriosis relating to self-report pain scores in a cohort of premenopausal adolescents to adults assigned female sex at birth. More research is required at the level of brain circuitry to understand the impact of EAP on the early and developed brain to generate novel therapeutics in people with endometriosis.

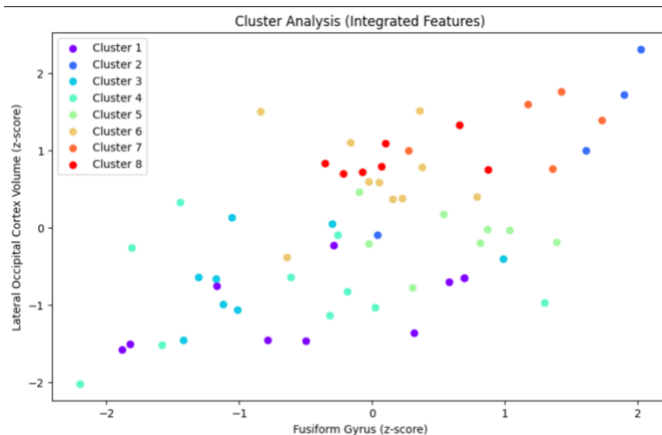
Key Figures:



Left: Plots of significant clusters and scatter plots showing individual data from significant clusters. The relationship between cortical thickness of the superior frontal gyrus and age in both the control and SCE cohorts is plotted. A regression line is added for the SCE cohort to demonstrate the significant relationship between features that was not present in the NHE cohort.



Left: Group differences in brain volume. Significant differences are highlighted in blue in the left and right hemisphere. Two significance were observed that are highlighted.



Left: Affinity propagation cluster analysis output. Input features included age, anxiety and depression self-reporting, pain specific behaviors, and brain imaging. Brain volume (z-score) from the fusiform gyrus and the lateral occipital cortex are shown on the x- and y-axis, respectively. The eight observed clusters are plotted in different randomized colors. Data included in this cluster analysis is from clinical and control cohorts.

(4) *Endometriosis and comorbid migraine: Application of resting-state amplitude of low-frequency fluctuation (ALFF) in evaluating differences in brain functional circuits; Manuscript draft completed; planned submission by 12/31/23*

Background: Previous research has revealed high comorbidity between endometriosis and migraine headaches. Both conditions are well described pain conditions with intermittent or ongoing (chronic) pain and both may be considered ‘visceral’ pain. Comorbidity of pain conditions can lead to an exacerbation of the pain – a process known as cross-sensitization. Our aim was to investigate the spontaneous brain activation during rest in patients with surgically confirmed endometriosis with and without migraine headaches, measured by the amplitude of low-frequency fluctuation (ALFF). ALFF is a measure of spontaneous neural activity that detects changes in

regional intensity of neural function. Furthermore, as a key node of the pain modulatory function, we also aimed to analyze the functional connectivity of the periaqueductal gray (PAG).

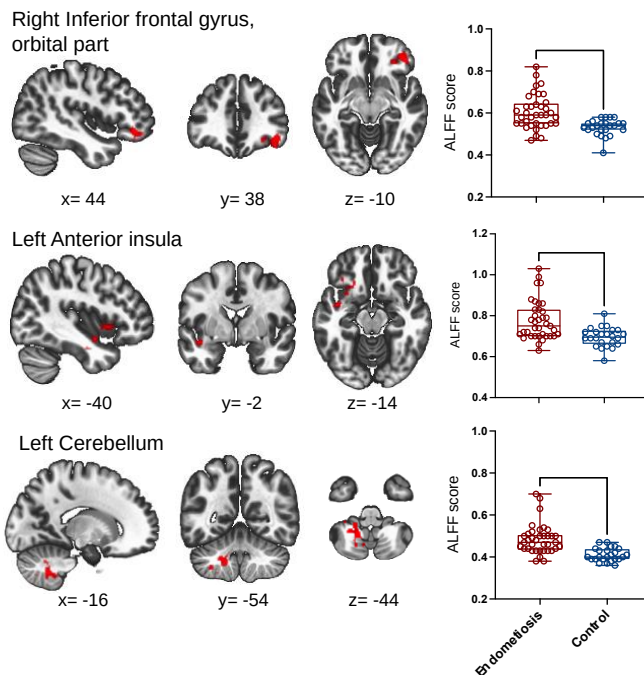
Methods: In this cross-sectional study, whole-brain resting-state functional MRI data were collected from 61 adult participants assigned female sex at birth (age range 18-42 years), including 37 patients with surgically diagnosed endometriosis (19 patients with endometriosis alone; 18 patients with comorbid endometriosis and migraine), and 24 healthy age-matched controls. Whole-brain ALFF maps and seed-based functional connectivity of the bilateral PAG were calculated and compared between groups. All imaging results were corrected for multiple comparison using False Discovery Rate correction method ($pFDR < 0.05$).

Results: In patients with endometriosis relative to controls, a significant ALFF increase was observed in three clusters within the orbitofrontal cortex, in the anterior insula, and in the cerebellum (posterior lobules). When comparing the subgroups, a significant decrease in ALFF was observed in the orbitofrontal cortex in patients with comorbid endometriosis and migraine relative to patients with endometriosis alone. In addition, increased functional connectivity was found between the right PAG and right middle frontal gyrus in patients with comorbid pain conditions compared to the controls.

Conclusion: Our findings support that endometriosis could be related to disruptions in the central pain modulation system. The comorbid condition resulting in a further reduction of low-frequency fluctuational amplitude is interpreted as a decrease in neural function in the orbitofrontal cortex and atypical connectivity between the PAG and middle frontal gyrus. We interpret our finding as a change in the efficacy of pain modulation (decreased inhibitory or increased facilitatory) that includes greater connectivity between the PAG and frontal areas, which are normally involved in pain processing and inhibition/analgesia.

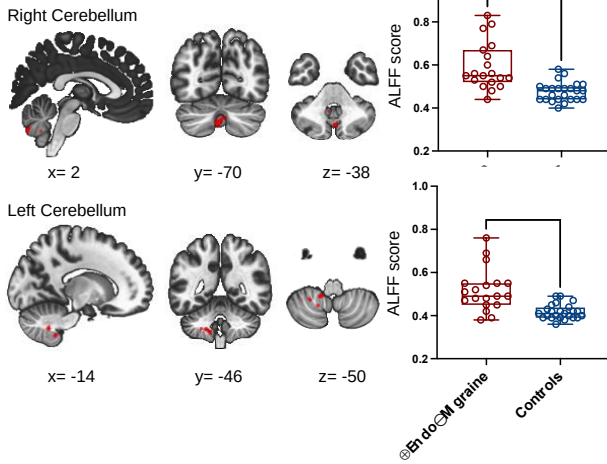
Key Figures:

Patients with Endometriosis > Controls



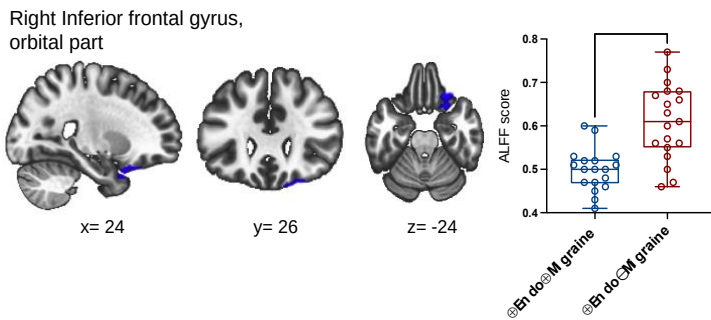
Left: Group differences in ALFF between patients with endometriosis and controls. Patients with endometriosis ($n=37$) showed increased ALFF in the right inferior frontal gyrus (orbital part), left anterior insula and left posterior cerebellum, compared to controls ($n=24$). The boxplots show median with quartiles, and individual ALFF values. Whiskers represent the minimum and maximum values. Coordinates are in MNI space. Results are cluster level corrected at $pFDR < 0.05$. **** $p < 0.0001$, *** $p < 0.001$.

$\oplus$ Endometriosis $\ominus$ Migraine > Controls

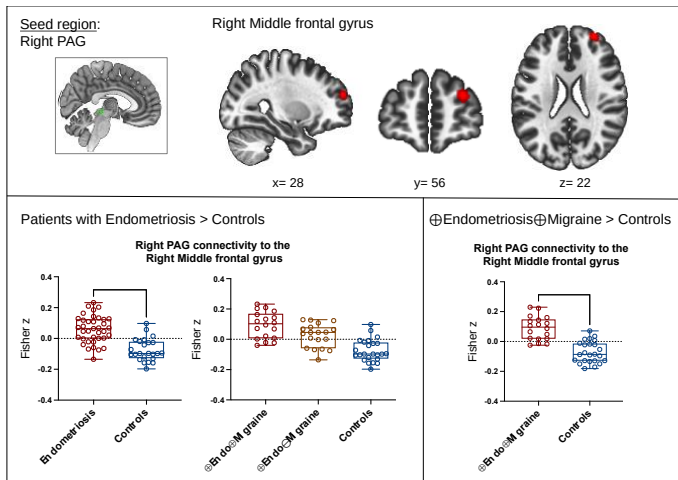


Left: Group differences in ALFF between patients with endometriosis alone and controls. Patients with endometriosis without migraine comorbidity (n=19) showed increased ALFF in the bilateral cerebellum (posterior lobules), compared to controls (n=24). The boxplots show median with quartiles, and individual ALFF values. Whiskers represent the minimum and maximum values. Coordinates are in MNI space. Results are cluster level corrected at $pFDR < 0.05$. **** $p < 0.0001$.

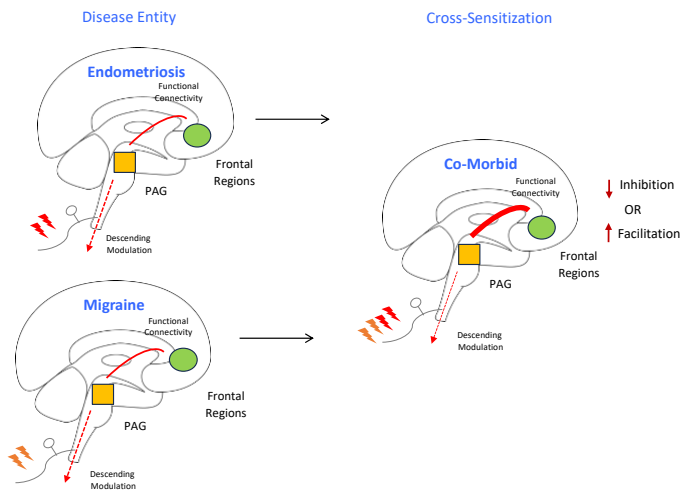
$\oplus$ Endometriosis $\oplus$ Migraine < $\oplus$ Endometriosis $\ominus$ Migraine



Left: Group differences in ALFF between patients with endometriosis with and without migraine. Patients with comorbid migraine and endometriosis showed decreased ALFF in the right inferior frontal gyrus (orbital part), compared to patients without migraine. The boxplots show median with quartiles, and individual ALFF values. Whiskers represent the minimum and maximum values. Coordinates are in MNI space. Results are cluster level corrected at $pFDR < 0.05$. **** $p < 0.0001$.



Left: Group differences in functional connectivity of the right periaqueductal gray (PAG) between patients with endometriosis and controls. Compared to controls (n=24), increased resting-state functional connectivity was observed between the right PAG and right middle frontal gyrus in patients with endometriosis (n=36), and patients with comorbid endometriosis and migraine (n=18). Coordinates are in Montreal Neurological Institute (MNI) space. Functional connectivity maps are corrected at $pFDR < 0.05$. The boxplots show median with quartiles and individual Fisher's z-transformed connectivity values. Whiskers represent the minimum and maximum values. **** $p < 0.0001$.



Left: Illustration of disrupted pain modulation processes underlying endometriosis and migraine comorbidity. Cross-sensitization may modify the functioning of neural circuitries and based on the current findings, increased connectivity between the right PAG and right middle frontal gyrus (part of the DLPFC) could indicate altered pain modulation. We hypothesize that coexisting pain conditions may result in reduced inhibitory or enhanced pain facilitatory processes via engagement of the PAG and prefrontal brain regions. These findings could also suggest that the observed changes in brain function may contribute to a submerged (subliminal) pain state (Borsook, Youssef, Barakat, et al., 2018).

(5) *The role of the brain in menstrual related pain: A pilot fNIRS study investigating descending pain inhibition and emotional functioning*; 1st manuscript draft completed, will be submitted as part of an invited special issue focused on innovative methodologies in pediatric psychology to *Journal of Pediatric Psychology* Spring 2024

Objectives: Understanding the underlying mechanisms of pain perception and processing is essential for developing effective management strategies, particularly in the context of young women experiencing menstrual-related pain.

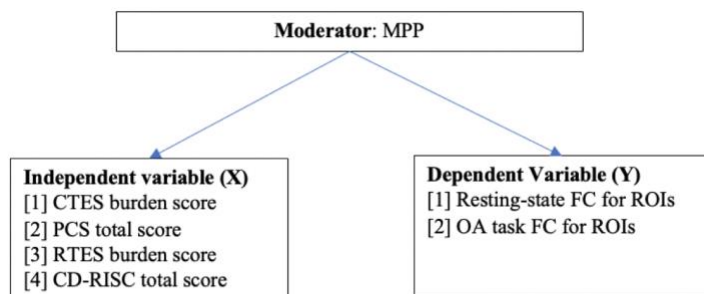
Methods: This pilot study utilized functional near-infrared spectroscopy (fNIRS) to investigate descending pain inhibition, via an Offset Analgesia (OA) paradigm, and behavioral self-report measures to assess the relationship between the brain's response to pain, pain self-report, and psychosocial functioning (e.g., pain catastrophizing; childhood & recent traumatic events; resiliency) in adolescent, young adult, and adult people assigned female sex at birth who have either dysmenorrhea or surgically confirmed endometriosis compared to age and sex-matched healthy, pain-free controls. Specifically, OA is a form of endogenous pain inhibition characterized by a disproportionately large reduction in pain perception after a small decrease in temperature during noxious thermal stimulation; however, OA is attenuated in patients with chronic pain (e.g., fibromyalgia and neuropathic pain). Pain inhibition is a neurobiological process that helps to modulate the perception of pain using different neural circuits and pathways in the brain that work together to diminish or block the transmission of pain signals. For OA, A δ fibres are primarily involved in the initial perception of intense pain due to a noxious stimulus. This suggests that A δ fibers' response to temperature changes plays a role in OA. Diminished robustness of OA measures would thus reflect an altered brain system in which there is an increased sensitivity to pain and increased resistance to treatment in conditions such as dysmenorrhea or endometriosis.

Results: Results indicated that the pain-free group generally reported lower scores on pain catastrophizing and adverse childhood experiences than participants with dysmenorrhea or endometriosis. Furthermore, fNIRS analysis revealed distinct differences among groups in pain inhibition and functional connectivity between the prefrontal and somatosensory regions. Specifically, the pain-free group demonstrated stronger pain inhibition and functional connectivity during the experimental task. Pain ratings, pain catastrophizing scores, and burden scores related to stress and trauma were found to be significantly associated with specific functional connectivity patterns in the prefrontal and somatosensory brain regions. These associations suggest that psychological factors and stress-related experiences influence both the subjective experience of pain and the underlying neural activity in pain-processing networks. These results contribute to our understanding of neural mechanisms in menstrual pain and provide insights into the complex interplay between psychological factors, brain activity, and pain perception.

Conclusion: The study supports the hypothesis that menstrual related pain may contribute to an attenuated pain inhibitory response, which may result in the maintenance and exacerbation of chronic pain. Additionally,

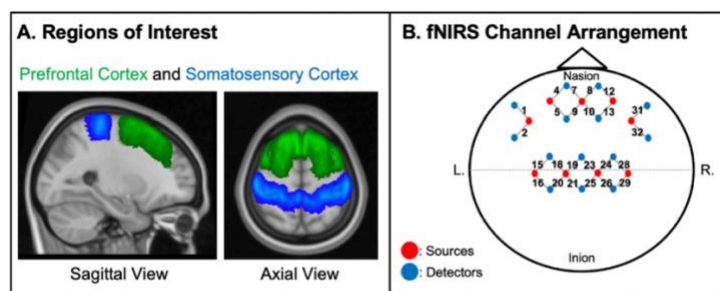
psychosocial functioning may impact this relationship. Elucidating the complex biobehavioral mechanisms contributing to dysmenorrhea and endometriosis-associated pain can hopefully lead to better preventative interventions and personalized treatment for this at-risk group.

Key Figures:



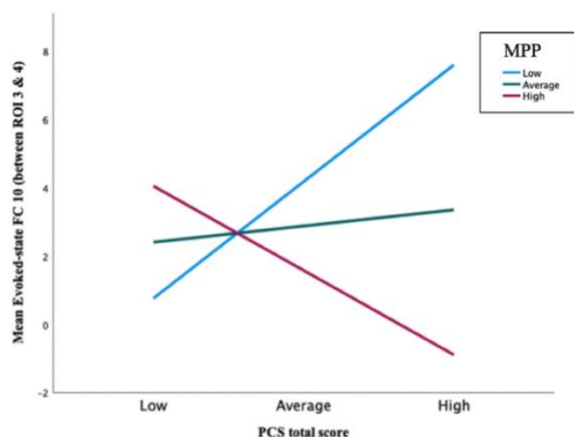
Left: Moderation models were used to examine the relationship between the psychological variables and brain activity for each of the 15 functional connectivity locations, specifically when experiencing higher levels of menstrual phase pain.

Abbreviations. MPP, menstrual phase pain; CTES, childhood traumatic events scale; PCS, pain catastrophising scale; RTES, recent traumatic events scale; CD-RISC, connor-davidson resilience scale; FC, functional connectivity; ROIs regions of interest



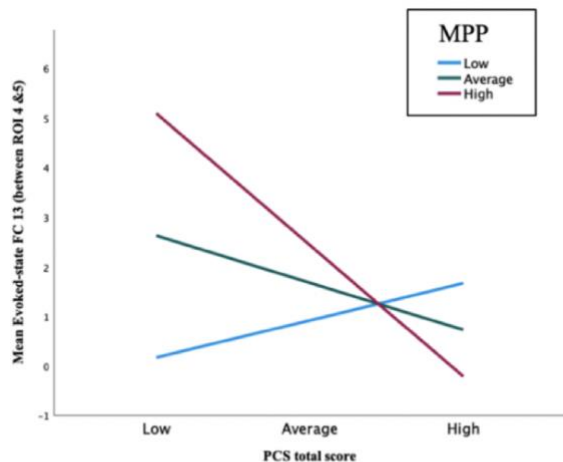
Left: Regions of interest (ROIs) & fNIRS channel arrangement. Prefrontal cortex, involved in cognitive and emotional aspects of pain, and the somatosensory cortex, associated with somatic sensations, were chosen as the brain ROIs.

- A. Regions of interest including bilateral prefrontal (green) and somatosensory cortices (blue).
 B. fNIRS channel arrangement (L: left; R: right; Lateral prefrontal cortices: channels 1, 2, 31, 32; Medial prefrontal cortices: channels 4, 5, 7, 8, 9, 10, 12, 13; Somatosensory cortices: channels 15, 16, 18, 19, 20, 21, 23, 24, 25, 26, 28, 29).



Abbreviations. PCS, pain catastrophising scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

Left: Significant interactions between pain catastrophizing and menstrual phase pain (MPP) for OA task location FC 10 (between the right medial prefrontal cortex & the Right lateral prefrontal cortex). The overall model was significant, with MPP, PCS total score, and their interaction, predicting brain activity better than chance, with 26% of the variance due to the three predictors. – so high pain & high PCS indicate decreased fc in these brain regions during the OA task & more specifically, The Johnson-Neyman technique (non-parametric test that provides the two values of the moderator at which the slope of the predictor goes from non-significant to significant)--showed that when pain is less than 3 (non—mild) and more than 9 (severe pain), the relationship between the PCS total score and the activity of OA Task location FC10 was significant.



Abbreviations. PCS, pain catastrophising scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

Left: Significant interactions between pain catastrophizing and menstrual phase pain (MPP) for OA task location FC 13 (Right lateral prefrontal cortex & the Left lateral somatosensory cortex). As pain increases, the relationship between PCS total score and the of OA Task location FC13 becomes increasingly significant with the higher pain score.

(6) *Task-based analysis of descending pain modulation*; data analysis completed, manuscript in preparation to be submitted Spring 2024.

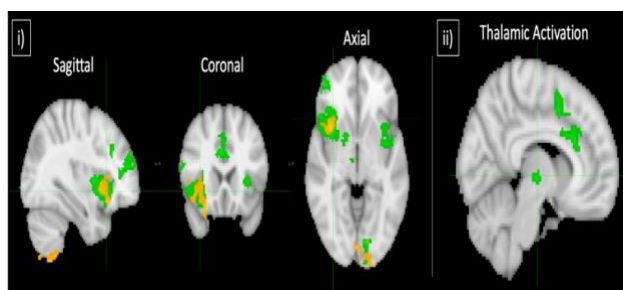
Objective: Processing of nociceptive stimuli is fundamentally different for persons with chronic pain. Endometriosis, a chronic pain condition for which there is little available in terms of pain treatment services, has a significant and debilitating impact on activities of daily living. In this investigation, we evaluated pain processing in people with surgically confirmed endometriosis and a cohort of healthy, pain-free controls using the OA paradigm described above.

Methods: This preliminary cohort of fourteen persons with surgically confirmed endometriosis (SCE), and eight healthy controls underwent the OA task in the fMRI.

Results: First, in healthy persons, we see activation of key pain regions including the insula which shows up, as would be predicted, contralateral to the applied heat stimulus. Alternatively, in the SCE cohort, we show the same insular activation seen in healthy controls, that is paralleled by activation of ipsilateral insula, and extensive frontal activation. These additional regions are those typically observed during pain modulation including the anterior cingulate cortex, and superior frontal gyrus. In addition, the SCE cohort demonstrates increased activation of subcortical areas including the thalamus and pallidum relative to a resting state.

Conclusions: Together, this preliminary information demonstrates atypical pain processing in people with SCE. This finding offers windows into potential treatment options including neuromodulation.

Key Figure:



Left: Findings from the task-based analysis of offset analgesia paradigm. Functional activity is observed in the OA task relative to a rest condition. Green represents activity observed in persons with surgically confirmed endometriosis (SCE), and orange represents activity observed in healthy controls. Panel (i) presents three viewpoints with a focus on the right hemisphere insula (cross hairs) and panel (ii) shows thalamic activation observed in the SCE, but not healthy control cohort.

Additionally, we are in the process of analyzing data for the prospective aim (pre/post-surgery for suspected endometriosis) and plan to finalize those results prior to the end of the year with the paper submitted by Spring/Summer 2024. The Partnering PI, Dr. Scott Holmes, has also conducted innovative analyses and novel methodologies on the data collected as part of the grant. His report goes into detail of these methods and results, which includes changes in brainstem structures, brain network structures using graph theory, and dynamic functional connectivity. Please refer to Dr. Holmes' report for details.

Summary:

In summary, the results that have been published, as well as the manuscripts in preparation, support our central thesis of atypical processing of descending pain modulatory networks in people with surgically confirmed endometriosis. We provide evidence of functional brain changes during an offset analgesia paradigm that directly support this interpretation. Moreover, we show that there are functional network changes that align with observed group differences in structural brain data (i.e., fusiform gyrus) that provide potential future targets for intervention having shown their involvement in pain, and deviant activity using both structure and function analyses. Additionally, stress and emotional functioning may impact these brain changes. Endometriosis is a condition that can start prior to puberty, and as our data show, has a life-long impact on how the brain is impacted.

What opportunities for training and professional development has the project provided?

There were numerous training and professional development opportunities for the postdoctoral fellows, graduate and undergraduate students, and research assistants (RA) who worked on the grant. Everyone attended weekly grant meetings and bi-weekly lab meetings. Dr. Sieberg met one-on-one with each postdoctoral fellow and her graduate students weekly and Dr. Holmes also held several data analyses and neuroimaging training meetings each month. He also met with his RAs and students from his lab regularly (see Dr. Holmes' Partnering PI report for details). Additionally, Dr. Edina Szabo, the postdoctoral fellow, and one of the graduate students, Claire Lunde, who worked on the project were accepted into and attended the prestigious and highly selective *European Pain School* (EPS), which was held in Siena, Italy in June 2022. The EPS founded at the University of Siena in 2002, is the first and still the premier school intended for students working on basic science and clinical topics related to acute and chronic pain. EPS has an interdisciplinary perspective and a distinct research orientation. Young scientists at the Ph.D. or postdoctoral levels (or equivalent) in all fields of pain science and pain medicine are encouraged to apply and a spot is highly coveted. The 2022 course directly aligned with the objectives of the grant with a focus on "Pain, Inflammation and the Guts", whereby the plural indicates that all abdominal organs are included. "Pain, Inflammation" includes joint pain (osteoarthritis, rheumatoid arthritis), pain in the GI tract (functional dyspepsia, inflammatory bowel diseases, irritable bowel syndrome) and female pelvic pain (dysmenorrhea, endometriosis, parturition). Attendees learned about the etiologies, pathophysiological mechanisms, and pharmacological options of these conditions.

Dr. Szabo, the postdoctoral fellow, and an RA also attended and presented posters at the *United States Association for the Study of Pain Conference* in May 2022. The postdoctoral fellows, Drs. Szabo and Wu, along with a graduate student and a research assistant attended and presented posters related to the DoD award at the *International Association for the Study of Pain (IASP) Conference* in Toronto in September 2022. Additionally, all of Dr. Sieberg's team attended the *Society for Functional Near-infrared Spectroscopy Conference* and workshop, with some poster presentations related to the award, held in Boston, MA in October 2022.

Overall, the trainees on this grant received unparalleled opportunities to learn about endometriosis, menstrual pain, neuroimaging data acquisition and analyses, pain psychophysics, and manuscript writing. All the trainees also had the opportunity to co-author manuscripts.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Through our publications and presentations at regional, national, and international conferences, our results should improve the public's knowledge and attitudes related to endometriosis related pain. We are hopeful that our results (1) enhance our understanding of the neurobiology of pelvic pain in patients with endometriosis; (2) provide a metric to follow such patients in the clinic; (3) potentially provide a metric for those who will chronify; (4) understand the age-related changes that may occur with the disease; and (5) define an initial paradigm that may enhance our capability for developing individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

What was the impact on other disciplines?

The results should help Obstetricians and Gynecologists and who treat people with endometriosis associated pain have a better understanding of the central and brain-based processes that result in the maintenance and exacerbation of chronic pain.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Through our publications and presentations at regional, national, and international conferences, our results should improve the public's, as well as women's health clinicians, researchers, policy makers, and stakeholders' knowledge and attitudes related to endometriosis and associated pain. Two important contributions include:

- (1) Given that endometriosis affects only people assigned female sex at birth, it can be challenging for non-binary, transgender, and gender expansive people coping with this disease. For example, evaluation for endometriosis is underutilized when transgender youth present with pelvic pain and dysmenorrhea. The impact of endometriosis must be considered for transgender and gender expansive (TGE) people in the context of the interpersonal and structural barriers to accessing sexual and reproductive health (SRH) care. PI, Dr. Sieberg, published a paper (**PMID: 36304055**) reviewing the SRH needs of transgender and gender expansive (TGE) people highlighting key areas with significant disparities in need of further research. Recommendations for clinicians and researchers were also provided with the goal of improving SRH care and obtaining wider representation in both clinical settings and research directed toward TGE youth.
- (2) As this grant utilized an evoked thermal pain paradigm (Offset Analgesia) in the fMRI scanner, Partnering PI, Dr. Holmes, lead a study analyzing data from a cohort of participants from the grant, to investigate the use of Quantitative Sensory Testing (QST) in a magnetic resonance environment with a focus on considerations for thermal sensitivity and patient safety (**PMID: 37766817**). Specifically, no studies have yet evaluated the impact of the MR environment on the perception of thermal stimuli. This study aimed to evaluate the differences in temperature sensitivity outside an MR environment and during an MRI scanning session. We hypothesized that there would be a difference in how participants reported their pain sensitivity between the two environments. There were statistically significant changes of 1.1°C in thermal sensitivity between environments. This increase in pain threshold was found in healthy participants and replicated in the clinical

cohort. Findings can be applied toward improving MR safety, the resolution of brain pathways underlying pain mechanisms, and to more broadly comment on the impact of the MR environment on investigations that integrate perception-influenced processes.

Overall, with the results from this grant and the publications produced, we are hopeful that our results (1) enhance our understanding of the neurobiology of pelvic pain in patients with endometriosis; (2) provide a metric to follow such patients in the clinic; (3) potentially provide a metric for those who will chronify; (4) understand the age-related changes that may occur with the disease; and (5) define an initial paradigm that may enhance our capability for developing individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

There were no delays during this reporting period (the NCE). The grant has ended and we are still working on some data analyses and manuscripts.

Changes that had a significant impact on expenditures

Unfortunately, during the grant, we had to endure the COVID-19 pandemic, which significantly delayed recruitment. Additionally, Dr. Borsook (Partnering PI) retired in 2021 and Dr. Holmes took over as Partnering PI. These delays and transitions and proposed solutions were outlined in previous progress reports. However, overall, despite these challenges, the NCE helped tremendously, and we were able to get deliverables for each grant objective. Some of the data has been published and presented. Other manuscripts are in preparation (drafts completed; editing stage), while data some data is still being processed and analyzed with the intention to submit additional papers this coming year.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

N/A for this project. Nothing to report.

Significant changes in use of biohazards and/or select agents

N/A for this project. Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

(1) Sieberg CB, Lunde CE, Borsook D. Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review. *Neurosci Biobehav Rev.* 2020 Jan;108:866-876. doi: 10.1016/j.neubiorev.2019.12.004. Epub 2019 Dec 17. PMID: 31862211; PMCID: PMC7175958.

(DoD Award acknowledged)

(2) Lunde CE, Szabo E, Holmes SA, Borsook D, Sieberg CB. Commentary: Novel Use of Offset Analgesia to Assess Adolescents and Adults with Treatment Resistant Endometriosis-Associated Pain. *J Pain Res.* 2020 Nov 2;13:2775-2782. doi: 10.2147/JPR.S276135. PMID: 33204144; PMCID: PMC7660453. (DoD Award acknowledged)

(3) Shafrir AL, Martel E, Missmer SA, Clauw DJ, Harte SE, As-Sanie S, Sieberg CB. Pelvic floor, abdominal and uterine tenderness in relation to pressure pain sensitivity among women with endometriosis and chronic pelvic pain. *Eur J Obstet Gynecol Reprod Biol.* 2021 Sep;264:247-253. doi: 10.1016/j.ejogrb.2021.07.029. Epub 2021 Jul 22. PMID: 34340095; PMCID: PMC8449805. (DoD Award acknowledged)

(4) Lunde CE, Spigel R, Gordon CM, Sieberg CB. Beyond the Binary: Sexual and Reproductive Health Considerations for Transgender and Gender Expansive Adolescents. *Front Reprod Health.* 2021 Oct 6;3:670919. doi: 10.3389/frph.2021.670919. PMID: 36304055; PMCID: PMC9580725 (DoD Award acknowledged)

(5) Szabo E, Timmers I, Borsook D, Simons LE, Sieberg CB. Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: Pilot resting-state fMRI study. *Eur J Paediatr Neurol.* 2022 Nov;41:80-90. doi: 10.1016/j.ejpn.2022.10.004. Epub 2022 Oct 29. PMID: 36375399; PMCID: PMC9722632. (DoD Award acknowledged)

(6) Kim AJ, Szabo E, Lunde CE, Comptdaer G, Zurakowski D, Sieberg CB, Holmes SA. Quantitative sensory testing in a magnetic resonance environment: considerations for thermal sensitivity and patient safety. *Front Pain Res (Lausanne).* 2023 Sep 12;4:1223239. doi: 10.3389/fpain.2023.1223239. PMID: 37766817; PMCID: PMC10520956. (DoD Award acknowledged)

Of note, an additional 4 other manuscripts have drafts that have been written and the plan is these manuscripts will be submitted Winter/Spring 2024. An additional 4 manuscripts are also underway and should be submitted by Summer 2024.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Oral Presentations by Christine B. Sieberg,:

2019 Chronic pelvic pain in adolescents with endometriosis: The role of psychophysical and inflammatory factors in the development of central sensitization/Accepted oral presentation as part of the Biological influences on adolescent pain: Sex, stress, and inflammation symposium
International Symposium on Pediatric Pain, Basel, Switzerland
2021 Reframing pain assessment and treatment in gynecology: Adolescents-adults
Department of Obstetrics & Gynecology/Invited Grand Rounds
NorthShore University Health System, Chicago, IL

2021 Translational approaches to categorizing chronic pelvic pain syndromes
Invited speaker as part of symposium
United States Association for the Study of Pain
2022 Scientific Meeting, Cincinnati, OH

2022 Elucidating the neural underpinnings of co-morbid endometriosis and migraine: A pilot fMRI investigation/Oral presentation
International Pelvic Pain Society
Orlando, FL

2022 Endometriosis associated pain: The path from clinical encounter to investigation
Tommy Fuss Center; Department of Psychiatry
Boston Children's Hospital, Boston, MA

2022 Co-Morbid Endometriosis & Migraine: A Pilot fMRI Investigation
Harvard Longwood Headache Seminar
Boston, MA

2023 Quantitative Sensory Testing in pediatric pain research: Methodology, current applications and future directions
Invited presenter for a hands-on workshop
International Symposium on Pediatric Pain
Halifax, Nova Scotia, Canada

2023 Building the translational research bridge in adolescent endometriosis-associated pain: The role of the pediatric psychologist
Invited speaker
Society of Pediatric Psychology Fall Virtual Conference

Oral Presentations by Edina Szabo- Postdoctoral Fellow on the Grant:

2021 Szabo, E., Lebel, A. A., Sieberg, C., B., & Borsook, D. Chronic nociceptive pain and neural sensitization in two pain conditions: New daily persistent headache (NDPH) and endometriosis [Presentation]. Chronic/Acute Pain Research Meeting, Boston Children's Hospital, Boston, MA, The United States.

2022 Szabo, E., Timmers, I., Borsook, D., Simons, L., E., & Sieberg, C. B. Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: A pilot resting-state fMRI study [Oral Presentation]. European Pain School (EPS), Siena, Italy.

2023 Szabo, E, Ayeong, JK, Comptdaer, G, Lunde, CE, Holmes, SA, Borsook, D, & Sieberg, CB Endometriosis and migraine: Functional brain alterations in two comorbid pain disorders. 1st International Headache Society/European Headache Federation (IHS/EHF) Research Academy. Baku, Azerbaijan

2023 Szabo, E., Ayeong, JK, Lunde, CE, Missmer, S, Borsook, D, Sieberg, CB, & Holmes, SA. Resting-state low-frequency fluctuation in patients with surgically confirmed endometriosis with and without migraine headaches. Human Pain Seminar Series, Centre for Multimodal Sensorimotor and Pain Research, Toronto, Canada. 2023

Please refer to Dr. Holmes' (Partnering PI) for additional oral presentations he may have given.

Poster Presentations:

Shafrir, A, Martel, E, Missmer, SA, Clauw, DJ, Harte, SJ, As-Sanie, S, Sieberg, CB Pelvic floor, abdominal, and uterine pain tenderness in relation to pressure pain sensitivity among women with endometriosis and chronic pelvic pain. Poster presented at the World Congress on Endometriosis, Virtual due to COVID 2021 Best Clinical Poster

Szabo, E, Timmers, I, Borsook, D, Simons, LE, & Sieberg, CB Brain functional connectivity changes in adolescent and young women with endometriosis-associated pain: A pilot resting state MRI study. Virtual 13th International Symposium on Pediatric Pain (ISPP). March 2022

Lunde, CE., Wu, Z., Szabo, E., Karunakaran, K., Kim, A., Holmes, SA., Borsook, D., Sieberg, CB. Assessing Pain Modulation and Childhood Trauma in People with Endometriosis. Judah Folkman Research Day, Harvard Medical School. June 2022

Lunde, CE., Wu, Z., Szabo, E., Karunakaran, K., Kim, A., Holmes, SA., Borsook, D., Sieberg, CB. Assessing Pain Modulation and Childhood Trauma in People with Endometriosis. Versus Arthritis 4th Annual Pain Research in the UK Conference July 2022

Lunde, CE, Holmes, SA, Sieberg, CB, Borsook, D Pilot study: Brain regions related to thermal pain differences during menstrual phases. Poster presented at the International Association for the Study of Pain, Toronto, ON, September 2022

Lunde, CE, Wu, Z, Szabo, E, Karunakaran, K, Kim, A, Holmes, SA, Borsook, D., Sieberg, CB Exploring the role of childhood trauma on descending pain inhibition in people with endometriosis using functional Near-infrared Spectroscopy. Poster presented at the International Association for the Study of Pain, Toronto, Canada, September 2022

Kim, A, Szabo, E, Lunde, CE, Sieberg, CB, Holmes, SA. Thermal sensitivity changes in the context of an MRI scanner: Application of quantitative sensory testing in mixed environments. Poster presented at the International Association for the Study of Pain, Toronto, Canada, September 2022

Szabo, E, Ayeong, JK, Lunde, CE, Missmer, S, Borsook, D, Sieberg, CB, & Holmes, SA Endometriosis and migraine: Exploring structural brain alterations in two comorbid pain disorders International Association for the Study of Pain (IASP) World Congress on Pain, Toronto, Canada. September 2022

Lunde, CE, Kim, A., Szabo, E, Holmes, SA., Borsook, D., Sieberg, CB. Endometriosis-associated pain and adverse childhood events: Is resiliency the missing puzzle piece? Poster presented International Pelvic Pain Society, Orlando, FL, October 2022

Lunde, CE, Kim, A., Szabo, E, Holmes, SA., Borsook, D, Sieberg, CB. Assessing inhibitory pain mechanisms and neural activity in patients with endometriosis-associated pain. Poster presented at the Society for Functional Near-infrared Spectroscopy, Boston, MA, October 2022

Lunde, CE, Szabo, E, Wu, Z, Karunakaran, K, Kim, A., Holmes, SA., Borsook, D, Sieberg, CB. Does offset analgesia vary as a function of adverse childhood events and resilience? Poster presented at the Society for Neuroscience, San Diego, CA, November 2022.

Szabo, E., Comptdaer, G, Ayeong, JK, Lunde, CE, Borsook, D., Holmes, SA, & Sieberg, CB. Alterations in resting-state low-frequency fluctuation in patients with surgically confirmed endometriosis. 2023 Annual Scientific Meeting of the US Association for the Study of Pain (USASP), Durham, NC, The United States. April 2023

Szabo, E., Comptdaer, G, Ayeong, JK., Lunde, CE, Sieberg, CB, Borsook, D & Holmes, SA. Functional brain alterations in patients with endometriosis with and without migraine comorbidity. Organization for Human Brain Mapping (OHBM) Annual Meeting, Montréal, Canada. July 2023

Szabo, E, Comptdaer, G, Ayeong, JK, Lunde, CE, Borsook, D, Holmes, SA, & Sieberg, CB (2023). Alterations in Resting-State Low-Frequency Fluctuation in Patients with Surgically Confirmed Endometriosis. The Journal of Pain, 24(4, Supplement), 76. <https://doi.org/10.1016/j.jpain.2023.02.222> [Published Abstract]

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

This grant afforded us the opportunity to create, to our knowledge, the first neuroimaging database (both fMRI & fNIRS) on adolescents-adults with endometriosis. Additionally, this database includes data on the novel application of a paradigm of descending pain inhibition (Offset Analgesia), which has not previously been investigated inside the scanner as an evoked pain assessment for this population. Understanding the neural underpinnings of this disease is critical for better diagnosis and treatment and for the development of more optimal therapies to treat the debilitating pain associated with endometriosis.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Corresponding PI: Dr. Christine Sieberg, no change

Partnering PI: Dr. Scott Holmes, no change

Consultant: Dr. David Borsook, no change

Consultant: Dr. Amy Danehy, no change

Co-Investigator: Dr. Stacey Missmer, no change

Post-doctoral fellow: Dr. Edina Szabo, no change

Post-doctoral fellow: Dr. Ziyang Wu

Research Coordinator: Claire Lunde, no change

Research Assistant: Ayeong Kim, no change

Research Assistant: Gabriela Comptdaer

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Both Dr. Sieberg and Dr. Holmes (Partnering PIs) were both responsible for each task to completed at Boston Children's Hospital where all participant testing took place, as well as the analyses and manuscript preparation and publication. Per the agreement, in addition to this report, Dr. Holmes is also submitting his own.

9. APPENDICES:

The Award Chart, Transition Plan, and copies of all published manuscripts from this award are included.



Award Log Number: Award Title

PI: Christine B. Sieberg (PI); Scott Holmes Partnering PI)

Budget: \$1,038,196

Topic Area: Endometriosis

Mechanism: Investigator-Initiated- Partnering PI

Research Area(s): Endometriosis; Chronic Pain

Award Status: 8/15/19-8/14/23; Final

Study Goals: To address a critical gap in knowledge pertaining to **endometriosis**; specifically, **neural mechanisms contributing to chronic pelvic pain (CPP)** in this population.

Specific Aims:

AIM 1a: To define changes in brain structure and function as a correlate of subjective measures of pain and psychophysical functioning in adolescent, young adult, and adult women with surgically confirmed endometriosis vs. healthy controls. **AIM 1b:** To correlate psychophysical measures (Quantitative Sensory Testing (QST) responses & psychological questionnaires) and brain changes with levels of Offset Analgesia (OA);

AIM 2a: To longitudinally compare brain metrics pre and post-surgery (structure and function) using fMRI with the same subjective measures noted in Aim 1 (QST responses & psychological questionnaires) in young women (ages 12-25) presenting for surgery for endometriosis. **AIM 2b:** To correlate psychophysical measures with levels of OA.

AIM 3: To compare brain metrics of adolescents, young adults, and adult women with endometriosis in Aim 1 with female patients ages 12-44 with migraines in our existing databases who have undergone structural and functional MRIs.

Key Accomplishments and Outcomes:

Publications: See attached in Appendix for copies of manuscripts and final report for details on manuscripts in preparation. PMIDs include: 31862211 ; 33204144 ; 34340095 ; 36375399; 36304055; 37766817

Patents: none to date

Funding Obtained: none to date

Transition Plan Questionnaire

Directions: Please answer all questions that apply for each product under development. Please fill out one document per product. *This is not an application for funding; however, answers will help us understand the outcomes and products from your award.*

1. After the award closes, would you be willing to periodically provide voluntary information (via email) regarding the project status (i.e. where the research is headed)? Yes ☒ or No ☐

These responses will help CDMRP demonstrate the return on its investments and will help demonstrate that the CDMRP is a responsible and successful steward of federal research funding.

2. What **conclusion(s)** does your final data support?

Collectively, the results from the final indicate that endometriosis and the associated pain confer central brain changes and significantly impact pain behavior and emotional functioning. The results from this grant enhance our understanding of the neurobiology of endometriosis associated pain, including age-related changes resulting from the disease, define an initial paradigm that may enhance the evaluation of patients in the clinic, and provide a step towards the use of objective measures for individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

3. Will you/have you applied for/obtained follow-on-funding for this project? **If yes**, please list (a) funding organization, (b) total budget requested/obtained, and (c) title of the funded proposal. *This information will be recorded as an outcome to this award.*

Unfortunately, I have applied three times to the DoD for new grants that would allow us to extend the findings of this grant and none were funded. The grants were entitled:

(1) Elucidating the biobehavioral pain mechanisms contributing to co-morbid endometriosis and migraines: A neuroimaging and proteomics approach (\$2,562,717); (2) Elucidating the biobehavioral pain mechanisms contributing to co-morbid endometriosis and migraines: A developmental perspective (\$3,736,432); & (3) Biobehavioral Mechanisms Contributing to Endometriosis-Associated Pain: A Neuroimaging Exploration of the Role of Stress in Adolescent and Adult Women (pre-proposal letter, no budget specified)

4. What will be the **next step(s)** for this project?

The Partnering PI and I will complete analyses and submit manuscripts for publication. I aim to take my ideas noted above that were not funded by the DoD and explore other funding opportunities such as the NIH. Endometriosis and the associated pain is a significant humanitarian and socio-economic burden impacting millions of women and warrants further investigation in order to devise more effective interventions.

5. How would you classify your **lead candidate product**? 

(a) Therapeutic (Small Molecule, Biologic, Cell/Gene Therapy): Please choose, if applicable

(b) Diagnostic

(c) Device

(d) Research Tool to Address a Research Bottleneck

(e) Knowledge Product (Non-material product such as a compound library, database, something that improves clinical practice, education, etc.)

(f) Other - Please Specify:

6. How does your candidate product aid the Warfighter, Veteran, Beneficiary, and/or General Population?

The information garnered from this research can be extrapolated to all women, military or civilian, as endometriosis impacts approximately 10-20% of women and is the leading cause of pelvic pain. Given that chronic pain, including CPP, encompasses alterations in sensory, emotional, cognitive and autonomic brain function that may significantly alter behavioral adaptation to various work, home and social environments during and after service or as a spouse to a serving member, an understanding of these mechanisms can provide a basis to mitigate the effects (through current and future treatments) of this condition in women during their most productive years and improve overall function.

7. Therapy / Product Development, Transition Strategies, and Intellectual Property

Describe the steps and relevant strategies required to move the candidate product (knowledge or tangible) to the next phase of development and/or commercialization. Please address any issues with intellectual property.

PIs are encouraged to explore the technical requirements and the current regulatory strategies involved in product development as well as to work with their organization's Technology Transfer Office (or equivalent regulatory/legal office), federal/international regulatory experts, to develop the transition plan and to explore developing relationships with industry, DoD advanced developers (e.g. USAMMDA), and/or other funding agencies to facilitate moving the product into the next phase.

Results of this study are already being disseminated through presentations at regional, national, and international conferences and peer-reviewed, open-access publications. Additionally, in order to best disseminate knowledge and advance the field, there is a need to engage with patient partners and to raise public awareness. In February 2024, Dr. Sieberg is transitioning to the Mass General Hospital Center for Health Outcomes and Interdisciplinary Research (CHOIR) where she will be able to collaborate with world experts in implementation science. Dr. Sieberg is also an invited member of the Society for Womens Health Research (SWHR), a national non-profit organization that is dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education with a focus on patient and caregiver partnerships. Part of the dissemination of the knowledge product of this grant will be aimed at working with the SWHR to determine if there is a way to translate this data and knowledge to the public, perhaps through toolkits on the SWHR website.

Additionally, in recent years, the concept of female-led technology (FemTech) industry- technology and software companies focused on addressing women's health needs has grown and is predicted to grow to \$1.07 trillion by 2026. " FemTech " has grown to encompass a range of technology-enabled, consumer-centric products and solutions addressing womens health. Dr. Sieberg plan to engage with " FemTech " in thinking of how to best disseminate our research findings related to women's health to clinicians and patient partners. Specifically, Dr. Sieberg is interested in taking the predictive models of pain we generate in the grant and devise mobile health applications for disease screening and treatment.

Further, based on the data produced in this grant, especially related to co-morbid endometriosis and migraine, approaches that include repurposing of drugs for this indication (EAP & migraines) would have commercial interest in biotech. Grant consultant Dr. David Borsook has extensive knowledge about commercialization having started multiple biotechs and have many contacts in industry.



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Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review

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Abstract

Endometriosis, a condition in which uterine tissue grows outside the uterus, is a debilitating disease, affecting millions of women and costing the United States approximately \$78 billion annually in pain-related disability. It is also the leading cause of chronic pelvic pain (CPP), which is often unresponsive to existing treatments. Adolescent women with the disease are at particular risk as there are often significant diagnostic delays, which in turn can exacerbate pain. Research and treatment guidelines for adolescents with endometriosis are largely based on studies for adult women due to the limited number of studies focusing on adolescents. The current paper critically reviews the literature as it pertains to endometriosis pathophysiology, mechanisms contributing to CPP, and treatment implications and recommendations with a focus on gaps related to adolescents.

Keywords

Endometriosis; Chronic pelvic pain; Inflammation; Nerve; Brain; Psychology; Treatment; Adolescence

1. Introduction

Endometriosis is a debilitating and incurable disease that is characterized by the presence of extrauterine endometrial glands and stroma anywhere outside of the uterine cavity and which affects 1 out of 10 women during the reproductive age (Klein et al., 2014). The subsequent inflammation and fibrosis can result in persistent pain, dyspareunia, infertility, and significant disruption of quality of life (Vercellini et al., 2014). The economic burden associated with endometriosis has been considered to be equivalent to other chronic diseases

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(*e.g.*, diabetes, Crohn's disease, Rheumatoid Arthritis (Simoens et al., 2012)) and is associated with lower health-related quality of life (Soliman et al., 2017). Details of the pathogenesis of the disease are considered elsewhere (Burney and Giudice, 2012). However, little is known about this disease in adolescent women, which is problematic given that earlier detection could yield better outcomes and change the trajectory of this debilitating condition from a disease, chronic pain, and quality of life standpoint.

Endometriosis is the leading cause of chronic pelvic pain (CPP), which is defined as noncyclic pain at or below the umbilicus of at least 3–6 months duration that interferes with daily activities (Powell, 2014). One-third of adolescents with CPP have endometriosis (Kontoravdis et al., 1999; Doyle et al., 2009), while prevalence rates for adult women range from 64 to 82% (Parazzini et al., 2017). For women who undergo surgery for endometriosis, up to 30 % of women report no postoperative improvement in pain and the degree of short-term pain improvement among the remaining patients varies (Abbott et al., 2004). Despite its high prevalence and negative effects, little is known about the pathophysiology underlying the development and persistence of CPP in endometriosis. Interestingly, endometriosis lesions are an incidental finding in 7–10 % of abdominal and pelvic surgeries and 20–25 % of women with endometriosis are asymptomatic (Bullett et al., 2010; Davis et al., 1993; Divasta et al., 2007; Stavroulis et al., 2006; Templeman, 2009; Tandoi et al., 2011) indicating that there is a subset of women with endometriosis who do not experience pelvic pain.

Multiple studies have determined that endometriosis within the adolescent population requires different considerations for treatment as it present differently. Studies on the effects of surgical treatment for adolescents are insufficient, though the treatment may effective for pain reduction. There are few studies that emphasize that complete laparoscopic excision can significantly reduce the recurrence rates of endometriosis in adolescents (Yeung et al., 2017). The largest prospective study of adolescents with endometriosis did not find disease reoccurrence (diagnosed visually or histologically) after complete laparoscopic excision of the disease in teenagers at a repeat laparoscopy for pain (Tandoi et al., 2011). There is no consensus within the field that adjuvant medical treatments are necessary for all adolescent patients nor that long-term problems such as disease recurrence, infertility, or chronic pain may be prevented (Tandoi et al., 2011). The European Society for Human Reproduction and Embryology (ESHRE) has provided guidelines on treatment for clinicians, which include counseling women presenting with endometriosis associated symptoms (*e.g.* dyspareunia, infertility, CPP), as well as providing known successful treatments of these symptoms, such as hormonal contraceptives, even if the cause is unknown (Dunselman et al., 2014). This is partially due to the invasiveness of laparoscopic surgery, as well as the ease of prescribing hormonal contraceptives, and its dual purpose of preventing pregnancy. This empirical treatment is especially common in adolescents with pelvic pain and dysmenorrhea (Yeung et al., 2017). However, the ESHRE has noted that recommending treatment of the symptoms instead of surgery for young women presenting with endometriosis symptoms may cause longer delays in diagnosis (Dunselman et al., 2014). Approximately 80 % of adolescent girls with CPP not responding to conventional medical therapy have endometriosis (Yeung et al., 2017). As surgery is currently the main procedure for diagnosing, this may result in young women carrying the painful condition into adulthood. Additionally, it has been shown that

using hormonal contraceptives in adolescents to treat of primary dysmenorrhea could be indicative of the diagnosis of deep endometriosis in later life (Chapron et al., 2011). The paradox of recommending empirical treatment to symptomatic adolescents might be perpetuating the significant delay in diagnosing endometriosis.

Despite high prevalence and disease burden, the precise pathophysiology of endometriosis, especially the association with CPP, is complex and is a combination of interacting processes that remain a mystery. However, the development of new technologies has provided progress in understanding the many intrinsic molecular mechanisms in the development of endometriosis, with progenitor and stem cells of the eutopic endometrium as the starting players and endometriotic lesions as the final pathomorphological trait. Baranov et al. (2018) hypothesized the existence of an endometriosis development genetic program that govern the origin of endometrium stem cells programmed for endometriosis, their transition (metaplasia) into mesenchymal stem cells, and their invasion of the peritoneum and progression to endometriotic lesions. Complex genomic and epigenetic interactions at different stages of the endometriosis process result in different forms of the disease, with specific features and clinical manifestations (Baranov et al., 2018; Greene et al., 2016; Bulun et al., 2015). Endometriosis and associated pain is complex (Fig. 1). The focus of the current paper is to outline the gaps the current literature on adult women with endometriosis and evaluate future opportunities for research going forward by applying what is known to adolescent women with endometriosis and CPP.

2. Beyond pain – sensation, functioning, fertility, and emerging comorbidities

2.1. The physical pain

While endometriosis is the leading cause of CPP; the distinction between pain that is expected with menstruation, pain that is expected in the context of an inflammatory disease, and pain that is exacerbated due to a myriad of poorly understood factors is unclear and results in diagnostic uncertainty and a poor prognosis.

What do we know about the origin of pain in endometriosis? One interesting advantage of the disease in humans is that the diagnosis is dependent on biopsy thus conferring a significant opportunity to define pathological processes in the human condition. There are a number of putative processes that include: (1) Ectopic: Endometriosis is found in the peritoneum, ovaries and rectovaginal space; (2) Invasiveness: Endometrial lesions can deeply infiltrate the intestines (Abrao et al., 2015), which may in turn affect nerves resulting in nerve entrapment (Medina and Lebovic, 2009); and (3) Inflammatory: Endometriosis is present in extrauterine locations that is estrogen dependent, thus an inflammatory process may affect normal nerves or damage nerves to produce a state dependent level of peripheral sensitization. Unfortunately, despite understanding these processes, there has been very little research into the mechanisms contributing to CPP associated with endometriosis relative to other diseases associated with chronic pain. Specifically, pain levels are not part of the existing classification systems for endometriosis (Haas et al., 2011), which is a missed opportunity given the clinical presentation of pain with this disease (Andres et al., 2018).

Improving the classification system to include pain will help to shift the field to consider this essential component of treatment. One study showed that women with endometriosis appear to have higher pelvic pain when compared to women with other gynecological conditions (Schliep et al., 2015). Symptoms of dyspareunia, dysmenorrhea, dyschezia and pain in the vaginal and abdominopelvic area are regularly reported among women undergoing laparoscopy, even among women with no identified gynecologic pathology. Future research is needed to understand the complex causes of chronic and acute pelvic pain among women who seek out gynecologic care but unidentified gynecologic pathology. Additionally, the investigation of the correlation between the stage of endometriosis and the pelvic pain classification system is needed to better predict outcomes for endometriosis patients with pelvic pain for both surgical and nonsurgical treatment (Schliep et al., 2015). There is a critical need to identify mechanisms contributing to CPP in endometriosis in order to identify those at greatest risk for pain and to identify brain and psychological factors that may predict the potential to undergo pain chronification. Given that most adult patients report symptoms of endometriosis as well as CPP during adolescence, this would be a critical time to intervene. This is especially important in the current opioid epidemic with new research highlighting that 24 % of Obstetrician/Gynecologists prescribe opioids for endometriosis-related pain (Madsen et al., 2018). Understanding the mechanisms that contribute to CPP in adolescent women with endometriosis will shift the field toward prevention and early intervention to allow for treatment before pain becomes disabling.

The guideline for treatment and approaching adolescents with endometriosis is based on studies examining adult women due to the limited number of studies focusing specifically on adolescents. It is recommended that the decision for surgical management of endometriosis should be based on clinical evaluation, imaging modality, and medical treatment response, with restrictive use of laparoscopy for diagnosis (Hwang et al., 2018). Although many clinicians prescribe gonadotropin-releasing hormone agonists to reduce inflammation, blood flow, and adhesions in endometriosis, research has shown that preoperative hormonal treatment may not reduce either endometriosis related pain or recurrence (Dunselman et al., 2014; Rolla, 2019). However, adjuvant hormonal treatment may result in pain relief from the effects of surgical treatment in the short term, and a suitable treatment (≥ 6 months) to prevent recurrence in the long term (Johnson et al., 2017).

2.2. Psychological distress

While many chronic conditions that result in pain can be psychologically distressing, there are unique considerations in women with endometriosis; for example, endometriosis can result in infertility (Tanbo and Fedorcsak, 2017). A young woman who is diagnosed will not ultimately know if her fertility has been compromised until she tries to become pregnant. This uncertainty can significantly impact quality of life in a way that is unique from other diseases. For example, while cancer treatments can result in infertility, many women are given the option to freeze their eggs prior to starting treatment (Bouchlariotou et al., 2012), which is also an option for women with endometriosis. As such, it is best to freeze eggs when women are younger and are likely to have improved responses to hormonal stimulation and the disease may not affect their ovaries; however, if there is a delay in diagnosis, as is often the case; this may not be an option.

Psychological factors also assume an important role in determining the severity of symptoms, and women diagnosed with endometriosis report high levels of anxiety, depression and other psychiatric disorders (Lagana et al., 2017). Additionally, it has been demonstrated that high levels of anxiety and depression can amplify the severity of pain (Cavaggioni et al., 2014). Moreover, several studies have described the influence of CPP on the quality of life and well-being of patients with endometriosis (Jia et al., 2012; Vitale et al., 2017; Siedentopf et al., 2008) and it has been shown to significantly influence emotive functioning (Friedl et al., 2015). Population-based studies that examine psychological outcomes for adolescents and young women are scant; however, one study (Rowlands et al., 2016) did find that young women, ages 18–23 years, with endometriosis had a greater risk of moderate to severe psychological distress compared to women without a history of this condition. Another study (Gallagher et al., 2018) of adolescents with endometriosis found that adolescents and young adult women with endometriosis had significantly worse reports of quality of life compared to peers unaffected by endometriosis.

There is a lack of literature on the influence of psychological factors and psychiatric comorbidities on the effectiveness of treatments for endometriosis within both adult and adolescent populations. It is important to evaluate the presence of previous psychiatric diseases to select patient specific treatment approaches. It is unclear if these comorbidities are a result of endometriosis itself or other factors; therefore the relationship between endometriosis and psychological diseases remains a mystery.

2.3. Comorbid conditions

Among adults, the risk of developing a comorbid condition among endometriosis patients was at least twice as large for the following comorbidities: infertility/subfertility, ovarian cyst, uterine fibroids, pelvic inflammatory disorder, interstitial cystitis, irritable bowel syndrome, constipation/dyschezia, ovarian cancer, and endometrial cancer (Surrey et al., 2018). Additionally, the incidence of developing many other comorbidities was significantly higher among endometriosis patients compared with matched women without endometriosis. Two recent and thorough reviews of the epidemiological literature described a number of factors associated with the development of endometriosis, including genetic profile, inflammation, hormonal activity, increased exposure to menstruation, immunological dysfunction, and environmental toxicants (Parazzini et al., 2017; Kvaskoff et al., 2015). Additionally, it was shown that endometriosis is associated with higher rates of a variety of conditions, including ovarian and other gynecological cancers, thyroid cancer, autoimmune diseases, asthma/atopic diseases, and cardiovascular diseases (Kvaskoff et al., 2015). Investigating comorbidities offers multiple benefits, including informing clinical surveillance, helping to develop prevention and early detection guidelines, and improving patient outcomes (Missmer, 2009). It is unknown if women with comorbid conditions experience heightened pain secondary to endometriosis; however, this should be explored when investigating comorbid conditions. Particularly, the association and degree of impact has not been studied or identified among adolescent and young women with endometriosis.

2.3.1. Diagnostic challenges across the ages—Given that endometriosis presents differently in adolescent women compared to adult women both in lesion appearance and

pain (*e.g.*, adolescents typically present with cyclic and non-cyclic pelvic pain (Laufer, 2008)) it is surprising that there has not been research exploring age-related differences in this disease. Such insight could result in novel treatments.

2.3.1.1. Prevalence - what about adolescents?: While endometriosis affects 1 in 10 women, endometriosis is also present in adolescents, with documented cases as young as age eight (Young et al., 2017). One study found that two-thirds of women diagnosed with endometriosis in adulthood presented with symptoms of the disease before age 20 (Stuparich et al., 2017; Sinaii et al., 2002) and it has been shown that endometriosis can occur prior to menarche (M.R. L., 2000).

2.3.1.2. Delay in diagnosis.: The non-cyclic pain presentation in adolescents can make the diagnosis difficult to infer resulting in a delay of an average of seven years between symptom onset and diagnosis (Laufer et al., 2003; Ballweg and Campbell, 2003); thus the incidence of endometriosis in adolescents has been difficult to quantify with estimates varying among different studies (Dessole et al., 2012). Additionally, it has been found that patients who report symptoms as adolescents are evaluated on average by four or more physicians before receiving a diagnosis of endometriosis (Ballweg, 2003). Similarly, the presence of comorbid conditions (*e.g.*, inflammatory, neuroendocrine, chronic pain) further complicating diagnosis (Sinaii et al., 2002; Bulletins–Gynecology ACoP, 2004; Mirkin et al., 2007). Lastly, the delay in the diagnosis is also attributed to the fact that laparoscopy with biopsy is the only way to diagnose endometriosis in the adolescent population, and depends on recognition of atypical manifestations of the disease as lesions in adolescents often appear differently than lesions in adult women (*i.e.*, adolescents tend to have clear, red, white, and/or yellow-brown lesions more frequently than black or blue lesions) and thus may be missed (Laufer et al., 2003). The lack of diagnostic biomarkers is a significant issue likely contributing to the poor long-term pain problems with this population. This delay in diagnosis is problematic as it may predispose women to more chronic pain, as ‘pain predicts pain’ (Katz and Seltzer, 2009), thus resulting in the development of a sensitized nervous system and a propensity to develop CPP and other chronic pain syndromes.

2.3.1.3. Progression – centralization of pain.: Intermittent or ongoing pain resulting from a disease can produce a sensitized peripheral and central nervous system (peripheral and central sensitization) that becomes maladaptive (centralization of pain). This can be especially true for those adolescent women with the disease who are not diagnosed until adulthood. Once the pain becomes centralized, profound changes in neural networks that involve anxiety, cognition, memory, and normal function of the brain's pain inhibitory (descending modulation) systems are thought to take place (Giamberardino et al., 2014; Whitaker et al., 2016; Simis et al., 2015). Most pelvic organs, as well as somatic pelvic tissues to which the pain is referred, share at least part of their central sensory projection. This may trigger the phenomena of cross-sensitization and central sensitization (Jarrell et al., 2014). However, this process is poorly understood as it relates to endometriosis and the secondary pelvic pain, which has resulted in few treatment options for this vulnerable population.

3. The origin of pain in endometriosis

3.1. The lesion

While lesions may be painful, this is not a linear process. Similar to other pain conditions, the presence and severity of pelvic pathology has been shown to not correlate with symptom burden (Dun et al., 2015) and pain frequently recurs even without visible disease at repeat laparoscopy (As-Sanie et al., 2013) so it is unlikely that the lesion is the specific cause of CPP.

3.2. The pain producing processes

Rodent models of endometriosis support the theory that a process of central sensitization likely results in CPP in this population via a viscera-visceral referred hyperalgesia, process in which increased input to the nervous system from one visceral domain can sensitize neurons that receive convergent input from another visceral domain (Berkley et al., 2001). Specifically, in the rat, it has been found that input from the uterus to the spinal cord is mainly by way of hypogastric nerve at the thoracic level, and that from the cervix is by way of both the pelvic and hypogastric nerves suggesting possible routes of referred pain (Berkley et al., 1993a). Neurons within both sets of segments have demonstrated to respond convergently to stimulation of the uterus, colon, and vagina and significant interactions exist between these two separated sets of caudal spinal segments (Berkley et al., 1993a, b). Additionally, the auto-transplanted ectopic endometrial cystic fragments develop their own innervation including sympathetic efferent as well as sensory fibers (Berkley et al., 2004), which may impact the nervous system. These studies support the theory that sensitized afferents innervate regions surrounding the endometrial growths result in central sensitization within the caudal spinal cord that is then referred to the vaginal canal (Berkley et al., 2001). This cross-talk between nerves and blood vessels by which lesions develop a unique local neuronal and vascular supply is referred to as neuroangiogenesis (Asante and Taylor, 2011) and can result in a direct and two-way interaction between the endometrial lesions and the CNS thus resulting in pain (Stratton and Berkley, 2011). Rat models of endometriosis have also revealed vaginal hyperalgesia (Berkley et al., 2001) as well as hyperalgesia of the paw (Hernandez et al., 2017), a non-pain site, a phenomenon also seen in women with endometriosis (As-Sanie et al., 2013). While mouse models of endometriosis have not been used as extensively as rats, Greaves et al. (2017) found that the peritoneal lesions in mice with endometriosis have an upregulation of prostaglandins as well as changes in gene expression both in the dorsal root ganglia and the CNS, and altered behavior including increased mechanical pain sensitivity suggesting complex biochemical and neurobiological mechanisms that interact to produce localized and referred pain.

3.3. Psychobiology and endometriosis associated pain

Psychophysiological factors are believed to assume a role in the development of central sensitization. Activation of the stress-response network lowers pain thresholds in both animals and humans, and high levels of anxiety are consistently related to higher pain sensitivity (Hirsh et al., 2008). Many studies have shown a prior history of anxiety, depression, and physical and psychological trauma, to be significantly predictive of the onset of chronic pain later in life (McLean et al., 2005; Talbot et al., 2009; Nicol et al., 2016). This

evidence suggests that pre-existing dysregulation of the nervous system may result in high susceptibility to the development of chronic pain via the development of central sensitization, but needs to be explored more specifically in regards to CPP and endometriosis. While there is mounting evidence on psychological factors contributing to CPP (Miller-Matero et al., 2016; Romao et al., 2009; Roth et al., 2011; Savidge and Slade, 1997), there is less known about CPP as it specifically relates to endometriosis. Similar to many other diseases associated with pain and chronic pain states, pain catastrophizing has emerged as an important determining factor in pain-related outcomes and is consistently associated with higher pain levels in women with endometriosis (Carey et al., 2014; Martin et al., 2011; Facchin et al., 2015). Similarly, high levels of anxiety and depression have been found in women with endometriosis (Lagana et al., 2017). One study Souza et al. (2011) found that women with endometriosis and CPP had worse quality of life and mental health compared to women with asymptomatic endometriosis; notably the asymptomatic group was not significantly different on mental health or quality of life variables from the control group, which suggests that the CPP may have a greater impact on psychological functioning than suffering from the actual disease state.

When examining the animal literature, the exploration of psychological factors contributing to CPP in animal models of endometriosis is scarce. While some studies have interestingly examined the role of stress in disease progression (Torres-Reveron et al., 2018; Cuevas et al., 2018), the role of stress on endometriosis-related pain specifically has not been studied extensively. Interestingly, one study (Hernandez et al., 2017) found that in rats with endometriosis that were exposed to stress compared to an endometriosis/no stress group and a sham-no stress group, the endometriosis with stress group had more adverse disease related issues such as increased colonic damage, vesicle mast cell infiltration and more severe vesicles. The endometriosis with stress group also developed significant hyperalgesia but stress interestingly reversed the allodynic effect found in endometriosis, which could be the result of a stress-induced analgesia phenomenon (Cuevas et al., 2018).

Outside of stress, there has been minimal animal research conducted on other salient psychological variables, such as anxiety and depression, on CPP in endometriosis. However, one recent study (Aso and Conrad, 1997), utilized a mouse model to explore the effect of endometriosis on CNS function, electrophysiology, and gene expression specifically to determine whether endometriosis can result in central pain sensitization, anxiety, and depression and to identify the molecular changes in the brain that are mechanistically responsible. Confirming what we know in human females with endometriosis, mice with endometriosis demonstrated more depressive, anxious, and pain behaviors compared to the sham control mice, even after the expected recovery period post-surgery. Microarray analyses revealed that genes involved in anxiety, locomotion and pain were altered; specifically, *Gpr88*, *Gla3* in the insula, *Chrb4*, *Npas4* in the hippocampus, and *Lcn2* in the amygdala were up-regulated, while *Lct*, *Serpina3n* in the insula and *Nptx2* in the amygdala were down-regulated. Additionally, patch clamp recordings in the amygdala were altered in the mice with endometriosis. The results of this study are important because they suggest that having endometriosis can impact brain electrophysiology and modulate gene expression, which may in turn result in pain sensitization as well as the anxiety and depressive symptoms frequently reported by women with this disease. Given that

endometriosis associated pain is still often conceptualized as peripherally driven, the findings from these animal studies underscore the likely centrally driven mechanisms contributing to CPP in this population, which could impact the development of centrally driven treatments.

3.4. Quantitative sensory testing (QST) - insights into pain sensitization

QST is used to assess responses to standardized noxious stimuli in a controlled laboratory setting and is the only method to assess central sensitization. Research using QST has highlighted variability in pain sensitivity and pain modulation as a putative phenotypic contributor to the risk for development of chronic pain (Rolke et al., 2006; Wilder-Smith, 2011; Shy et al., 2003). Reference values of the face, hand, and foot in sex and age matched healthy adults has been established (Rolke et al., 2006); however, no reference values for QST pelvic pain thresholds exist. CPP secondary to endometriosis has not been extensively explored via the use of QST and has focused on pressure pain. Tu et al. (2008) performed an initial validation and reliability assessment of vaginal pressure-pain thresholds in healthy women through the use of a vaginal pressure algometer and concluded that pressure pain threshold may be a valid and reliable measure of pelvic floor somatic pain sensitivity in healthy women. As a follow-up study utilizing this device, Hellman et al. (2015) found that women with CPP or painful bladder syndrome exhibited enhanced pain sensitivity with lower pressure pain thresholds compared to pain-free participants; however, both the CPP and painful bladder syndrome groups included women with endometriosis and as endometriosis was not the focus of this study the effect of this internal pressure paradigm on women with endometriosis with and without CPP is unknown. As-Sanie et al. (2013); however, did find that that peripheral pressure-pain thresholds were lower in women with endometriosis and CPP and in women with CPP without endometriosis when compared to both women with endometriosis and no CPP and pain-free women suggesting that perhaps the endometrial lesions are not driving the CPP.

There is scant literature on other QST modalities outside of pressure pain as it relates to endometriosis and nothing in adolescent women. A recent study (Grundstrom et al., 2019) did examine thermal and pressure thresholds in 13 women with surgically confirmed endometriosis and 24 women without but who had CPP compared to 55 healthy control women ages 18–40. QST sites included areas of presumed menstrual pain (*i.e.*, abdominal wall) compared to a control site (*i.e.*, dominant leg). Results indicated that women with CPP, regardless of endometriosis status, endorsed significantly lower quality of life as well as significantly greater symptoms of anxiety and depression compared to the control group. Additionally, the CPP group, again regardless of endometriosis diagnosis, had reduced pain thresholds compared to the control women, with duration of pelvic pain significantly negatively correlated with pain threshold. More research conducted on larger samples and other QST modalities such as mechanical pain, temporal summation, and conditioned pain modulation is warranted to further elucidate the relationship between sensory functioning and CPP. Additionally, research on adolescent women is warranted as endometriosis presents differently in this age group (Laufer et al., 2003).

3.5. Brain imaging – peripheral nerve lesions driving central brain changes

Little research on how CPP confers changes to the brain that result in increased resistance to treatment or chronification has been conducted across adolescent or adult populations with endometriosis (*i.e.*, from early onset to major manifestations during development). Some pilot studies conducted in adult women with endometriosis and/or CPP suggest that adult women with CPP have decreases in regional gray matter volume in brain regions associated with pain processing including the thalamus, cingulate gyrus, putamen, and insula (As-Sanie et al., 2012), suggestive of pain amplification related to CNS changes found in other chronic pain conditions such as fibromyalgia (Gracely et al., 2002) and vulvodynia (Harris et al., 2013). Additionally, another study by the same group (As-Sanie et al., 2016) found that women with endometriosis-associated CPP demonstrated increased concentrations of excitatory neurotransmitters in the anterior insula and had greater intrinsic connectivity of the same anterior insula region to the medial prefrontal cortex both known to be regions important in pain processing and reward neurocircuitry. Additionally, increased connectivity between these two regions was positively correlated with anterior insula combined glutamate and glutamine concentrations, as well as with pain intensity, anxiety and depression symptom severity. These studies suggest that pelvic pain is likely not sufficiently explained by the presence of endometriosis and may be due to dysfunction in the CNS pain regulatory system; however, these studies included small samples with only adult participants. How endometriosis and CPP impact the adolescent brain is not understood. Brain correlates utilizing fMRI of these and other changes known to occur in chronic pain have not been previously examined in adolescent or young adult women with endometriosis and are warranted in order to understand the age-related changes that may occur with the disease.

A recent study (Yano et al., 2019) examined pain-related behavior and brain activation in five cynomolgus macaques with naturally occurring endometriosis compared to three healthy female macaques. The macaques underwent pressure algometer pain sensitivity testing of the abdomen after undergoing a single dose of morphine, meloxicam and acetaminophen (a 3-day washout interval was used between drugs). One week following drug testing, brain activation in three of the macaques with endometriosis in response to non-noxious abdominal stimulation and the effect of a single dose of morphine on brain activation were examined with fMRI. For comparison, the effect of non-noxious abdominal stimulation on brain activation in three healthy, control macaques was also assessed compared to the healthy controls. One month following fMRI, treatment stimulation responses were obtained from five macaques with endometriosis. Following baseline determinations, macaques with endometriosis were treated for 8 weeks with dienogest and stimulation-evoked brain activation was assessed with fMRI on the eighth week of dienogest treatment. Response thresholds were measured two and four weeks after cessation of dienogest treatment. Results found that pain response thresholds were significantly less in the macaques with endometriosis compared to the healthy controls. Additionally, the non-noxious abdominal stimulation activated the insula and thalamus, brain regions implicated in pain processing, which was reduced by treatment with morphine and dienogest; however, significant residual non-noxious force-evoked activation of the thalamus was still present at the end of dienogest treatment suggestive of a central sensitization process.

3.5.1. Preemptive processes - getting to the brain before the disease does

3.5.1.1. Brain state and modifying disease trait.: Mechanisms contributing to CPP secondary to endometriosis would be further advanced in research if a common conceptual model was adopted. Specifically, a model that incorporates the complex interplay between centralized pain, psychological impact, environmental influences, and social variables, with more precise language for describing CPP measures. Conceptualizing CPP associated with endometriosis as a peripherally driven phenomenon is a disservice to the millions of women suffering from this disease. Simply removing lesions (often multiple times) is not going to fix the problem of what the evidence suggests is a centralized pain problem and will likely only exacerbate the pain. This is just one component contributing to the extreme delay in diagnosis and treatment for CPP associated with endometriosis - it takes an average of 7 years for a woman to be diagnosed with endometriosis after the onset of symptoms (Arruda et al., 2003). This is in part because CPP is not a monolithic concept but rather an emergent process that involves interactions between individual factors, environmental factors, and psychological and physiological reactivity. A purely physiological approach to pain assumes that pain intensity relates to the degree of tissue damage, but this often cannot explain the wide range of reactions in humans in response to a painful stimulus (Brawn et al., 2014; Sullivan et al., 2001). One aspect that is often neglected in endometriosis research and treatment is the psychological effects of the disease. It has been well documented that the health-related quality of life is impaired in women with endometriosis when compared with healthy control women. Similarly, pain intensity and pain cognition are independent factors influencing the health-related quality of life of women with endometriosis. Patients with endometriosis report more negative pain cognition when compared with controls and also report more pain anxiety, catastrophizing, and hypervigilance toward pain (Sullivan et al., 2001).

Empirical studies also indicate that specific psychosocial factors may modulate pain experience, pain-related distress and treatment outcomes. Recently, adverse early life events have been associated with the risk for endometriosis. One study (Liebermann et al., 2018) showed that women with endometriosis, compared to healthy control women reported significantly more often a history of sexual abuse, emotional abuse, and emotional neglect. The associations between abuse and endometriosis were stronger among women presenting without infertility, a group that was more likely to have been symptomatic with respect to pain (Harris et al., 2018). Additionally, severity, chronicity and accumulation of types of abuse were associated with greater risk for endometriosis. A link to maltreatment during childhood needs to be considered during the diagnosis and treatment process of women with endometriosis, as well as the research community. Additionally, research has also suggested a link between exposure to dioxins and dioxin-like chemicals and the development of endometriosis in women (Soave et al., 2015). Dioxin and dioxin-like compounds have long biological half-lives, can accumulate within the organism, and could negatively affect several physiological processes. However, the exact mechanism through which they operate is unclear. It is hypothesized that they could interfere with both immune and endocrine systems and may be an important environmental consideration. Understanding the mechanisms underlying these relations may better define the related pathophysiology of

endometriosis and associated pain and should be incorporated into a new conceptualized model of studying the disease.

3.5.2. Treatment approaches—In endometriosis, multidimensional and personalized pain treatment has been elusive. The targets for analgesic treatment fall into the usual categories of prevention or limiting the disease; peripherally acting and centrally acting medications; psychological approaches; and non-invasive procedures such as focused ultrasound. For chronic pain, the target is to reset the brain state using one or a combination of approaches. Below we summarize various therapeutic options.

3.5.2.1. Pharmacological treatments.: Standard treatments for endometrial pain are not specific and few randomized clinical trials for pain have been performed with commonly available medications used for chronic pain. Standard treatments for endometrial pain are not specific and few randomized clinical trials for pain have been performed with commonly available medications used for chronic pain. However, there are a number of trials ($n = 165$) when searched for interventional studies of endometriosis and pain as listed in clinicaltrials.gov, of which 85 utilize pharmacotherapy. Clinical trials for adolescents resulted in fewer studies ($n = 17$), of which two utilize pharmacotherapy, are noted in Table 1. New medical treatments for painful endometriosis are summarized in a recent guideline (Dunselman et al., 2014). Considering there are few pharmacological studies specifically targeting adolescent endometriosis, adult studies are also included in Table 1.

While treatments include hormonal agents (*e.g.*, dienogest, aromatase inhibitor (AI), gonadotrophine-releasing hormone (GnRH) antagonist, ant- tumor necrosing factor (TNF)- α , selective estrogen receptor modulator (SERM) (Tosti et al., 2017), & estrogen-progestin and progestins therapies (Vercellini et al., 2016)), novel treatments in the future may focus on the inflammatory response in the diseases. The effects on nerves from endometriosis entail both physical ‘entrapment’ and chemical ‘irritation’. Both activate immune responses. The immune response to tissue damage and its role in pain has been documented in detail elsewhere (Ren and Dubner, 2010; Totsch and Sorge, 2017; Pinho-Ribeiro et al., 2017). In endometriosis, not only may there be a response to tissue damage, but the immune response may be altered and indeed dysfunctional (Herington et al., 2011) rendering a hypersensitivity to pro-inflammatory stimuli or molecules. As such the condition may be responsive to treatments that target specific immune processes (Symons et al., 2018). Such treatments have involved non-specific immune modulators such as ketamine (De Kock et al., 2013; Beilin et al., 2007) to more focused pharmacotherapies (Vercellini et al., 2014) to current development of novel targets.

3.5.3. Behavioral based treatments—There is very little evidence for the efficacy of non-pharmacological approaches to the treatment of endometrial pain (Wattier, 2018) and empirically-based, non-pharmacological interventions for the treatment of endometriosis and CPP are rare. It is, however, well-established in the literature that CPP is highly distressing for women, associated with disability, comorbid with other mental health conditions, and often involves inconclusive and unsatisfactory medical investigations (Dalpiaz et al., 2008; Ghaly and Chien, 2000; Weijenborg et al., 2007). Existing psychologically-based pain treatment interventions, such as Cognitive-Behavioral Therapy

(CBT) or Acceptance and Commitment Therapy (ACT), could be modified to address the unique needs facing women with endometriosis and/or CPP. CBT has been established as a valid and effective treatment for chronic pain conditions (Morley et al., 2008; Niv and Devor, 2007), however, CBT studies that investigate interventions specifically targeting endometriosis and/or CPP in women are lacking. Stones and colleagues¹¹⁸ examined a range of behavioral and medical treatments addressing CPP in women and concluded that psychological therapies are shown to be effective for CPP in women; however in practice, treatment recommendations generally come from single studies, and the authors make an urgent call for more research (Stones and Mountfield, 2000). Nevertheless, CBT interventions have been shown to be effective in reducing pain, managing distress, improving sexual function and reducing disability for a range of gynecological conditions that are associated with CPP (Bergeron et al., 2001; Brown et al., 2009; Masheb et al., 2009).

Studies have also shown that endometriosis can adversely affect women and their partners' general psychological well-being, relationship adjustment and overall quality of life (Aso and Conrad, 1997). Furthermore, women with endometriosis report significantly more sexual dysfunctions compared to healthy women. Research on psychosexual interventions in endometriosis treatment is limited but shows to be effective in reducing endometriosis-related pain and associated psychosexual outcomes. Specifically, an individualized, couple-centered, multimodal approach to care, integrating psychosexual and medical management for endometriosis, is thought to be optimal.

3.5.3.1. Treating endometriosis associated pain in adolescents.: Endometriosis in adolescents requires unique considerations for treatment approaches, as it presents particular challenges in terms of diagnosis, variable presentation and symptoms, and choice of treatment (Laufer, 2008). The evidence of what we know about endometriosis and CPP supports advocating for increased awareness among adolescents and their health care providers about the need for early *clinical diagnosis* of endometriosis and timely treatment of severe dysmenorrhea/pelvic pain, usually with medical therapy as first line.

Once the disease is diagnosed and treated, these patients have favorable outcomes with hormonal and nonhormonal therapy (Dun et al., 2015); however, for those who do undergo surgery, about 30 % of women still report ongoing pelvic pain after surgery despite taking these medications (Abbott et al., 2004). Therapeutic options have been developed and successfully used to achieve controlling pain (Vercellini et al., 2018), improving quality of life when coupled with surgery (Marqui, 2015), and suppression of the hormonally active endometriotic tissue, although, they can come with unwanted side effects (Rafique and Decherney, 2017). There also is a great need for a specific conceptual model for adolescents with endometriosis; the younger the woman at onset of symptoms, the longer the duration until diagnosis is made (Benagiano et al., 2018). Early diagnosis and treatment is of paramount importance due to the reduced quality of life in young patients and for the possibility of progression that could endanger their reproductive potential.

4. Conclusions

Endometriosis in adolescents is a challenging clinical problem as it may present with a number of clinical and pathological differences versus adult women. Nevertheless, given the chronicity of the disease, the challenge is to avoid a delay in diagnosis, understand the disease and direct effective therapies at an early age. Given that endometriosis and accompanying CPP is a multi-faceted and complex problem there is in desperate need for a new approach from a diagnosis and treatment perspective. This will be accomplished by translational research methods.

While endometriosis can be treated by surgical excision of the lesions and/or hormonal treatment, sometimes combined with anti-inflammatory drugs, medical treatments are not curative and approximately 30 % of women who undergo surgery report ongoing pain after surgical excision of the lesions (Abbott et al., 2004). However, it should be noted that pharmacological treatments, while not curative, can be helpful following surgery and may be an effective strategy to limit the recurrence of the disease (Johnson et al., 2017). By understanding the neural underpinnings of the disease and risk factors for chronification, translational research could provide a basis for evaluating novel treatments and potentially lay the foundation for successful personalized, precision medicine to shorten diagnostic delay and maximize successful pain remediation.

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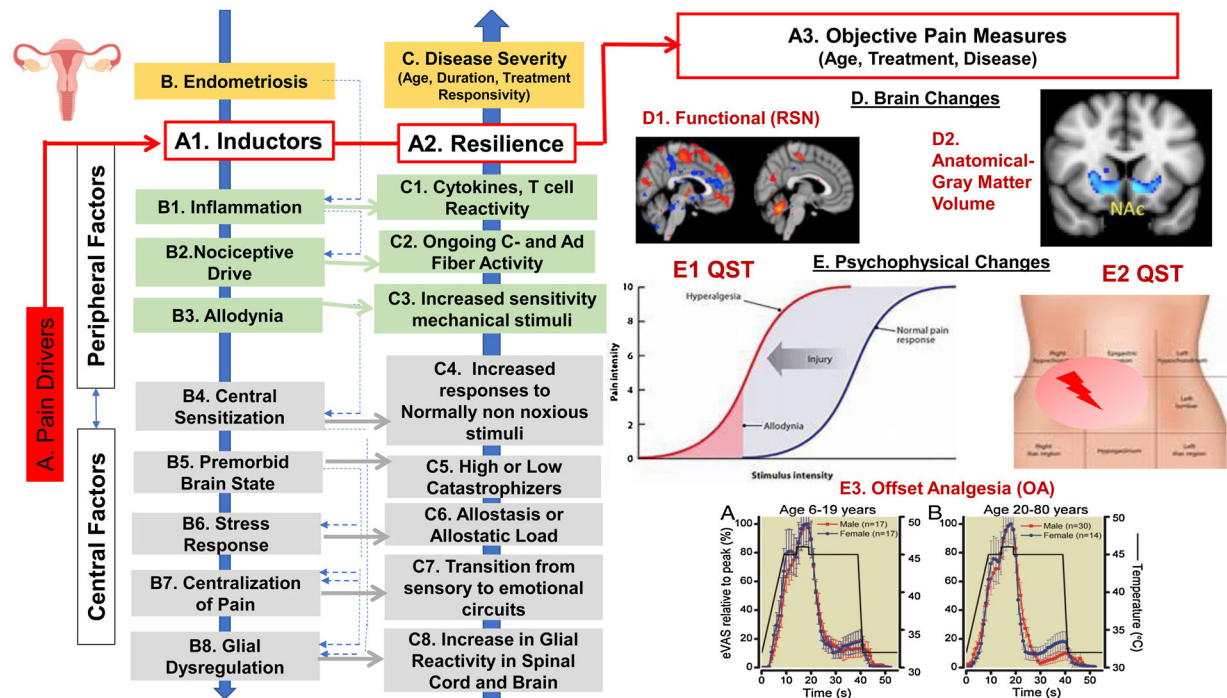


Fig. 1.

Mechanisms Contributing to Chronic Pain in Patients with Endometriosis.

This figure describes the multiple factors impacting pain in endometriosis, specifically the pain drivers, peripheral and central factors as either inductors or protectors against pain development, brain changes, and psychophysical changes. **A. Pain Drivers** including inductors of pain and resiliency factors impact and predict objective pain measures (red). **B. Disease & C. Disease Severity** factors are influenced by both peripheral factors (B1-B3) and central factors (B4-B8) that can be either inductors of pain or protective against the development of chronic pain. **D. Brain Changes**, which can include assessment of (1) functional – using resting state measures (RSN) (D1) and structural (D2) – gray matter volume (unpublished data from our group). **E. Psychophysical Changes**- Quantitative Sensory Testing (QST) can be used to produce measures of ongoing Peripheral Nervous System (PNS) and Central Nervous System (CNS) Sensitization (E1-E2). Offset Analgesia (OA) (E3) can be used for measures of CNS Modulatory Responsivity such as normal or intact OA (E3A- in male vs female volunteers ages 6–19 years; including rapid and large decrease in pain levels with a small decrease in pain stimulus, and Disrupted OA (E3B in males vs. female volunteers ages 20–80 years), including minimal decrease in pain levels with a small decrease in pain stimulus (Niesters et al., 2011). Responses for both E3A & E3B are percentage of peak response.

Table 1

Examples of endometriosis and pain pharmacological clinical trials (data collected from clinicaltrials.gov).

Drug	Phase	Mechanisms of action	Age of participants	ClinicalTrials Identifier
Ulipristal (other names: Ulipristal Acetate; Ella)	4	Progesterone receptor modulation (Bressler et al., 2017)	18–50 Years	NCT02213081
Gefapixant (other name: MK-7264)	2	Antagonist P2 × 3 and P2 × 2/3 receptors (Richards et al., 2019)	18–49 Years	NCT03654326
Relugolix	1 3 2 3 3 3	Active nonpeptide gonadotropin-releasing hormone (GnRH)-receptor antagonist (Markham, 2019)	1 18–50 Years 2 18–51 Years 3 20+ Years	1 NCT03204318 2 NCT03654274 3 NCT03931915
Estradiol/norethindrone acetate (other names: EZ/NETA; Activella)	1 3 2 3 3 3	Hormonal therapy - steroids bind to their receptor, activating hormone response elements and gene transcription; this subsequently activates hormone response proteins that influence cell function and differentiation (Casey and Murray, 2008)	1 18–50 Years 2 18–49 Years 3 18–51 Years	1 NCT03204318 2 NCT03343067 3 NCT03654274
Lidocaine	1 NA 2 2	Synthetic aminoethylamide with local anesthetic and antiarrhythmic properties (Wickstrom et al., 2013)	1 18–50 Years 2 21+ Years	1 NCT01968694 2 NCT01329796
Quinagolide	1 2 2 2	non-ergot dopamine agonist (Delgado-Rosas et al., 2011)	1 18 Years 2 18–45 Years	1 NCT03692403 2 NCT03749109
Thalidomide	1	anti-angiogenic (Paravar and Lee, 2008)	18+ Years	NCT01028781
Elagolix (other name: NBI-56418)	1 3 2 3 3 3 4 3 5 3 6 3 7 2 8 2 9 2 10 2	Active non-peptidic GnRH antagonist (Vercellini et al., 2019)	1 18–49 Years 2 18–49 Years 3 18–49 Years 4 18 to 50 Years 5 18–49 Years 6 18–50 Years 7 18–49 Years 8 18–45 Years 9 18–45 Years 10 18–55 Years	1 NCT03213457 2 NCT03343067 3 NCT01931670 4 NCT01760954 5 NCT01620528 6 NCT02143713 7 NCT00619866 8 NCT00797225 9 NCT00109512 10 NCT00458458
Depot-Leuprolide/Norethindrone	3	GnRH agonist (Homstein et al., 1998)	18 to 52 Years	NCT00229996
Yasmin	1 3 2 4 NA	Oral contraceptive (Fahizadeh et al., 2010)	1 18–52 Years 2 18–45 Years 18–50 Years	1 NCT00229996 2 NCT02237131 NCT02372903
Palmitoyl ethanolamide-polydatin		Endogenous fatty acid amide and Polydatin is a natural precursor of resveratrol (Gugliandolo et al., 2017)		

Drug	Phase	Mechanisms of action	Age of participants	ClinicalTrials Identifier
Infliximab	2	anti TNF α monoclonal antibody (Ceyhan et al., 2011)	20–45 Years	NCT00604864
Atorvastatin + oral contraceptive (other name: Arox 20)	NA	HMG-CoA reductase inhibitors (Simsek et al., 2014)	18–45 Years	NCT00675779
Mercilon	NA	Oral contraceptive (Anon., 1989)	18–45 Years	NCT00675779
Linzagolix (other names: OBE2109, KLH-2109)	1 3 2 2 3 2 4 2	GnRH antagonist (Greene et al., 2016)	1 18–49 Years 2 18–45 Years 3 18+ Years 4 18+ Years	1 NCT03986944 2 NCT02778399 3 NCT01629420 4 NCT01395940
Resveratrol	4	Plant-derived polyphenolic phytoalexin (Delgado-Rosas et al., 2011)	20–50 Years	NCT02475564
Cabergoline	2	dopamine agonist (Jouhari et al., 2018)	15–40 Years	NCT03928288
ASP1707	2	GnRH antagonist (D'Hooghe et al., 2019)	18–45 Years	NCT01767090
Leuprorelin acetate (other name: Prostag® SR)	1 2 2 2 3 2 4 2 5 4	synthetic nonapeptide that is a potent GnRHR agonist (Wilson et al., 2007)	1 18–45 Years 2 20+ Years 3 20+ Years 4 20+ Years 5 18–40 Years	1 NCT01767090 2 NCT01458301 3 NCT01452685 4 NCT02778919 5 NCT02393482
Desogestrel (other name: Cerazette)	NA	GnRH inhibitor (Tannahasamut et al., 2017)	18–45 Years	NCT01559480
Tanezumab	2	Monoclonal antibody against nerve growth factor (Goenka et al., 2017)	18–49 Years	NCT00784693
Leflunomide (other names: BGS649)	1 2 2 2	Aromatase inhibitor (Vercellini et al., 2014)	1 18–49 Years 2 18–40 Years	1 NCT01116440 2 NCT01190475
Letrozole	1 2 2 2	Non-steroidal aromatase inhibitor (Nothnick, 2011)	1 18–42 Years 2 18+ Years	1 NCT04002141 2 NCT00240942
depot medroxyprogesterone acetate (DMPA)	1 4 2 4	Intramuscular injection for long-term contraception (Mishell, 1996)	1 18–45 Years 2 18–45 Years	1 NCT01056042 2 NCT02534688
DLBS1442 (Dismeno)	2	Bioactive fraction extracted from the fruit of the native Indonesian plant (Tandrasasmita et al., 2015)	18–50 Years	NCT01942122
Decapeptyl (other names: Triptorelin acetate)	1 4 2 3	GnRH agonist (Leone Roberti Maggiore et al., 2014)	1 18–45 Years 2 18–45 Years	1 NCT00735852 2 NCT03232281
Dichloroacetate (other names: DCA)	NA	inhibit pyruvate dehydrogenase kinase (Michelakis et al., 2008)	18+ Years	NCT04046081
Levonorgestrel (other names: Mirena)	1 4 2 2 3 4	Levonorgestrel releasing intrauterine system - contraceptive (Beatty and Blumenthal, 2009)	1 18–45 Years 2 18+ Years 3 18–45 Years	1 NCT02480647 2 NCT02203331 3 NCT02534688

Drug	Phase	Mechanisms of action	Age of participants	ClinicalTrials Identifier
BAY1128688	2	AKR1C3 protein inhibitors (Greene et al., 2016)	18+ Years	NCT03373422
Pravastatin (other name: Pravastatin sodium)	NA	HMG-CoA reductase inhibitors (Sokalska et al., 2019)	18–38 Years	NCT02079974
Anastrozole	4	nonsteroidal inhibitor of aromatase (Chia et al., 2008)	18–50 Years	NCT01769781
Danazol	2	derivative of the synthetic steroid ethisterone (Godin and Marcoux, 2015)	18–50 Years	NCT00758953
Melatonin	2	Hormone produced by pineal - endometriosis mechanisms unknown (Mosher et al., 2019)	18–55 Years	NCT03782740
Degarelix (other name: firmagon)	3	GnRH receptor antagonist (Santen, 1992)	20–45 Years	NCT01712763
Goserelin (other name: decapeptyle)	3	GnRH agonist (Moore et al., 2015)	20–45 Years	NCT01712763
Anakinra (other name: Kineret)	1	Markers of inflammation - nonglycosylated human interleukin-1 receptor antagonist (IL-1Ra) (Stocks et al., 2017)	18–40 Years	NCT03991520
Dienogest	1 3	Orally-active semisynthetic progestogen (Ferrero et al., 2015)	1 20+ Years	1 NCT01697111
	2 NA		2 18 –38 Years	2 NCT03142035
	3 3		3 18–45 Years	3 NCT01822080
	4 4		4 18–40 Years	4 NCT03789123
	5 2		5 12–17 Years	5 NCT01283724
	6 4		6 18–51 Years	6 NCT02385448
Rosiglitazone (other name: Avandia)	2	Increase insulin sensitivity (de Oliveira et al., 2017)	18–45 Years	NCT00115661
ERB-041	2	Estrogen receptors (Chaudhary et al., 2014)	18–45 Years	NCT00318500
Proellex	12	Progesterone receptor blocker (Goenka et al., 2017)	1 18–48 Years	1 NCT00556075
	2 2		2 18–47 Years	2 NCT01728454
	3 2		3 18–48 Years	3 NCT00958412
	4 2		4 18–47 Years	4 NCT01961908
Vilaprisan (BAY1002670)	12	Synthetic and steroidal selective progesterone receptor modulator (Moller et al., 2018)	1 18+ Years	1 NCT03573336
	2 3		2 18–45 Years	2 NCT00225186
Asoprisnil	3 2	Synthetic, steroidal selective progesterone receptor modulator (DeManno et al., 2003)	1 18–40 Years	1 NCT00160446
	1 2		2 18–40 Years	2 NCT00160420
	2 2		3 18–40 Years	3 NCT00160433
Cannabinoid	2	Cannabinoid receptor (Bouaziz et al., 2017)	18–40 Years	NCT03875261
PGL2001	2	Steroid sulfatase inhibitor (Pohl et al., 2014)	18–45 Years	NCT01631981
Loestrin (other name: microgestin)	4	Contraception: norethindrone (a progestin) and ethinyl estradiol (an estrogen) (Greene et al., 2016)	18–45 Years	NCT02214550

Commentary: Novel Use of Offset Analgesia to Assess Adolescents and Adults with Treatment Resistant Endometriosis-Associated Pain

This article was published in the following Dove Press journal:
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Background and Objective: Endometriosis, affecting approximately 176 million adults and adolescents worldwide, is a debilitating condition in which uterine tissue grows outside the uterus. The condition costs the US economy approximately \$78 billion annually in pain-related disability. By understanding the neural underpinnings of endometriosis-associated pain (EAP) and risk factors for chronification, translational research methods could lessen diagnostic delays and maximize successful pain remediation. This can be accomplished by the novel use of a known method, offset analgesia (OA), to better elucidate the neural mechanisms that may contribute to and maintain EAP. This commentary will provide justification and rationale for the use of OA in the study of EAP.

Conclusion: Utilizing an OA paradigm in patients with endometriosis, especially adolescents, may (1) provide insight into neural mechanisms contributing to pain maintenance, which could capture those at-risk for the transition to chronic pelvic pain, (2) provide a metric for the development of future centrally mediated treatment options for this population, and (3) elucidate the brain changes that result in resistance to treatment and pain chronification.

Keywords: endometriosis, chronic pain, offset analgesia, central nervous system

Endometriosis and Pain

Endometriosis, a debilitating condition in which uterine tissue grows outside the uterus, affects approximately 176 million adults and adolescents worldwide¹ and costs the US economy approximately \$78 billion annually in pain-related disability.² It has a deleterious impact on physical and emotional functioning, as well as quality of life, and is the leading cause of chronic pelvic pain (CPP).³ Following laparoscopic surgery, to both confirm the diagnosis and remove the ectopic tissue, patients are commonly managed with a hormonal regimen during the childbearing years. Despite these treatments, approximately 30% of women report no improvement in pain after surgery and many other patients report frequently recurring endometriosis-associated pain (EAP) without evidence of recurrent disease.⁴ With this high prevalence of pain and disease burden, there is a lack of effective treatments for this subset of treatment non-responders who continue to experience EAP.⁵ Endometriosis in adolescents is an even more challenging problem as it may present with a number of clinical and pathological differences that are not observed in adult women. Nevertheless, given the chronicity of the disease, the challenge is to avoid a delay in diagnosis, understand

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the disease, and direct effective therapies at an early age.⁶ Small pilot studies^{7,8} in adult women have shown the maintenance and chronicity of EAP to be associated with structural and functional alterations in regions related to pain modulation suggesting that EAP is not explained by endometriosis alone, but alternatively may be explained by dysfunction in the Central Nervous System (CNS) either as a defective pain modulatory system or an increase in neuronal responsivity in central sensory and emotional pain pathways. Recent animal models have shown that the type of nerve that innervates the endometriosis lesion, as well as the location of the lesion, impact the CNS differently and thus dictate how the pain is modulated, such as peripherally, centrally, and by other central dynamic processes.⁹ As the onset of this condition may begin before menarche^{10,11} and adult women report their symptoms beginning during adolescence,¹² addressing early pre-symptomatic markers of pain chronification in the pediatric brain may change the prognosis by increasing the quality of life and protecting the health and reproductive system of adolescents with endometriosis. This can be accomplished by the novel use of a known method to better elucidate the neural mechanisms that may contribute to and maintain EAP – offset analgesia (OA). OA is increasingly used to measure endogenous pain inhibition, which is considered one of the central mechanisms facilitating (or preventing) pain and contributing to pain chronification.

Peripheral or Central Processing of Pain

One main reason for the lack of effective treatments is a poor understanding of the neural mechanisms contributing to the maintenance and exacerbation of pain in this population. Historically, the pain associated with endometriosis has been conceptualized and treated peripherally (eg, surgical excision of the lesion, oral contraceptives, NSAIDs, etc.) resulting from inflammatory nociceptive molecules or damaged nerves, leaving the role of the CNS largely ignored.⁶ Studies exploring changes in the CNS have found increased sensitivity to pain within and outside of the areas of the pelvis among endometriosis patients, as well as decreased gray matter volume (GMV) and increased functional connectivity in brain regions involved in pain processing such as the medial prefrontal cortex, anterior insula, cingulate gyrus, thalamus and putamen.^{7,8} In line with this, endometriosis patients without CPP did not show hyperalgesia and reduced GMV, but

they exhibited increased GMV in the periaqueductal gray (PAG) which is an important structure in the endogenous pain modulation system.⁸ Such findings support the notion that the alterations in the central processing of pain likely contribute to CPP in endometriosis.

Offset Analgesia in Experimental Settings

Overview – Why OA?

The most frequently used assessment paradigms for capturing this inhibitory pain mechanism are conditioned pain modulation (CPM) and OA. While CPM measures spatial filtering of pain perception (eg, the pain induced by one noxious stimulus is inhibited by another noxious stimulus applied to a remote area of the body), OA is related to filtering nociceptive information in the temporal domain.¹³ OA was first defined by Grill and Coghill¹⁴ as a form of endogenous pain inhibition characterized by a disproportionately large reduction in pain perception after a small decrease in temperature during noxious thermal stimulation. Although it has been proposed that both OA and CPM are mediated by central and peripheral mechanisms,¹⁵ OA seems to be related to increased activation in brain regions involved in pain modulation (eg, PAG, dorsolateral prefrontal cortex, anterior insula, brainstem), whereas CPM induces activity reduction in regions connected to afferent nociceptive processing which might implicate more brain-derived pain modulation during OA.¹³ OA is increasingly used to measure endogenous pain inhibition because when compared to CPM, it applies a noxious stimulus that evokes only moderate pain and the duration of the painful stimulus is also shorter which makes the paradigm more suitable for patients, particularly for adolescents.¹⁵ In addition, OA responses are not affected by centrally-acting drugs, while in some studies, CPM effects appear to diminish considerably after taking these medications.¹⁵ Hence, OA occurs predominantly by an opioid-independent mechanism which emphasizes the role of other neurotransmitters involved in the modulation of pain measured by this paradigm.¹⁶ Notably, some of these studies also reported that OA responses could not be modified in patients with chronic pain by analgesics such as ketamine,¹⁷ morphine vs placebo,¹⁷ NSAIDs and acetaminophen,¹⁸ tapentadol,¹⁹ and hydromorphone.²⁰

Human studies of EAP as a centrally mediating phenomenon, especially in adolescents, are lacking. Instead,

Quantitative Sensory Testing (QST),²¹ a set of psychophysical methods assessing pain sensitivity and sensory nerves, to produce measures of ongoing CNS and Peripheral Nervous System sensitization, has been the main focus in the field. General chronic pain,²² complex regional pain syndrome,²³ migraines,²⁴ abdominal pain,²⁵ sickle cell disease,^{26,27} fibromyalgia,²⁸ juvenile idiopathic arthritis,²⁹ and cerebral palsy,³⁰ have been the focus of adolescent QST studies, which all suggest that pediatric chronic pain can lead to maladaptive peripheral and central sensory processing. As more recent findings have suggested³¹ the central effects of EAP should be further explored and the use of OA could provide insight to the underlying neural mechanisms and persistence of CPP.

The OA Paradigm

Many OA paradigms have been described (see reviews^{15,32} on multiple paradigms); however, OA in the magnetic resonance imaging (MRI) setting,^{33–36} typically uses the 3-temperature paradigm (Figure 1)¹⁴ defined by a rating of 5 out of 10 on a visual analog scale (VAS). Notably, this standard 3-temperature paradigm has not been tested in a MRI setting with a pediatric population; however, OA was assessed in youth with chronic pain one time (outside MRI), applying an individualized noxious thermal stimulus of 50/100 on a VAS.³⁷ Using a thermal stimulator which is placed in contact with the skin, a preset computer-controlled temperature paradigm delivers the specific temperature pattern with the subject rating their pain in real time. A response to this dynamic test stimulus or offset trial (Figure 1A) consists of a reduction in self-reported pain intensity when the test temperature is applied for 5 seconds, raised by 1°C for 5 seconds, reduced by 1°C, and held for 20 seconds. The response to a constant test stimulus (Figure 1B) on the skin consists of a reduction in self-reported pain intensity when the test temperature is applied at a constant rate for 30 seconds. Lastly, the response to a controlled stimulus (Figure 1C) on the skin consists of a reduction in self-reported pain intensity when the test temperature is applied for 5 seconds, reduced to 32°C, and held for 30 seconds. One common method for quantifying the magnitude of OA is by determining the percentage of difference between the highest VAS scores during the second temperature and the lowest VAS scores during the third temperature. However, as OA responses can be partially due to adaptation effects, including the constant temperature trial is recommended to calculate OA effects. Accounting for the time-dependent

changes might mitigate overestimating the magnitude of OA.¹⁴ Functional MRI (fMRI) studies also used the constant thermal trial to evaluate OA responses in terms of pain adaptation and habituation.^{36,38} In the study of Zhang et al,³⁶ the constant stimulus trials served as control blocks to investigate brain activations to the attenuated OA effects in patients with various chronic pain disorders. Compared to healthy controls, reduced brain activation was found in regions associated with the descending pain modulatory, such as the anterior cingulate cortex, dorso-lateral prefrontal cortex, and reward systems, such as the medial prefrontal cortex, putamen, nucleus accumbens.

Offset Analgesia as a Clinical Tool

Recent studies report decreased or absent OA responses in patients with fibromyalgia,³⁸ neuropathic pain,¹⁷ migraine,³⁹ and chronic pain of various etiologies.^{36,37,40} In addition, three studies focusing only on chronic patients indicated decreased OA responses in patients with diabetic polyneuropathy, knee osteoarthritis,¹⁹ and chronic radicular pain^{17,18,20} although there was large interindividual variation. In patients with chronic pain, the attenuation of OA effects was observed by delayed offset and a relatively minor decrease in pain scores following the 1°C decrease in temperature as opposed to the disproportionately large reduction in pain perception among healthy controls (Figure 1). The body of literature on OA does provide strong evidence that attenuated OA responses are consistently found in patients with chronic pain, indicating a lack of ability to modulate changes in pain perception. Alterations of central pain inhibitory and reward systems might be associated with pain chronification, and the magnitude of OA could be a useful index to distinguish the 30% of patients with endometriosis who have persistent EAP after treatment.

Offset Analgesia in Endometriosis

Although OA responses have been found to be attenuated in patients with various chronic pain conditions, it is unknown in EAP. Only two studies have used CPM on patients with EAP⁴¹ and patients with dysmenorrhea⁴² (common symptom and predictor of endometriosis) which reported inconsistent results, calling for further investigation within this population. Furthermore, less efficient CPM was reported in comparable disorders such as irritable bowel syndrome⁴³ or CPP syndrome,⁴⁴ but not in premenstrual dysphoric disorder.⁴⁵ It should be also noted that the role of female-specific reproductive hormones on

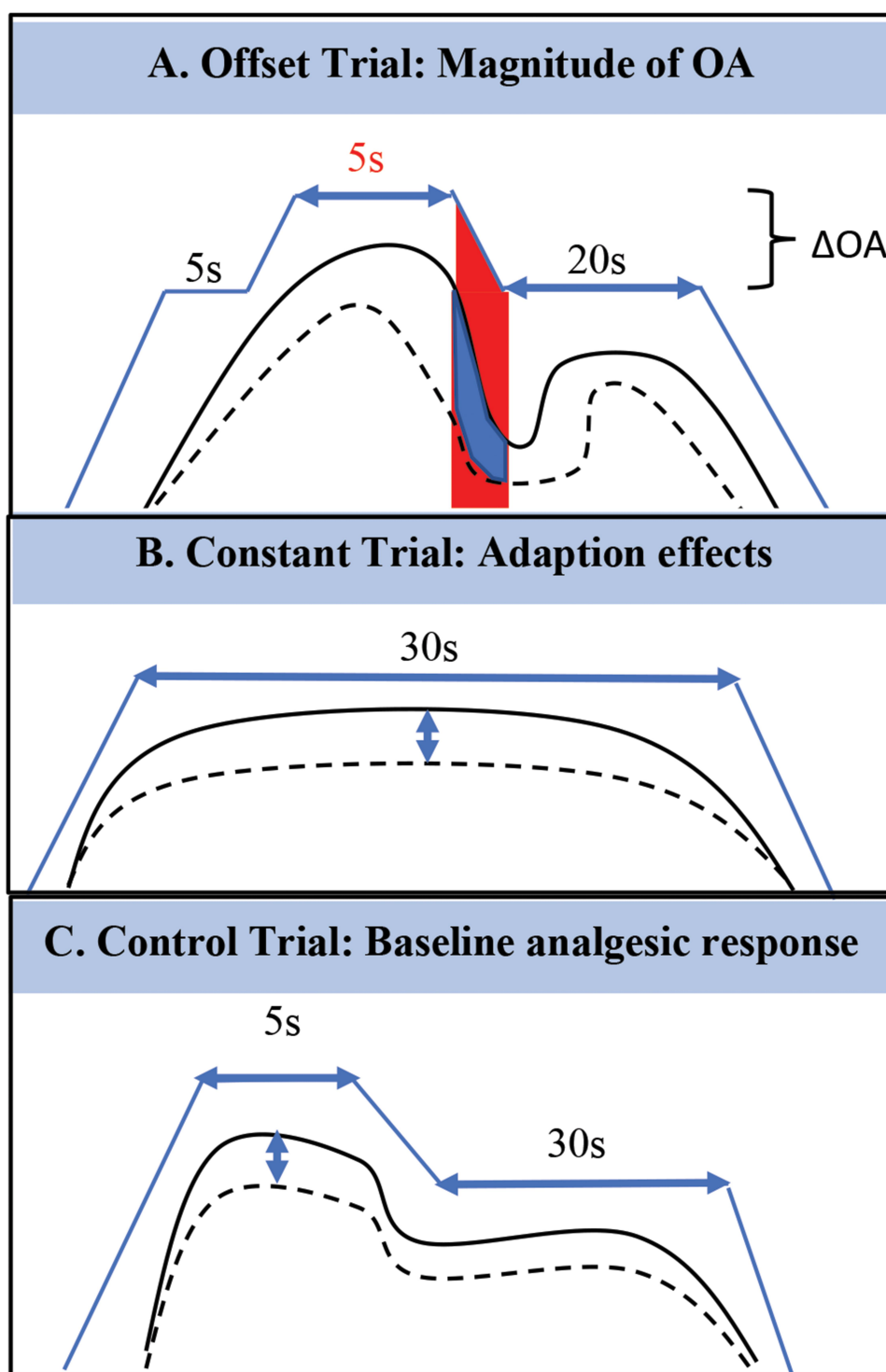


Figure 1 A commonly used 3-temperature OA paradigm includes Offset, Constant and Control trials. The x-axis represents time (seconds), with the y-axis representing temperature (Celsius). Participants continuously rate their pain using a visual analog scale (VAS) of 0–100. **(A)** The Offset Trial consists of individualized temperature 50/100 VAS for 5s, with a 10°C increase for 5s, and ending with a decrease in 10°C for 20s. **(B)** The Constant Trial consists of 30s at 20°C below the 50/100 VAS. **(C)** The Control Trial consists of 5s at 50/100 VAS and then 30s at 32°C. A 40s interval between each test is suggested. The red line below highlights the Offset Analgesia: a small decrease (10°C) in temperature during noxious thermal stimulation which leads to a disproportionately large reduction in pain perception. One method for measuring the magnitude of OA is determining the percentage of difference between the highest VAS scores during the second temperature (VAS_{max} 5s) and the lowest VAS scores during the third temperature (VAS_{min} 20s) in the Offset Trial: $\Delta OA = VAS_{max} 5s - VAS_{min} 20s$. Including a Constant Trial is recommended for calculating the OA magnitude to rule out adaptation effects. This OA paradigm captures endogenous pain inhibition, and it is associated with decreased brain activation of the descending pain modulatory and reward systems in patients with chronic pain.

sensation and perception is not fully understood, although some studies have found that the menstrual cycle influences pain sensations elicited by noxious stimuli.^{46–49} In line with this, OA has been found to be somatotopically organized in episodic migraine, a cyclic disease where pain perception changes according to the migraine phase.³⁹ Specifically, OA responses were measured at the forehead and forearm during the headache-free period, and the impaired pain inhibition was restricted to the affected area (the head). Based on these results, measuring OA on the lower abdomen (besides the forearm, which is the most commonly used examination site) should be considered in patients with EAP.

With ongoing pain (intermittent or constant), alterations in the sensitivity/responsivity of neural networks encompass those beyond the classic sensory pathways (eg, spinothalamic tract) and involve anxiety, cognition, memory, and the normal function of the brain's pain inhibitory (descending modulation) systems are thought to take place.⁵⁰ Through these changes in neural networks, one measurable process is a change in descending pain inhibition, which can be evaluated using the described OA paradigm. Given that EAP is a multifaceted and complex problem, there is a desperate need for a new approach to understand the neural mechanisms in both adult and pediatric cases of endometriosis. This could be accomplished by using translational research methods, such as OA, to determine if the brain regions associated with pain evolution and maintenance have been altered, leading to increased pain sensitivity which in turn could lead to an earlier finding of a more effective treatment. Based on the aforementioned results, the diminished endogenous pain inhibition measured with OA would thus be a reflection of an altered brain system in which there is an increased sensitivity to pain and increased resistance to treatment in conditions such as CPP associated with endometriosis.

A better understanding of the neural mechanisms occurring in the CNS and of the role of the brain's inhibitory response system in the development, maintenance, and exacerbation of EAP would provide a necessary paradigm shift for the field of adolescent and adult female reproductive health. Specifically, assessing the OA response in this patient population would: (1) enhance our understanding of the structural and functional alterations in the CNS pain regulatory system due to CPP in patients with endometriosis; (2) provide a measurable change in the brain's structure to follow such patients in the clinic; (3) potentially provide a measurable change in the brain for those who will develop EAP; and (4) define

an initial paradigm that may enhance our capability for developing individually tailored patient-oriented interventions.

Paradigm Shift for the Treatment of EAP

Evaluating OA responses could be beneficial in a clinical setting because it would give further information about the patient responses to different interventions. There have only been a few studies assessing the role of pharmacological interventions on the OA response and indicate that while the magnitude of OA was not affected by different analgesics, the reported clinical pain intensity decreased after treatment,^{17,18,20} indicating that pain relief may not necessarily be associated with the normalization of the central pain inhibiting system. Other centrally targeted therapies, such as Cognitive Behavioral Therapy, have largely been unexplored as they relate to the OA response. Patients with endometriosis and CPP appear to be a heterogeneous group with different levels of peripheral and central sensitization. Thus, some patients are likely to react better to therapies involving pharmacologic and cognitive-behavioral approaches that focus on the central aspect of pain than to repeated surgeries aimed at treating endometriosis. The OA paradigm might provide a useful tool to predict or confirm treatment responders vs non-responders and to reveal the extent to which different treatments can contribute to reversing the central changes.

Conclusion

By understanding the neural underpinnings of endometriosis-associated pain and risk factors for chronification, translational research methods, such as OA, could lessen diagnostic delays and maximize successful pain remediation. As OA has been administered at the volar side of the arm and the same time intervals (5 s, 5 s, 20 s) for many studies, this can be the recommended procedure for future studies of adolescents and women with treatment resistant endometriosis-associated EAP. Additionally, using the lower abdomen as an examination site should be considered. There is great need for estimating OA in patients with endometriosis, especially adolescents, as the way forward because it can: (1) provide insight into neural mechanisms contributing to pain maintenance, which could capture those at-risk for the transition to CPP, (2) provide a metric for the development of future centrally mediated treatment options for this population, and (3)

elucidate the brain changes that result in resistance to treatment and pain chronification. This novel use of an existing tool is of paramount importance due to the reduced quality of life in young patients and for the known grim condition outcomes in adulthood. To date, no previous studies have explored OA in adult or pediatric patients with EAP and given that most patients report symptoms of EAP during adolescence, this would be a critical time to investigate pain modulation with the goal of decreasing pain in women with endometriosis. More research in understanding the underlying neural mechanisms and centralized effects of pain within adolescents and adults with endometriosis is of great importance and the proposed utilization of OA in this population will hopefully move the field of reproductive health forward.

Author Contributions

ES and CEL conducted the literature review. SAH, CBS, and DB contributed to manuscript preparation. All authors made a significant contribution to the work reported, whether that is in the conception, and took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Ms. Lunde and Dr. Szabo both equally contributed to first authorship of this manuscript.

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Disclosure

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Pelvic floor, abdominal and uterine tenderness in relation to pressure pain sensitivity among women with endometriosis and chronic pelvic pain

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Abstract

Objective: Pelvic floor pain, abdominal wall pain, and central nervous system pain amplification can be contributing factors in chronic pelvic pain (CPP), however; limited research has investigated the association of pelvic floor, abdominal, and uterine tenderness with central nervous system pain amplification. We assessed whether pressure pain thresholds on the non-dominant thumbnail, a marker of central nervous system pain amplification, were associated with pelvic floor, abdominal, and uterine tenderness among women with endometriosis or CPP.

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Study Design: We conducted a cross-sectional study among 88 females with endometriosis and/or CPP. Abdominal (6 locations), pelvic floor (6 locations) and uterine (1 location) tenderness were assessed via a standardized physical exam. Participants reported their pain levels (0–10 scale) with application of 2 kg of pressure at each area, with a pain rating of ≥ 4 on the 0–10 scale considered moderate to severe pain. Pain sensitivity was measured on the non-dominant thumbnail by applying discrete pressure stimuli using a previously validated protocol.

Results: Overall, 50% (44/88), 42% (37/88), and 58% (51/88) of participants reported high pelvic floor, abdominal, and uterine tenderness, respectively. Pressure intensities needed to elicit ‘faint’ and ‘mild’ pain were lower for participants with high vs. low pelvic floor tenderness (median intensity for ‘faint’ pain=0.50 kgf/cm²(min-max:0.25–3.25) vs. 1.06(0.25–3.00), p-value=0.006; median intensity for ‘mild’ pain=2.00(0.63–4.88) vs. 2.63(0.75–6.00), p-value=0.03). No association was observed between pressure pain sensitivity and abdominal or uterine tenderness (p>0.11). Participants with endometriosis without pain were less likely to have high pelvic floor (22.2%), abdominal (11.1%), and uterine (25.9%) tenderness compared to participants with endometriosis with pain (63.0%, 50%, 65.2%, respectively) and participants with chronic pelvic pain (60%, 73.3%, 93.3%, respectively).

Conclusions: These results suggest that high pelvic floor tenderness among women with endometriosis/ CPP may be a marker of heightened pain sensitivity suggestive of central nervous system pain amplification and may impact treatment response. Future research should examine whether this clinical phenotype predicts response to medical and behavioral treatments (*e.g.*, anti-convulsants, behavioral therapy, Physical Therapy).

Keywords

generalized nociceptive hypersensitivity; pressure pain sensitivity; quantitative sensory testing; nociplastic pain; endometriosis; chronic pelvic pain

1. Introduction

Chronic pelvic pain (CPP) affects approximately 6–25% of reproductive-aged women and up to 70% of women with CPP will also have identifiable endometriosis.[1,2] While the mechanisms underlying CPP are not fully understood, it is thought that in some individuals with CPP, pain is caused (entirely or in part) due to peripheral or central nervous system (CNS) sensitization rather than as solely a direct result of endometriosis or other pelvic pathology – termed nociplastic pain by the International Association for the Study of Pain.[3] Abdominal wall and pelvic floor myofascial pain are known contributors to CPP, including among women with endometriosis.[4] However, it is currently unknown how abdominal and pelvic floor pain among CPP patients relates to CNS pain amplification.[5,6]

One assessment method of CNS sensitization or pain amplification is through the evaluation of evoked pain sensitivity at body sites distant from the clinical pain site, a form of Quantitative Sensory Testing (QST). QST research has highlighted variability in pain sensitivity and modulation as a risk factor for chronic pain development.[7–9] Previous studies have noted lower nonpelvic and abdominal/pelvic pressure pain thresholds (PPTs) among endometriosis and CPP patients compared to healthy controls,[10–13] including

research among the current study population.[11] Additionally, CPP patients have been shown to have lower pelvic floor muscle PPTs and higher pelvic floor muscle tenderness compared to healthy controls.[14] Recently, Phan *et al* (2021) reported that women with endometriosis-associated CPP had widespread pelvic floor myofascial dysfunction with low PPTs and palpable myofascial trigger points at pelvic floor muscles.[15] Additionally, the authors reported that endometriosis participants reporting diffuse pelvic pain were more likely to have at least 10 painful body territories, suggestive of widespread pain sensitization, compared to participants reporting local pain. However, it is not known how these two factors, nonpelvic PPTs and pelvic floor muscle tenderness relate to each other among women with CPP and endometriosis and no research has been conducted to assess pelvic floor muscle tenderness among endometriosis patients. Given that standard treatments for endometriosis, CPP, and pelvic floor myofascial pain (e.g. physical therapy) do not benefit all patients, a better understanding of the relationship between pelvic and abdominal tenderness and CNS pain amplification are necessary to identify personalized treatment plans for women with CPP and endometriosis.

In order to identify simple clinical findings that may be correlated with central sensitization and thus help guide treatment decisions, we sought to determine if patients with increased pelvic floor, abdominal and uterine tenderness have lower pressure pain thresholds on the non-dominant thumbnail among women with endometriosis or CPP. Additionally, we assessed the relationship of pelvic floor, abdominal, and uterine tenderness with quality of life and symptom severity including dysmenorrhea, dyspareunia, and dysuria.

2. Materials and Methods

2.1 Study Participants

The present analyses are a secondary analysis of the data presented in As-Sanie *et al* 2013 (refer to this paper for the full study details).[11] These analyses were limited to women with CPP or endometriosis. Premenopausal women aged 18–50 years, with CPP or surgically-confirmed endometriosis, and pelvic surgery within the last five years to confirm the presence or absence of endometriosis, were recruited between June 2006 and April 2010. [11] Participants were recruited from a tertiary-care endometriosis and pelvic pain referral center in addition to advertisements in the local community. Women who were pregnant, lactating, or menopausal, or who had a history of hysterectomy or oophorectomy were excluded from participation. Approval for this study was obtained from the University of Michigan Institutional Review Board and all participants provided signed informed consent.

2.2 Surgical, Medical and Demographic Information

Participants completed standardized questionnaires to assess demographics, medical history including surgical history and medication use, menstrual patterns, reproductive history, and pelvic pain history including severity, pattern, and symptom characteristics. Participants numerically rated the severity of their pelvic pain from 0–10 (0 = no pain, 10 = worst imaginable pain), and reported the average number of days per month in which they suffered from moderate to severe pelvic pain (defined as ≥ 4 on the 0–10 pain scale). Additionally, participants completed the Endometriosis Health Profile (EHP)-30[16,17] and the McGill

Present Pain Intensity scale.[18] Body mass index (BMI) was calculated as weight (in kg) divided by height (in meters) squared.

An author blinded to all study data and with expertise in surgical evaluation of gynecologic disorders (SA) reviewed the most recent operative reports for all endometriosis and CPP participants. Pathology results were not required, but were used when available. Endometriosis was staged in accordance with the revised American Fertility Society endometriosis scoring system.[19] Participants were categorized into three groups as previously described: (1) endometriosis with ≤ 4 days of moderate to severe pelvic pain per month (EndoØPain), (2) endometriosis with > 4 days of moderate to severe pelvic pain per month (Endo+Pain), and (3) CPP without endometriosis (CPPØEndo). As previously defined by this group, CPP is moderate to severe pelvic pain lasting ≥ 6 months and occurring ≥ 14 days monthly.

2.3 Nonpelvic Pressure Pain Sensitivity

All participants underwent pressure pain sensitivity testing by a blinded researcher. Testing was conducted using the multiple random staircase method on the non-dominant thumbnail as previously described by our group.[11] Initially, discrete pressure stimuli were applied to the thumbnail using a 1-cm² rubber probe in an ascending pattern starting at 0.25 kgf/cm² and increasing by 0.25–0.5 kgf/cm² steps until reaching each participant's individual pain tolerance or 10 kgf/cm². Perceived pain intensity for each pressure stimuli was measured using the Gracely Box Scale (GBS), a 0–20 numerical descriptor scale.[20] Response-dependent multiple random staircase pressure application was then applied to the non-dominant thumbnail to determine the pressure stimulus intensity (kgf/cm²) needed to elicit “faint” pain (0.5 on GBS), “mild” pain (7.5 GBS), and “slightly intense” pain (13.5 GBS).[21] Participants were asked to abstain from opioid analgesic use for at least 48 hours prior to their study visit and testing was performed between days 2 and 10 of the menstrual cycle, to limit hormonal variability.

2.4 Standardized Abdominal and Pelvic Exam

All participants underwent a standardized physical exam to assess abdominal, pelvic floor, and uterine tenderness using a standardized case report form and conducted by the same physician (SA) who was blinded to the patient's questionnaire data and pelvic pain status. Approximately 2 kg of pressure was applied using a single digit to four abdominal quadrants (right upper, left upper, right lower, and left lower), as well as the umbilicus and suprapubic areas. Participants reported each abdominal area to be either tender or nontender. An internal, single digit exam was then used to assess uterine tenderness and pelvic floor tenderness at the bilateral pubococcygeus, iliococcygeus, and coccygeus muscles. As previously described by Tu *et al*, the pelvic floor muscle locations were defined as follows: pubococcygeus is located anteromedial to the tendinous arch; iliococcygeus is located medial to the tendinous arch; coccygeus is located posteromedial to the ischial spine.[22,23] The coccygeus was examined 10 cm proximal to the introitus. All other pelvic floor muscle measurements were 5 cm from the introitus. Uterine tenderness was assessed vaginally at the posterior lower uterine segment. Approximately 2 kg of pressure

was applied to each pelvic floor and uterine site and participants were asked to rate their level of pain from 0–10 (0=no pain, 10=worst imaginable pain).

2.5 Definition of Abdominal, Pelvic Floor, and Uterine Tenderness

Abdominal, pelvic floor and uterine tenderness were categorized as high and low tenderness based on the distribution of tenderness to determine cut-points. High abdominal tenderness was defined as reporting >1 abdominal area as tender. High uterine tenderness was defined as reporting uterine tenderness with a pain rating of >4 on the 0–10 pain scale (considered as moderate/severe pain[24–26]). Finally, high pelvic floor tenderness was defined as reporting >2 tender pelvic floor areas with a pain rating of >4 on the 0–10 pain scale for each area.

2.6 Statistical Analyses

Participants were eligible for inclusion in analyses if they had complete data from the physical exam. Of the 114 endometriosis and CPP patients enrolled into the study, 88 had complete physical exam data. In these exploratory analyses, we used Chi-square and Fisher's Exact tests, where appropriate, to quantify the associations between high tenderness and the following categorical variables: endometriosis/ CPP status (EndoØPain, Endo+Pain, CPPØEndo), endometriosis stage (I/II, III/IV), number of abdominal surgeries (1, 2, ≥3), dysmenorrhea (none/mild, moderate/severe), dysuria (none/mild, moderate/severe), dyschezia (none/mild, moderate/severe), dyspareunia (deep pain: none/mild, moderate/severe), dyspareunia (pain with entry: none/mild, moderate/severe), and McGill Present Pain Intensity (no/mild pain, discomforting/distressing pain, horrible/excruciating pain). We used T-tests and Wilcoxon Rank Sum tests, where appropriate to assess the associations between high tenderness on physical exam and 'faint', 'mild', and 'slightly intense' pressure pain levels (kgf/cm²), duration of pelvic pain (years), and the EHP-30 scales (Pain, Control and helplessness, Emotion, Social, Self-image). Participants missing any of the variables above were excluded in the separate individual analyses.

All analyses were performed using SAS 9.4 (Cary, NC). All p-values were 2-sided and considered statistically significant if less than 0.05.

3. Results

3.1 Study Population Characteristics

Among the 88 study participants, the majority were White, nulliparous, current hormone users, and reported severe dysmenorrhea (Table 1). The average age was 31.3 years and approximately half of the participants reported at least 4.5 years of pelvic pain. Among all participants, 27 were classified as EndoØPain, 46 as Endo+Pain and 15 as CPPØEndo. Approximately 42% of participants reported >1 abdominal tender area (high abdominal tenderness; Figure 1), with the majority experiencing tenderness located in the lower quadrants (Supplemental Table 1). Additionally, 50% of participants reported >2 moderate/severe pelvic floor tender areas (high pelvic floor tenderness; Figure 1), with the median pelvic floor pain scores ranging from 4.0–6.0 (Supplemental Table 1). For uterine tenderness, 58% reported moderate/severe uterine tenderness (high uterine tenderness).

Overall, 32% of participants reported high tenderness for each of the three areas (abdominal, pelvic floor, uterine; Supplemental Figure 1).

3.2 Nonpelvic Pressure Pain Sensitivity and Endometriosis/CPP Characteristics

High pelvic floor tenderness was associated with lower pressure intensities needed to elicit 'faint' and 'mild' pressure pain at the non-dominant thumbnail compared to participants with low pelvic floor tenderness ($p=0.006$ and 0.03 , respectively; Table 2). High pelvic floor tenderness was also associated with lower pressure intensities needed to elicit 'slightly intense' at the non-dominant thumbnail; however, the association was not statistically significant ($p=0.12$). No significant differences for pressure pain sensitivity were observed for abdominal and uterine tenderness ($p>0.10$). Those with high tenderness in each of the three regions (abdominal wall, pelvic floor, uterus) were significantly more likely to have Endo+Pain or CPPØEndo compared to EndoØPain. Additionally, participants with high abdominal and uterine tenderness were more likely to have reported three or more previous abdominal surgeries compared to those with low tenderness ($p=0.06$ and 0.09 , respectively).

3.3 Pain Symptoms and Quality of Life

Women with high pelvic floor, uterine and abdominal wall tenderness reported higher (worse) EHP scores for each of the eight sub-scales of the EHP-30 compared to women with low tenderness (Table 3). Women with high uterine tenderness were more likely to report longer duration of pain compared to women with low tenderness (5.0 vs. 2.0 years; $p=0.04$) and there was a suggestion of longer pain duration among women with high abdominal tenderness compared to low (5.0 vs. 3.5 years; $p=0.09$). For each of the regions (abdominal wall, pelvic floor and uterus), women with high tenderness were also significantly more likely to report moderate/severe dysmenorrhea, and moderate/severe dyspareunia (both deep pain and pain with entry; $p<0.0001$). Pelvic floor, uterine and abdominal tenderness were not associated with severity of dysuria and dyschezia except that high uterine tenderness was associated with moderate/severe dyschezia ($p=0.01$). Finally, high tenderness for each of the regions was significantly associated with worse ratings on the McGill Present Pain Intensity scale with approximately 18% of high pelvic floor tenderness participants (vs. 7% low tenderness), 25% of high abdominal tenderness (vs. 4% low tenderness), and 23% of high uterine tenderness (vs. 0% low tenderness) reporting horrible/excruciating pain.

4. Discussion

The high prevalence of both endometriosis and CPP among women of reproductive age necessitates an improved understanding of the mechanisms contributing to both conditions, especially when they co-occur, in order to improve early detection for risk of CPP and to inform treatment decisions. The results of the present study indicate that women with CPP, both with and without endometriosis, had high pelvic floor, abdominal and uterine tenderness when compared to women with endometriosis without pain. Additionally, higher pelvic floor tenderness was associated with higher pressure pain sensitivities on the non-dominant thumbnail. These findings suggest that high pelvic floor tenderness is associated with CNS pain amplification in at least some women with CPP. Tenderness in each of the three areas was also related to worse pain intensity, including dysmenorrhea and

dyspareunia, as well as overall worse emotional functioning. Collectively, these results offer potentially important insight into the mechanisms of pain in women with CPP or endometriosis, which in turn could impact personalized treatment options.

Our results are consistent with other findings of high pelvic floor and abdominal tenderness among CPP patients and of higher pressure pain sensitivities in women with endometriosis with pain or CPP.[14,22,27,28] Similar to our results, Montenegro *et al* (2010) observed a prevalence of 58.3% for pelvic floor tenderness among CPP patients with higher pelvic floor tenderness associated with higher Beck Depression Index scores, dyspareunia, and constipation.[27] Additionally, previous research has shown that endometriosis patients have significantly lower PPTs at an abdominal wall tender point compared to healthy controls while women with CPP had lower PPTs at pelvic floor muscles compared to pain-free women.[12,14] However, this study is the first to examine how nonpelvic pain sensitivities relate to external and internal abdominal, uterine, and pelvic floor tender areas and to examine tenderness in all three areas with endometriosis pain status. More research is needed on larger samples to confirm our results and to explore other salient QST variables (e.g. temporal summation and conditioned pain modulation) or functional neuroimaging in order to further elucidate the relationship between sensory functioning and endometriosis pain/ CPP. Additionally, it would be important for future studies to explore how abdominal, pelvic floor, and uterine tender areas may be a potential marker for future development of CPP.

Treatment for endometriosis has traditionally focused on the lesions; however, endometriosis is a heterogeneous disease with multiple pain mechanisms that are not limited to only the lesions. Currently, there are no valid assessments to distinguish patients with different mechanisms of pain. The results of this study suggest that testing for pelvic floor tenderness as a part of a routine pelvic examination may be one component that is useful in identifying women with heightened overall pain sensitivity, and should be examined further in future research. Currently, pelvic examinations vary widely with many internal pelvic exams focusing on nodularity or masses, but not necessarily trying to identify focal tenderness of distinct pelvic areas,[29,30] suggesting there is a need to develop and implement standardized assessments for pelvic tenderness during examinations.[31,32] Further, co-existing pelvic floor tenderness and CNS pain amplification may explain why some women with pelvic floor tenderness do not respond solely to peripherally directed treatments such as pelvic floor physical therapy. These women may be refractory to standard treatments such as NSAIDS and repeated surgeries that largely target the peripheral nervous system and neglect the role of the CNS in the maintenance and exacerbation of pain. Rather this population may benefit from an interdisciplinary pain treatment approach, such as integrated behavioral therapy, physical therapy, and/or medications that target the nervous system (e.g., anti-convulsant; tricyclic anti-depressants).

The assessment of pelvic tender areas was not based on validated assessment tools; however, the procedures were performed by a single clinician blinded to patient clinical status, standardized across all participants allowing for consistency throughout the study, and adapted from a pelvic exam tenderness protocol previously published.[22,23] Further, the sample of this study was fairly small with a mostly White population and while we had

specific hypotheses about pressure pain thresholds and tenderness, the remaining analyses should be considered hypothesis generating. Future studies should include larger, more diverse populations. Finally, the definition of high and low tenderness was not based on a previously validated method, and future studies should explore additional cut-points in a bigger sample. A major strength of this study was the detailed information, operative reports and self-report pain symptoms, used to classify the endometriosis and CPP participants resulting in minimal misclassification. Additional strengths included the utilization of a researcher blinded to all study data and a standard protocol for the pressure pain sensitivity measurements.

5. Conclusions

Our findings that higher pelvic floor tenderness is associated with higher pressure pain sensitivity may explain why some women with pelvic tenderness do not respond solely to peripherally directed treatments as this pelvic tenderness may be a marker or consequence of concurrent CNS pain amplification in this subset of women. Future research should investigate whether comprehensive assessment of abdominal and pelvic tenderness may help to define a clinical phenotype that may predict differential treatment outcomes and even provide a step towards the use of more objective measures for individually tailored patient-oriented interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declarations of Interest:

S.A. has served as a consultant for Abbvie, Bayer, Myovant Sciences and Merck, and receives royalties as an author for UpToDate. D.J.C. has served as a consultant for Pfizer, Lilly, Tonix, Aptinyx, Samumed, Zynerva, and has received research funding from Aptinyx. S.E.H. has served as a consultant for Aptinyx, and has received research funding from Arbor Medical Innovations and Aptinyx. S.A.M. has served as an advisory board member for Abbvie and Roche. A.L.S., E.M., and C.B.S. report no conflict of interest.

Abbreviations

BMI	Body Mass Index
CNS	Central nervous system
CPP	Chronic pelvic pain
EHP	Endometriosis Health Profile-30

EndoØPain	Endometriosis with ≤4 days of moderate to severe pelvic pain per month
Endo+Pain	Endometriosis with >4 days of moderate to severe pelvic pain per month
CPPØEndo	Chronic pelvic pain without endometriosis
GBS	Gracely Box Scale
QST	Quantitative Sensory Testing
PPT	Pressure pain threshold

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Highlights

- About half of participants had high pelvic floor, abdominal, and uterine tenderness
- Endometriosis Health Profile-30 scores lower for those with high tenderness
- Pressure intensity levels were lower for those with high vs. low pelvic floor tenderness
- High pelvic floor tenderness may be a marker of heightened pain sensitivity

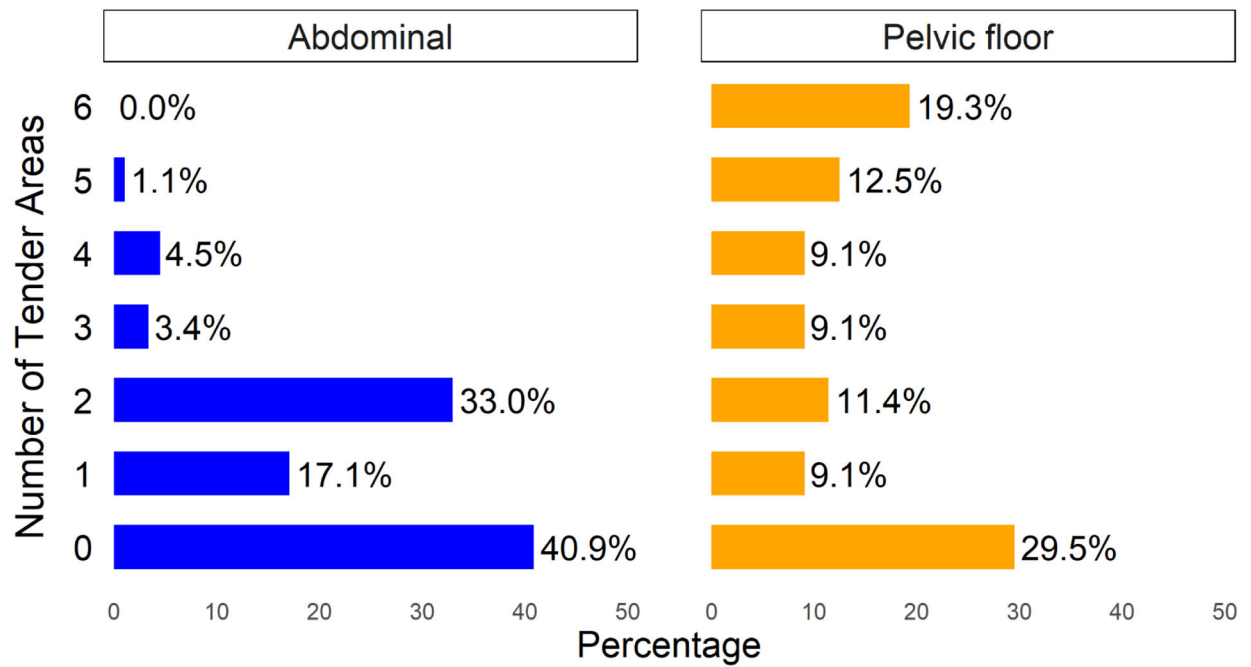


Figure 1: Number of abdominal and moderate/severe pelvic floor tender areas among endometriosis and chronic pelvic pain patients.

Blue = abdominal; Orange = pelvic floor; Abdominal tenderness assessed at right/left upper abdomen, right/left lower abdomen, suprapubic area, and umbilical area. Pelvic floor tenderness assessed at right/left pubococcygeus, right/left iliococcygeus, and right/left coccygeus muscles. Moderate/severe pelvic floor tenderness based on pain rating of ≥ 4 on a 0–10 pain scale at a specific tender area.

Table 1.Demographic, reproductive and pain characteristics of the study population (n=88)^{1,2}

	N	Mean (SD)
Age (years)	88	31.3 (8.5)
Body mass index (kg/m ²)	87	25.9 (5.4)
	N	Median (IQR)
Pain duration (years)	86	4.5 (1.5–9)
	N	%
Race		
White	77	88.5
Non-white	10	11.5
Current hormone use		
No	42	48.3
Yes	45	51.7
Current narcotic use		
No	72	81.8
Yes	16	18.2
Current antidepressant use		
No	76	86.4
Yes	12	13.6
Current physical therapy for pelvic pain		
No	84	95.5
Yes	3	4.5
Parity		
Nulliparous	55	62.5
Parous	33	37.5
Endometriosis/CPP status ³		
EndoØPain	27	30.7
Endo+Pain	46	52.3
CPPØEndo	15	17.1
Dysmenorrhea		
None/mild	16	18.6
Moderate	13	15.1
Severe	57	66.3

¹SD=standard deviation, IQR=interquartile range²Sample size does not always equal to 88 due to missing data – 2 missing for pain duration and dysmenorrhea, 1 missing for body mass index, race, and current hormone use³EndoØPain=endometriosis participants without dysmenorrhea or chronic pelvic pain; Endo+Pain=endometriosis participants with dysmenorrhea or chronic pelvic pain; CPPØEndo=chronic pelvic pain participants without endometriosis

Table 2.

Associations of pressure pain sensitivity and endometriosis/CPP characteristics with the number of tender areas in the pelvic floor, abdomen, and uterus¹

	Pelvic floor tender areas ²		Abdominal tender areas ³		Uterine tenderness ⁴		p-value ⁵
	Low Tenderness (N=44)	High Tenderness (N=44)	Low Tenderness (N=51)	High Tenderness (N=37)	Low Tenderness (N=37)	High Tenderness (N=51)	
Pressure intensity (kgf/cm ²) at non-dominant thumbnail needed to elicit							
‘faint’ pain	1.06 (0.25–3.00)	0.50 (0.25–3.25)	0.88 (0.25–3.00)	0.63 (0.25–3.25)	1.00 (0.25–3.00)	0.63 (0.25–3.25)	0.11
‘mild’ pain	2.63 (0.75–6.00)	2.00 (0.63–4.88)	2.25 (0.63–6.00)	2.50 (0.75–4.88)	2.63 (0.75–6.00)	2.25 (0.63–5.75)	0.33
‘slightly intense’ pain	4.13 (1.13–10.0)	3.31 (1.38–7.63)	4.13 (1.13–10.0)	3.44 (1.13–7.63)	4.25 (1.13–7.65)	3.44 (1.38–10.0)	0.30
Endometriosis and CPP status							
Endo∅Pain	21 (47.7)	6 (13.6)	24 (47.1)	3 (8.1)	20 (54.1)	7 (13.7)	<0.001
Endo+Pain	17 (38.6)	29 (65.9)	23 (45.1)	23 (62.2)	16 (43.2)	30 (58.8)	
CPP∅Endo	6 (13.6)	9 (20.4)	4 (7.8)	11 (29.7)	1 (2.7)	14 (27.5)	
Endometriosis stage ⁶							
Stage I/II	13 (34.2)	27 (81.8)	20 (44.4)	20 (76.9)	11 (31.4)	29 (80.6)	<0.001
Stage III/IV	25 (65.8)	6 (18.2)	25 (55.6)	6 (23.1)	24 (68.6)	7 (19.4)	
Number of abdominal surgeries (laparoscopy or laparotomy)							
One	20 (47.6)	22 (51.2)	29 (60.4)	13 (35.1)	22 (62.9)	20 (40.0)	0.09
Two	12 (28.6)	11 (25.6)	11 (22.9)	12 (32.4)	8 (22.8)	15 (30.0)	
Three or more	10 (23.8)	10 (23.3)	8 (16.7)	12 (32.4)	5 (14.3)	15 (30.0)	

¹Data are given as median (range) for continuous variables and sample size (percentage) for categorical variables.

²Pelvic floor tender areas assessed at right/left pubococcygeus, right/left ilioococcygeus, and right/left coccygeus. Each area reported as tender was palpated with 2kg of pressure and a 0–10 pain rating was obtained. High tenderness defined as >2 areas with pain rating of ≥4 on 0–10 scale (moderate/severe pain).

³Abdominal tender areas assessed at right/left upper and right/left lower abdominal, suprapubic and umbilical areas. High tenderness defined as >1 tender area reported as tender.

⁴Uterine tenderness assessed at posterior lower uterine segment with single digit vaginal exam. Participants with uterine tenderness had 2kg of pressure applied to the area and reported a 0–10 pain rating. High tenderness was defined as uterine tenderness with a pain rating of ≥4 on 0–10 scale (moderate/severe pain).

⁵Two-sided probability values from Chi-square or Fisher’s exact test for categorical variables and from Wilcoxon Rank Sum for continuous variables

⁶Among endometriosis cases with information on stage (n=70)

⁷Three participants were missing information on number of laparoscopic surgeries/laparotomies

Table 3.

Associations of pain symptoms and Endometriosis Health Profile-30 scales with the number of tender areas in the pelvic floor, abdomen, and uterus^{1,2}

	Pelvic floor tender areas ³			Abdominal tender areas ⁴			Uterine tenderness ⁵		
	Low Tenderness (N=44)	High Tenderness (N=44)	p-value ⁶	Low Tenderness (N=51)	High Tenderness (N=37)	p-value ⁶	Low Tenderness (N=37)	High Tenderness (N=51)	p-value ⁶
Duration of pain (years)	4.50 (0–29)	4.50 (0–20)	0.71	3.50 (0–26)	5.00 (0.83–29.0)	0.09	2.00 (0–29)	5.00 (0.83–23)	0.04
Endometriosis Health Profile-30									
Pain	9.09 (0–56.8)	38.6 (0–75.0)	<0.001	13.6 (0–68.2)	38.6 (0–75.0)	<0.001	4.55 (0–68.2)	40.9 (0–75.0)	<0.001
Control and helplessness	4.17 (0–91.7)	50.0 (0–95.8)	<0.001	16.7 (0–91.7)	50.0 (0–95.8)	<0.001	0 (0–83.3)	50.0 (0–95.8)	<0.001
Emotion	4.17 (0–58.3)	33.3 (0–79.2)	<0.001	8.33 (0–62.5)	29.2 (0–79.2)	0.004	0 (0–62.5)	33.3 (0–79.2)	<0.001
Social	6.25 (0–81.3)	37.5 (0–100)	0.001	6.25 (0–75.0)	37.5 (0–100)	0.002	6.25 (0–68.8)	37.5 (0–100)	<0.001
Self-image	8.33 (0–75)	41.7 (0–83.3)	<0.001	16.7 (0–75.0)	50.0 (0–83.3)	<0.001	0 (0–58.3)	41.7 (0–83.3)	<0.001
Dysmenorrhea									
None/mild	15 (35.7)	1 (2.3)	<0.001	16 (32.0)	0 (0.0)	<0.001	14 (37.8)	2 (4.1)	<0.001
Moderate/Severe	27 (64.3)	43 (97.7)		34 (68.0)	36 (100)		23 (62.2)	47 (95.9)	
Dysuria									
None/mild	39 (92.9)	37 (84.1)	0.31	44 (88.0)	32 (88.9)	0.99	34 (94.4)	42 (84.0)	0.18
Moderate/Severe	3 (7.1)	7 (15.9)		6 (12.0)	4 (11.1)		2 (5.6)	8 (16.0)	
Dyschezia									
None/mild	30 (71.4)	24 (54.5)	0.11	33 (66.0)	21 (58.3)	0.47	28 (77.8)	26 (52.0)	0.01
Moderate/Severe	12 (28.6)	20 (45.5)		17 (34.0)	15 (41.7)		8 (22.2)	24 (48.0)	
Dyspareunia (deep pain)									
None/mild	26 (63.4)	9 (21.4)	<0.001	29 (59.2)	6 (17.6)	<0.001	24 (68.6)	11 (22.9)	<0.001
Moderate/Severe	15 (36.6)	33 (78.6)		20 (40.8)	28 (82.4)		11 (31.4)	37 (77.1)	
Dyspareunia (pain with entry)									
None/mild	35 (85.4)	23 (54.8)	0.002	40 (83.3)	18 (51.4)	0.002	32 (91.4)	26 (54.2)	<0.001
Moderate/Severe	6 (14.6)	19 (45.2)		8 (16.7)	17 (48.6)		3 (8.6)	22 (45.8)	
McGill Present Pain Intensity									
No/mild pain	31 (73.8)	12 (27.3)	<0.001	36 (72.0)	7 (19.4)	<0.001	30 (81.1)	13 (26.5)	<0.001
Discomforting/ distressing pain	8 (19.1)	24 (54.5)		12 (24.0)	20 (55.6)		7 (18.9)	25 (51.0)	

	Pelvic floor tender areas ³		Abdominal tender areas ⁴		Uterine tenderness ⁵		p-value ⁶
	Low Tenderness (N=44)	High Tenderness (N=44)	Low Tenderness (N=51)	High Tenderness (N=37)	Low Tenderness (N=37)	High Tenderness (N=51)	
Horrible/excruciating pain	3 (7.1)	8 (18.2)	2 (4.0)	9 (25.0)	0 (0.0)	11 (22.5)	

¹Data are given as median (range) for continuous variables and sample size (percentage) for categorical variables.

²Sample size is 86 for pain duration, dysmenorrhea, dysuria, dyschezia, and McGill present pain intensity; sample size is 83 for dyspareunia (deep pain) and dyspareunia (pain with entry); sample size is 80 for Endometriosis Health Profile-30 scales

³Pelvic floor tender areas assessed at right/left pubococcygeus, right/left ilioococcygeus, and right/left coccygeus. Each area reported as tender was palpated with 2kg of pressure and a 0–10 pain rating was obtained. High tenderness defined as >2 areas with pain rating of ≥4 on 0–10 scale (moderate/severe pain).

⁴Abdominal tender areas assessed at right/left upper and right/left lower abdominal, suprapubic and umbilical areas. High tenderness defined as >1 tender area reported as tender.

⁵Uterine tenderness assessed at posterior lower uterine segment with single digit vaginal exam. Participants with uterine tenderness had 2kg of pressure applied to the area and reported a 0–10 pain rating. High tenderness was defined as uterine tenderness with a pain rating of ≥4 on 0–10 scale (moderate/severe pain).

⁶Two-sided probability values from Chi-square or Fisher's exact test for categorical variables and from Wilcoxon Rank Sum for continuous variables



Beyond the Binary: Sexual and Reproductive Health Considerations for Transgender and Gender Expansive Adolescents

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Awareness and visibility of transgender individuals have grown exponentially. However, conceptualizing sexual and reproductive health (SRH) as “women’s” or “men’s” health services further marginalizes transgender and gender-expansive (TGE) youth. Multiple reviews and commentaries have been published on the topic of SRH care for adults under the umbrella term of sexual and gender minorities, all with a call to action for more inclusive care and the need for more clinical research involving TGE individuals, and notably, TGE youth. Results from adult TGE studies are often translated to describe adolescent models. However, models specific to adolescent TGE populations are needed to understand their unique SRH needs. This review will describe the current literature relating to SRH needs of TGE youth and adults, highlighting key areas with significant disparities in need of further research. This comprehensive summary will also provide recommendations for clinicians and researchers with the goal of improving SRH care and obtaining wider representation in both clinical settings and research directed toward TGE youth.

Keywords: adolescent, sexual health, transgender, reproductive health, gender-affirming care, gender expansive

CASE STUDY

In May 2019, the *New England Journal of Medicine* published a case study describing the power and limits of classifying sex and gender within medicine (1). Sam, 32 years old, presented to an emergency department with severe and intermittent abdominal pain. Despite disclosing his transgender identity, the electronic medical system indicated his affirmed gender, and therefore, medical staff evaluated him as a man with a non-urgent condition. Several hours later, Sam delivered a stillborn baby. This tragic case begs the following questions: What are the healthcare experiences of transgender and gender-expansive (TGE) individuals with sexual and reproductive health (SRH) needs? What is the empirical evidence supporting the needs of this population? What is the frequency of cases like Sam’s? Most importantly, what do clinicians and researchers need to learn from this case to prevent SRH injustices from reoccurring? Selected studies were compared

and summarized by the authors, leading to our suggestions and recommendations for treating TGE youth, which may then prevent adults, such as Sam, from experiencing poor medical care.

INTRODUCTION

SRH healthcare is often conceptualized as “women’s” or “men’s” health services, which may be excluding many people from seeking care. Using the inclusive umbrella term will allow health care professionals to use an organ inventory as opposed to the currently used, often binary, options (2). Health care professionals should be sensitive and understand how gender, as opposed to sex assigned at birth, can directly affect clinical practice. Those who identify as transgender have a gender identity that differs from the sex that was assigned at birth; those who identify as non-binary may have a more complex, fluid, multifaceted, or otherwise less clearly defined gender than a transgender person (3). Those who identify as transgender can be further divided into two groups: transgender women (assigned male at birth) and transgender men (assigned female at birth). Although often incorporated into the same broad “sexual and gender minority” category, TGE individuals have healthcare needs that are distinct from those who identify as lesbian, gay, and bisexual (LGB). LGB issues are often *interpersonal*, related to their relationships with others, while gender issues are *intrapersonal*, with an emphasis on an individual’s identity and self-expression. This distinction is rarely emphasized in the literature (4). Furthermore, TGE individuals have unique SRH health needs, but are often excluded from gynecological and reproductive practices, as current guidelines and recommendations exist within a gender binary, heteronormative system, catering care to those who identify as heterosexual and cisgender (5). Awareness and visibility of transgender individuals have exponentially increased over recent years. Multiple reviews and commentaries have been published on the topic of SRH care under the umbrella term of “sexual and gender minorities”, (6–16) and include a call to action for more inclusive care and clinical research involving TGE individuals. However, TGE youth face unique barriers in receiving care and this subset population remains vastly under-researched. This review will discuss barriers to care for TGE adolescents and young adults, emphasizing the unique SRH care needs of this population and ultimately providing recommendations for U.S. clinicians and researchers with the goal of improving SRH care for TGE youth.

The prevalence of TGE individuals, particularly adolescents, remains relatively undefined and existing data are likely underestimated (17, 18). The American College of Obstetrics and Gynecology Committee Opinion published in March 2021 estimated 150,000 youth and 1.4 million adults living in the U.S. identify as transgender (19). Previous estimates include data from: (1) The 2011 National Transgender Discrimination Survey (20) which included 6,450 participants ages 18 to 89 and found that 33% of respondents did not identify as exclusively male or female, and 14% identified as gender-nonconforming; and (2)

The 2015 U.S. Transgender Survey (18) which included 27,715 participants over 18 years old with 31% identifying as non-binary. As social stigma decreases and education surrounding sex and gender increases, (21) the prevalence of adolescents identifying as a gender other than cisgender has been increasing (3% in 2018) (22). However, according to the Harris Poll, (23) 2019 societal acceptance decreased and was accompanied by an increase in LGBTQ discrimination because of sexual orientation or gender identity (24). This is thought to be a product of a lack of non-discrimination laws for the LGBTQ community and the political and cultural divide brought on by the election year of 2016. Transgender, and specifically non-binary adolescent populations, are underrepresented in clinical and biomedical research and as a result, vast knowledge gaps exist.

THE PROBLEM: BARRIERS TO CARE

TGE youth encounter significant interpersonal and structural barriers to receipt of high-quality healthcare, including discrimination, lack of clinician knowledge and health systems obstacles. TGE youth often experience social stigma, harassment, and rejection, and unlike adults, TGE youth are embedded in families and schools which may make such stigma difficult to escape (25). Health care settings are often sites of mistreatment, where discriminatory practices range from refusal of care to verbal, physical or sexual abuse (26). A secondary analysis from the 2015 U.S. Transgender Survey ($N = 19,157$) found that almost one-quarter of transgender adults avoided healthcare due to anticipated discrimination, with the highest prevalence among transgender men (27). The intimate nature of SRH makes this issue particularly acute: 33% of transgender people and 48% of transgender men have delayed healthcare or avoided preventive measures (*e.g.*, pelvic exams or STI screening) out of fear of discrimination or disrespect (28). Compared to cisgender, LGB-identifying individuals, transgender adults are more likely to delay care and report negative effects of disclosure to their clinician (29). Racial disparities also exist, as transgender people of color experience significantly higher levels of transphobic discrimination compared to their White counterparts in accessing health services (30). Barriers to care are even more pronounced and complex for transgender youth who are reliant on parental support and insurance coverage for care. A 2016 study aimed at understanding perceived barriers to care among transgender youth (ages 14–22 years) and their caregivers identified six themes (31): (1) few accessible pediatric providers are trained in gender-affirming health care; (2) lack of consistently applied protocols; (3) inconsistent use of chosen name/pronoun; (4) uncoordinated care and gatekeeping; (5) limited/delayed access to pubertal blockers and cross-sex hormones; and (6) insurance exclusions.

The lack of adequate clinician training is one of the most often cited barriers to quality care for TGE populations (32). The 2011 National Transgender Discrimination Survey found that 50% of respondents reported having to teach their clinicians about their own healthcare needs that may be specific to TGE individuals, such as hormone usage, reproductive

conditions and menstruation suppression (20). Researchers have responded by surveying clinicians about their knowledge and attitudes towards caring for TGE individuals. (33, 34) A 2015 survey of 141 obstetrician-gynecologists across nine academic hospitals found that 80% did not receive training in residency regarding the care of transgender patients; only 35% and 29% felt comfortable caring for male-to-female and female-to-male transgender patients, respectively (33). The findings from another recent study are equally discouraging (35); of the 169 board-certified obstetrician-gynecologists surveyed in 2018, less than half (43%) reported training specific to the healthcare needs of LGB or TGE individuals. Moreover, this study found previous clinician training was not associated with increased comfort in taking care of TGE patients. Mounting research suggests that increasing hours of TGE health education is not sufficient; rather, future training should address personal biases and internalized transphobia (36).

Structural inequities imbedded within the healthcare system can limit access to healthcare for transgender people. Many transgender individuals lack health insurance, which may be partially due to the higher prevalence of unemployment and poverty faced by these individuals relative to the general US population (37). TGE adolescents and young adults are at a further disadvantage, as they are reliant on their parents for not only insurance coverage (31, 38) but also support of their gender identity, which they often do not have (39). As a result, transgender individuals, particularly youth, are disproportionately represented in the homeless population (40). Even for those individuals and families who are insured, barriers persist, as private insurers have historically excluded coverage for medical interventions related to gender affirmation and transition (41). A study examining barriers to gender transition-related healthcare in Massachusetts found that mental health coverage emerged as one of the factors most strongly associated with an inability to access care (42). Previously, a diagnosis of gender dysphoria by a mental health professional was required before approval was granted to cover gender affirming therapy or surgery (43). With new informed consent models, patients are able to access gender-affirming hormones through their primary care clinician without a diagnosis of gender dysphoria, (44) which is the feeling of discomfort or distress that might occur in people whose gender identity differs from their sex assigned at birth or sex-related physical characteristics. However, not all clinics use informed consent models, and most insurers still require a diagnosis for those seeking gender affirming surgery. Similarly, electronic health records (EHRs) may pose as a structural barrier if gender identity is not included as an important variable to care. For example, birth sex auto-populates medical recommendations for clinicians that may be needed for a person assigned female or male at birth during specific ages (e.g., menstruation preparation, prostate exam). Including both sex and gender as important clinical variables in EHRs could aid in decreasing both structural and interpersonal barriers for TGE youth and young adults when receiving SRH care (45). Advocacy work is needed to eliminate roadblocks to accessing medically necessary transition-related care for TGE youth across the U.S (46).

These barriers to healthcare result in increased health risk and an increased likelihood of negative health outcomes for an already vulnerable population. The consequences of inadequate care are staggering. According to one retrospective cohort study, 56% of youth who identified as transgender reported previous suicidal ideation, and 31% reported a previous suicide attempt, compared with 20% and 11% among matched youth who identified as cisgender, respectively (12). The social and economic marginalization and abuse experienced by TGE individuals has been shown to increase these health risks (47). It is imperative that clinicians, researchers and public health officials collaborate to mitigate these barriers and improve both access and quality of care for this population.

THE ROLE OF THE OBSTETRICIAN-GYNECOLOGIST

Current Expectations

As highlighted above, lack of adequate provider training often poses a significant barrier to TGE individuals obtaining sensitive SRH care. Thus, gynecologists striving to provide inclusive SRH care should be informed on the reproductive health needs and considerations of *all* genders, not only those who are cisgender. In 2011, the American College of Obstetricians and Gynecologists assembled a committee to assist gender-diverse individuals in obtaining routine treatment and screening, as well as gender-affirming care needs (48). Transgender males who have internal and external female anatomy will need standard SRH care such as contraception counseling, reproductive health education, breast, and gynecologic cancer screenings, STI testing, and menstrual management. However, it is important for obstetrician-gynecologists to understand the various options for hormonal and surgical gender affirmation, as these interventions impact the SRH needs and considerations of TGE individuals. The following section first defines medical options to affirm gender and thereafter explores implications across key SRH domains.

Medical Options to Affirm Gender

Delaying pubertal changes through administration of gonadotropin-release hormone (GnRH) agonists, may decrease discomfort and improve quality of life while creating time and space for gender identity exploration (7). New evidence suggests that affirming interventions during adolescence improve psychosocial outcomes, such as decreasing suicidality and increasing attainment of higher education, employment, and reliable housing (49). Pubertal suppression may also reduce the need for later surgery because physical changes that are otherwise irreversible (protrusion of the Adam's apple, male pattern baldness, voice change, breast growth, etc.) are prevented (50). Gender affirming hormones (GAH), (i.e., testosterone and estrogen), enable TGE individuals to gain characteristics that match their gender identity. The most recent Endocrine Society guidelines indicate that medications can be started in patients younger than 16 years old (51). A wide range of gender-affirming surgeries (previously referred to as gender reassignment surgeries) are also available to TGE individuals

such as feminizing vaginoplasty, masculinizing phalloplasty, metoidioplasty (clitoral enlargement), as well as face and voice procedures (52).

Sexual Desire and Function

TGE youth who may or may not be receiving medications for transition are often exploring their sexual identity and sexual pleasure. TGE receiving GAH, such as pubertal suppression and cross-sex hormones, may experience side effects from these medications that impact their sexual health. For example, a multicenter one-year prospective clinical trial of 53 trans men and 53 trans women receiving GAH showed a significant increase in sexual desire and clitoral pain in trans men receiving testosterone (53). Trans women in this study reported decreased sexual desire as a side effect of decreased testosterone concentrations. TGE youth taking pubertal suppression medication may also experience decreased libido as a side effect (54). Gender affirming surgeries also impact sexual functioning. A study examining the outcomes of vaginoplasty, the procedure that restructures the head of the penis into a clitoris and creates a vaginal cavity, found that 90% of trans females who had the surgery reported that they were still able to have an orgasm with 75% reporting that their orgasms were either the same or more intense than before (55). Research on procedures for trans men (e.g., phalloplasty and metoidioplasty), have shown generally positive outcomes; however, for some decreased phallic sensation and the inability to penetrate negatively impacted sexual wellbeing (56). Those using puberty blockers or testosterone/estrogens may be navigating changes to libido. When counseling trans men, clinicians should discuss how patients might develop pleasurable sex and how erogenous stimulation may have to be rediscovered. Youth, particularly TGE youth, show variable amounts of comfort with discussing physical intimacy and sexual intercourse with peers, partners, and providers and may not even know what questions to ask (57).

Menstruation

Menstruation may lead to dysphoria for TGE youth with female anatomy (58). A recent survey of TGE adults with masculine identities showed mixed attitudes toward menstruation, with most reporting feeling unsafe and uncomfortable using men's restrooms during times of menstruation (59). Medications that lead to cessation of menses can be an important first step in gender-affirming care and may be used on their own or with GAH. This may be helpful for TGE youth who do not have access to GAH therapy, as there are no documented adverse outcomes, and only benefits reported with respect to an individual's quality of life (60–63).

Contraception

All transgender people who have gonads and engage in sexual activity that could result in pregnancy should be counseled on the need for contraception (64). GAH should not be used as a form of contraception. Particularly, testosterone, a known teratogen, may lead to abnormalities of physiological development of the embryo if a patient becomes pregnant (65). Unintended pregnancies have occurred in transgender men receiving testosterone.

Therefore, contraceptive needs should be addressed, especially in patients who have maintained their uterus (66). Moreover, some TGE individuals may be at risk for engaging in high-risk sexual behavior. Specifically, TGE youth are at high risk for sexual abuse and engaging in commercial or survival sex, (67) increasing the need for appropriate contraceptive counseling and sexually transmitted infection protection. The interpersonal and structural barriers to high-quality healthcare outlined above have led to contraception access issues, including the inability to afford services, lack of clinicians with expertise in gender-affirming therapy, difficulty in securing health insurance, and misconceptions about unintended pregnancy (68). Health care professionals, and those who care for adolescents, need to be aware of who may require and should receive advice about pregnancy prevention and contraception. Rather than assuming a patient's sexual orientation, clinicians should take a thorough sexual history based on the patient's identity and anatomy, with the understanding that gender identity does not determine sexuality (69). Additionally, clinicians and researchers should be aware and sensitive to issues that may affect gender and sexual health, notably gender affirming-hormone therapies that may affect fertility and libido.

Pregnancy

Numerous studies have documented increased pregnancy rates in adolescent sexual and gender minorities compared with their heterosexual counterparts, with an estimated increased risk of adolescent pregnancy rate between 2 and 10 times (56, 70–72). This finding may be explained by a broad spectrum of sexual health risks experienced by TGE individuals, including an earlier age of first sexual intercourse, exposure to sexual abuse, and a higher number of sexual partners (73). TGE youth face conflict with their gender identity and potentially their sexual orientation. It is likely that their experience is similar to cisgender LGB adolescents as it pertains to reproductive health considerations. As outlined, the principles of obstetrical practice regarding pregnancy in a transgender male are not complex once a clinician has received appropriate training. However, the barriers to care and societal discrimination may cause pregnancy-related psychological distress. Two studies highlight both psychological issues experienced by transgender men contemplating pregnancy or bearing a child, as well as the unique medical implications for both the parent and fetus (66, 74). Similar to pregnancy research in TGE youth, few data exist on abortions in this population. Abortion-providing clinicians and advocates have long recognized the need for high-quality, gender-affirming care for their patients, although little is known about these services at facilities that provide abortions (75). Current abortion care should be adapted to include and affirm the experiences of this underserved population (76).

Fertility Options and Attitudes

TGE individuals, similar to cisgender people, may want to become pregnant and reproductive desire has found to be high among transgender individuals. A recent Australian study surveyed 409 transgender and non-binary adults and found that, of participants who were not already parents, 33% hoped to

have children in the future (77). A 2016 survey ($n = 156$) showed 71% of transgender and non-binary people surveyed were interested in adoption and 35.9% in biological parenthood (63). More gender nonconforming youth (44%) than transgender youth (26%) expressed interest in biological fertility. Medical interventions, such as GAH and surgeries, pose significant risk to reproductive potential and fertility outcomes. Specifically, the long-term effects of GAH on reproductive function are unknown (78). The World Professional Association of Transgender Health, the American Society for Reproductive Medicine, and the Endocrine Society recommend that all transgender patients be counseled on options for fertility preservation prior to initiating gender-affirming surgeries or hormonal transition (78–80). There are relatively limited data specific to fertility preservation for transgender individuals and current approaches are extrapolated from options for fertility preservation after oncologic diagnoses (80).

Options for individuals assigned female at birth vary by pubertal status and include embryo and oocyte cryopreservation, both of which are established in practice (81). Notably, both oocyte and embryo cryopreservation require controlled ovarian stimulation with repeated assessment by transvaginal ultrasound, which may be uncomfortable or emotionally distressing for these patients (80). Transgender men who have already initiated GAH therapy (testosterone) may still pursue oocyte or embryo cryopreservation (80). Recent findings have shown ovarian tissue cryopreservation to be a promising option. In 2019, the American Society of Reproductive Medicine opinion report on fertility preservation stated: “ovarian tissue cryopreservation is no longer considered experimental should be considered an established medical procedure” (82). A recent study showed that ovarian tissue does not seem to be morphologically affected by prolonged testosterone treatment; (83) however, there are conflicting data in the literature (84) and more research is needed in this area. Despite potential interventions, the use of reproductive options is surprisingly low (85). Some transgender adolescents have expressed discomfort with the idea of using their own body parts for reproduction (63) and oocyte cryopreservation has been shown to be associated with worsening gender dysphoria (86). Youth in these studies also identified cost, desire not to delay medical transition, and future plans to adopt children or no desire to have children as reasons for declining fertility preservation.

Endometriosis

The SRH community has become increasingly aware of how TGE youth are experiencing complications of gynecologic organs. For example, transgender male adolescents have a uterus and ovaries leaving them susceptible to developing painful gynecological medical conditions such as endometriosis. This common gynecological disease, leads to chronic pelvic pain, decreased quality of life, (87) and has the proclivity to adversely affect choices surrounding fertility options. In addition, endometriosis negatively impacts social/romantic relationships and sexual intimacy (88). Endometriosis in adolescence, the typical period of symptom onset, (87) is an even more challenging problem as the disease may present with several clinical and

pathological differences that are not observed in adult women (89). This disease affects at least 10% of cisgender women of reproductive age, although endometriosis also affects TGE people. To date, only one study has examined the prevalence, presentation, and impact of endometriosis in non-binary youth (90) with the conclusion that evaluation for endometriosis is underutilized when transgender youth present with pelvic pain and dysmenorrhea. Even for those with a known diagnosis, GAH therapy may not remedy endometriosis-associated pain. The impact of endometriosis must be considered for TGE youth in the context of the interpersonal and structural barriers to accessing SRH care, as outlined above. Further research is warranted regarding endometriosis and other gynecologic conditions in TGE individuals, particularly adolescents, to improve quality of care for this population.

RECOMMENDATIONS FOR PROVIDING GENDER-AFFIRMING SRH CARE TO TGE ADOLESCENTS

Adolescent medicine clinicians and researchers can lead the way in providing affirming and empowering care at a time when individuals are becoming aware of and developing their gender identities and sexual orientations. The gender-affirmative care model supports gender diversity as a normal part of human development, compared the others that may treat gender diversity as a disorder (6). The model uses strengths-based terminology, which emphasize an individual's self-determination and autonomy (Table 1). All clinical office staff also play a role in affirming a patient's gender identity. Frontline staff such as receptionists and clinical assistants can be involved in creating an affirming environment. Clinicians and staff should make direct and non-judgmental inquiries about a patient's experience and feelings before applying any labels. Thereafter, a patient-asserted name and pronouns should be used by staff and are ideally reflected in the electronic medical record without creating duplicate charts. In the clinical environment, making flyers available or displaying posters related to LGBTQ health issues, including information for children who identify as TGE and families, reveals inclusivity and awareness (50).

Support from a multidisciplinary and collaborative health care team would greatly improve health outcomes for TGE youth (91). Since 2007, when the first multidisciplinary gender clinic was established within a pediatric institution, (92) the number of such pediatric subspecialty programs has grown significantly (93). Despite the growing number of clinics, these valuable, affirming spaces remain inaccessible to some. Moreover, existing clinics often have high patient volumes leading to long waiting periods to be seen by a clinician. Gender affirming care may not always lead to gynecology referral as most care falls under the umbrella of primary care (69, 94). A 2016 study aimed at understanding perceived barriers to care among transgender youth (ages 14–22 years) and their caregivers also identified the following recommendations: (1) development of protocols for the care of young transgender patients, as well as roadmaps for families; (2) increased number of multidisciplinary

TABLE 1 | Relevant terms and definitions defined by the *World Health Organization's glossary for terms and tools* for providing gender-affirmative care.

Term	Definition
Cisgender	Individuals whose gender identity corresponds with the sex the person had or was identified as having at birth
Gender Expression	The outward manner in which an individual express or displays their gender (i.e., clothing, hairstyle, speech, mannerisms)
Gender Expansive	A person's identity or behavior is broader than the commonly held definitions of gender and gender expression in one or more aspects of their life.
Gender Identity	A person's internal sense of self and how they fit into the world, from the perspective of gender
Gender Non-conforming	The state of one's physical appearance or behaviors not aligning with societal expectations of their gender (a feminine boy, a masculine girl, etc.).
Gender Non-binary	Individuals who do not identify their gender as man or woman. Other terms to describe this identity include genderqueer, agender, bigender, gender creative, etc.
Gender-fluid	A person has a flexible gender identity and expression that can fluctuate by the hour, day, or longer interval of time.
Sexual and Gender Minority	An umbrella term referring to individuals who identify as gay, lesbian, or bisexual, or who are attracted to or have sexual contact with people of the same gender and/or whose gender identity (man, women, other) or expression (masculine, feminine, other) is different from their sex (male, female) assigned at birth.
Sex	An individual's biological status as male, female, or something else. Sex is assigned at birth and associated with physical attributes, such as anatomy and chromosomes.
Sexual Orientation	Composed of attraction, behavior, and orientation. Refers to a person's sexual and emotional attraction to another person and the behavior and/or social affiliation that may result from this attraction (lesbian, gay, bisexual, etc.)
Transgender	Individuals whose current gender identity differs from the sex they were assigned at birth.

The current definitions are listed in **Table 1**; however, these concepts may change as research continues. Additionally, it is important to consider these concepts as fluid as opposed to fixed categories.

gender clinics; (3) providing cross-sex hormones at an age that permits peer-congruent development; and (4) designating a navigator for transgender patients in clinics (31). An assessment of patient/caregiver satisfaction at a pediatric multidisciplinary gender clinic in Seattle, WA found that families were highly satisfied with multidisciplinary, coordinated health care with respondents endorsing the presence of a Care Navigator as integral to providing support to families during a process often fraught with barriers and emotional stress (95).

Re-conceptualizing outdated terminology may also serve to create an affirming environment. For example, endometriosis researchers have suggested relabeling the condition with the term “gendered disability”, as this is a more accurate depiction of the science and lived experiences of those with endometriosis (96). Additionally, researchers call for shifting the language used to describe endometriosis (96–98): (1) Discuss uterus/ovaries/penises and other body parts without assigning them a gender; (2) Use phrases like “internal/external reproductive organs”; (3) Use language such as “people who menstruate/are pregnant/ produce sperm;” and (4) Use “cisgender” rather than “biologically female/male”; (5) Use people with endometriosis instead of women or patients; (6) Refer to endometriosis family/siblings/friends, instead of ladies/sisters/cysters; and (7) Discuss endometriosis as a system-wide, gendered disability that impacts the organs, nervous system, cognitive abilities, mood, respiration, circulation, and digestive functions as well as the reproductive system.

Sexual and gender minority people, including members of the lesbian, gay, bisexual, transgender, and queer communities, are understudied and underrepresented in research. Recent studies have shed light on the LGBTQ community's perspective on how SGMs are addressed in current studies (99). Findings from focus groups and qualitative studies have revealed:

(1) sexual and gender questions did not allow for identity fluidity and complexity, reducing inclusion and representation; and (2) question stems and answer choices were often not clear as to whether gender identity or sexual orientation were being assessed (100). Measurement error from imprecise survey questions impose biases. A recent study aimed at the development of an affirming and customizable electronic survey of SRH experiences found that: (1) TGE community input from initial conceptualization to final implantation is essential; (2) investigators need to be mindful of gender-diversity and differences in sexual orientation when defining study eligibility criteria to directly reduce selection bias; and (3) the ability to use individualized, affirming, customized language for sexual and reproductive body parts and processes may avoid gender dysphoria evoked for some by medical terms (101). Lessons learned from these findings may inspire other researchers to innovate and think more inclusively, thereby creating affirming research for marginalized groups, such as TGE youth and adults. See **Table 2** for a synthesized summary of published recommendations for clinicians and researchers with the benefit of the patient described.

DISCUSSION

Women's health and men's health should be described as sexual and reproductive health. TGE individuals have been largely excluded from clinical care and clinical research leading to large gaps in knowledge regarding their experiences, options, and needs in both settings. Extrapolating data from other populations (e.g., solely transgender data, solely adult data) may not lead to accurate conclusions. Thus, research catering to TGE adolescents, young adults, and non-binary individuals, would

TABLE 2 | Suggestions for clinicians and researchers for providing care using the gender-affirming care model with the described patient benefit and source of recommendation.

Recommendation	Benefit to patient	First Author (publication date)
Use strengths-based terminology, which emphasize an individual's self-determination and autonomy boxes on patient intake forms and all medical records. Researchers should use inclusive language when recruiting study participants.	Reduce stigmatizing environment that hinders health care delivery.	1. Liszewski et al. (91) 2. Moseson et al. (75) 3. Tavits et al. (93) 4. Haseen et al. (9) 5. MacCarthy et al. (17)
Educate all healthcare staff, including clinicians, receptionists, etc. on becoming more gender-literate by receiving training in respecting patients' gender identity and gender expression	Establish open dialogue with patients, non-binary patients should not be obligated to educate health care professionals about their health care needs.	1. Liszewski (2018) (91) 2. Hodax et al. (7) 3. de Vries et al. (48) 4. Obedin-Maliver et al. (10) 5. White Hughto et al. (12)
Institutional nondiscrimination policies can be expanded to include gender identity and expression.	Processes for assessing patient satisfaction and lodging grievances should allow for confidential reporting of experiences relevant to patients' gender identity and expression.	1. Liszewski et al. (91) 2. Wang et al. (95) 3. Du Bois et al. (96)
The healthcare team should verbally express support, provide information on local support groups, educate teachers and school officials, and connect families to support organizations.	Decrease discrimination in school and lack support from teachers and peers which will then improve the patient's quality of life and potentially decrease depression and suicide in TGE adolescents. This may also decrease distress and associated psychological conditions and comorbid decrease often found in TGE adults.	1. Liszewski (2018) (91) 2. Wagner et al. (6) 3. Safer et al. (31)
The physical environment should also be optimized for inclusivity, such as providing gender-neutral restrooms, gender-neutral signage, and inclusive magazines.	Create safe spaces in waiting and examination rooms and communicate to the adolescent TGE patient that the healthcare team is an ally.	1. Liszewski et al. (91) 2. Moseson et al. (75) 3. Jones et al. (86)
Clinicians should use an "organ inventory" to document the presence or absence of specific organs to ensure appropriate screenings and evaluation	Assumptions about sex, gender, or anatomy can lead to inadequate care or a negative medical experience.	1. Liszewski et al. (91) 2. Deutsch et al. (97)
When taking a history, conducting an exam, or providing counseling, providers are encouraged to avoid using gendered terms.	Asking a patient what language they use to refer to their genitalia and menstruation, and mirroring that language, can help the provider avoid use of words that may be triggering.	1. Mehninger et al. (98) 2. Jones et al. (86) 3. Sczesny et al. (99) 4. Dinour et al. (100) 5. Likis et al. (101)
Adopt and advocate for electronic health records using a gender identity variable as well as birth sex. Gender identity should auto populate medical recommendations for clinicians that may be needed for a person identifying as TGE during particular ages.	Including both sex and gender as important clinical variables in EHRs could provide preventative care and aid in decreasing both structural and interpersonal barriers for TGE youths and young adults when receiving SRH care	1. Burgess (2019) (43) 2. Deutsch et al. (97) 3. Grasso et al. (102)

Research and healthcare teams should maintain openness when introducing the gender-affirming model as many people do not fit or remain in a single category. As patients may change preferences, healthcare providers must continuously assess their current sex and gender inclusivity, language, and policies.

be beneficial to the field of SRH. Obstetrician-gynecologists and other clinicians who specialize in gynecological care should assume their role in the care of TGE adolescents and young adults while maintaining awareness of the consequences of inadequate care, and the many existing interpersonal and structural barriers to receiving high quality SRH care. Adolescent clinicians and researchers can lead the way in providing affirming and empowering care at a time when individuals are becoming aware of and developing their gender identities and sexual orientations.

Inclusive clinical care and research that addresses the relationship between sex assigned at birth, gender identity and social determinants of health are crucial to achieving health equity (102). Commonly used or validated measures of sexual and reproductive health experiences typically use heteronormative and cis-normative assumptions and language, such as the types of sex people are having; (4, 103) the gender, sex assigned at birth, and current organs of people's

partners; and their capacity for pregnancy (98). Clinical care and research are interconnected, as questions that arise in clinical care motivate and drive research, and research subsequently informs the standard of care and new healthcare policies. TGE youth greatly need wider representation in both settings.

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CL and RS conducted the literature review and wrote the first draft of the manuscript. CG and CS contributed to manuscript preparation. All authors made a significant contribution to the work reported, whether that is in the conception, and took part in drafting, revising or critically reviewing the article gave final approval of the version to be published have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the

work. All authors contributed to the article and approved the submitted version.

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Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: Pilot resting-state fMRI study

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Abstract

Background: Endometriosis is the leading cause of chronic pelvic pain. Alterations in brain functional connectivity have been reported in adult women with endometriosis-associated pain (EAP), however, it is still unknown if similar patterns of changes exist in adolescents.

Methods: In this pilot study, resting-state fMRI scans were obtained from 11 adolescent women with EAP and 14 healthy female controls. Using a seed-to-voxel approach, we investigated functional connectivity between the anterior insula, medial prefrontal cortex, and the rest of the brain. Furthermore, we explored whether potential functional connectivity differences were correlated with clinical characteristics including disease duration, pain intensity, and different psychosocial factors (pain catastrophizing, fear of pain, functional disability, anxiety, and depression).

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Results: Our findings revealed that patients with EAP demonstrated significantly decreased connectivity between the right anterior insula and two clusters: one in the right cerebellum, and one in the left middle frontal gyrus compared to controls. Additionally, functional connectivity between the right anterior insula and the right cerebellum was positively associated with pain intensity levels. In patients with EAP, brain changes were also correlated with state anxiety and fear of pain.

Conclusions: Our results are relevant not only for understanding the brain characteristics underlying EAP at a younger age, but also in enhancing future pain treatment efforts by supporting the involvement of the central nervous system in endometriosis.

Keywords

adolescent endometriosis; resting-state fMRI; anterior insula; dorsolateral prefrontal cortex; cerebellum; anxiety; fear of pain

1. Introduction

Endometriosis is defined by the presence of ectopic endometrial tissue ('lesions') outside the uterus, and it is usually associated with pain and/or infertility (Giudice & Kao, 2004). The pathophysiology of endometriosis-associated pain (EAP) has remained unclear. Although the majority of studies has considered the lesions as the most probable source (Maddern et al., 2020), central sensitization may be particularly significant in endometriosis since: (1) many patients continue to report pain (or the pain recurs) even after endometrial lesions were treated or removed; (2) patients exhibit hyperalgesia outside of the areas of the pelvis as well; and (3) there is only weak association between endometriosis severity (disease stage) and pain intensity (As-Sanie et al., 2013; Carey et al., 2014; Vercellini et al., 2007). Additionally, many of the symptoms of endometriosis begin in adolescence or early adulthood, a period when the central nervous system (CNS) is still developing and sensitive to persistent or recurrent pain (Kalia, 2008).

However, little research has investigated central processing of pain via brain alterations in patients with EAP, and existing studies have focused on adult women. In the study by As-Sanie et al. (2012), decreased gray matter volume (GMV) was observed in regions implicated in pain processing, including the insula, thalamus, cingulate gyrus, and middle frontal gyrus, among patients with EAP compared to pain-free controls. Interestingly, these GMV reductions were found in women with both endometriosis and chronic pelvic pain but not in asymptomatic patients. Another study from the same research group found increased anterior insula functional connectivity to the medial prefrontal cortex, and greater levels of excitatory neurotransmitters within the right anterior insula which may be a key region in the pathophysiology of EAP (As-Sanie et al., 2016). Notably, functional connectivity between these two regions was related to pain intensity, and more severe anxiety and depressive symptoms in endometriosis.

While resting-state fMRI is commonly used to investigate CNS function, no previous studies have explored functional connectivity in adolescents and young women with EAP. Imaging studies in children with chronic pain are still limited, but further support the role of the

anterior insula and medial prefrontal cortex in different pain conditions (Becerra et al., 2014; Bhatt et al., 2020; Colon et al., 2019). Given that pediatric chronic pain in general has been linked with increased risk of anxiety and depression, greater physical and pain-related disability (Miller et al., 2018), it is reasonable to believe that, similar to adult women, these psychosocial indices are connected to neural alterations in adolescents with EAP. In addition, studies have shown that pain catastrophizing or pain-related worry (Sullivan et al., 2001) and pain-related fear (Simons et al., 2011) could be a significant marker for pain experience in youth (for a review, see Fisher et al., 2018).

To address some of the issues noted above, the current study sought to investigate resting-state functional connectivity in adolescent and young women with EAP. We hypothesized that: (1) functional connectivity of the anterior insula and the medial prefrontal cortex would differentiate patients with EAP and controls; and (2) that these alterations would be correlated with disease duration, pain intensity and psychosocial functioning in patients. As such, the data could provide a basis for understanding pain-psychosocial function as an index of severity and resistance to treatment.

2. Materials and Methods

2.1 Participants and study procedure

Twenty-eight right-handed young women were included in this study. Twelve patients diagnosed with endometriosis were recruited during a multidisciplinary evaluation for chronic pain at the Pain Treatment Service, at Boston Children's Hospital and 16 healthy participants were recruited through advertisements. From the 12 patients, 11 had surgically confirmed endometriosis, and one patient was clinically diagnosed by the same gynecologist surgeon based on symptoms and family history (the patient elected not to have surgery). This study was part of a larger project examining fear acquisition and extinction in adolescents and young adults with various chronic pain disorders (Heathcote et al., 2020; Timmers et al., 2021). Inclusion criteria included: ages 10–24 years, pain lasting for more than 3 months, and a confirmed diagnosis of endometriosis for the patient cohort. General exclusion criteria included significant cognitive impairment, severe psychiatric disorder, positive pregnancy and/or drug screening test, claustrophobia, and MRI incompatible implants. In addition, the same exclusion criteria were applied to the age-matched healthy controls, but they had no current or past history of chronic pain (symptoms present for more than 3 months) and identified as female. All procedures and protocols were approved by the Boston Children's Hospital Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Participants and legal guardians provided a written informed consent/assent before inclusion in the study.

2.2 Clinical measures

Participants self-reported age in years and their average pain intensity on a 10-point Likert scale (average pain during the past week; 0 = *no pain*, 10 = *worst possible pain*). Pain duration was calculated in months from the time patients reported onset of their pain to the date of the study visit. In addition, the day of menstrual cycle at the time of the scan visit and the length of menstrual cycle were assessed by using two items from the Pubertal

Development Scale (PDS; A. C. Petersen et al., 1988): the date of the first day in the last period and the date of the first day of the second to last period. Painful days per month and the current use of contraceptives were also recorded.

2.3 Psychosocial functioning

2.3.1 Pain Catastrophizing Scale for Children—Pain catastrophizing was assessed by the Pain Catastrophizing Scale for Children (PCS-C; Crombez et al., 2003). The PCS-C includes 13 items that are rated on a 5-point scale ranging from 0 = *not at all true* to 4 = *very true*. Higher scores indicate higher levels of negative thinking about pain (Cronbach's α was 0.87 in the present sample).

2.3.2 Fear of Pain Questionnaire for Children—Pain-related fear was measured by the Fear of Pain Questionnaire for Children (FOPQ-C; Simons et al., 2011). The FOPQ-C consists of 24 items, each item scored on a 5-point scale from 0 = *strongly disagree* to 4 = *strongly agree* (Cronbach's α in the present sample was 0.93).

2.3.3 Functional Disability Inventory—The Functional Disability Inventory (FDI; Walker & Greene, 1991) was used to assess difficulty in physical and psychosocial functioning due to pain. The instrument consists of 15 items that are rated on a 5-point scale ranging from 0 = *no trouble* to 4 = *impossible* (Cronbach's α in the present sample was 0.92).

2.3.4 State-Trait Anxiety Inventory for Children—Anxiety symptoms were assessed using the State-Trait Anxiety Inventory for Children (STAI-C; Spielberger et al., 1973). STAI-C consists of two 20-item scales that measure state and trait anxiety scored on a 5-point and 3-point scale (STAI-S: e.g., 0 = *not calm*, 4 = *very calm*; STAI-T: 0 = *hardly ever* to 2 = *often*). Higher scores indicate higher severity of symptoms (Cronbach's α values were STAI-S α =0.72 and STAI-T α =0.91 in the present sample).

2.3.5 Children's Depression Inventory-2—Children's Depression Inventory-2 (CDI-2; Kovacs, 1981) was applied to measure depressive symptoms. CDI-2 is a 28-item questionnaire, and the response options for each item are rated on a 3-point scale (0 = *no symptom*, 2 = *definite, marked symptom*) (Cronbach's α was 0.82 in the present sample). It is interpreted using *t*-scores based on age and sex-based norms.

2.4 Data analysis

Demographic data and clinical measure scores were analyzed with SPSS version 23.0 software (SPSS, Inc., Chicago, IL, USA). Independent *t*-tests or Mann-Whitney U tests were performed to determine whether patients with EAP and healthy controls differed in age, pain catastrophizing, fear of pain, pain related functional disability, anxiety, and depressive symptoms (pain duration and intensity data were available for the patient group only). In addition, chi square (χ^2) tests were conducted to compare hormonal contraceptive use. Significance levels were set at $p < 0.05$. Cronbach's alpha coefficients were calculated for all self-report measures.

2.5 Imaging

2.5.1 Image acquisition—Anatomical and functional imaging was performed using a 3 Tesla MR scanner (Siemens Magnetom TrioTim syngo MR B17) with a 12-channel head coil. Resting-state functional images were acquired using a T2*-weighted echo-planar-imaging (EPI) sequence with multi-band acceleration (simultaneous multi-slice or SMS) as follows: 51 axial slices (3mm isotropic) covering the entire cortical volume, repetition time (TR) = 1110 ms, echo time (TE) = 30 ms, flip angle = 70°, field of view (FOV) = 228 × 228 mm, slice acceleration factor = 3. In total, 425 functional volumes were acquired with eyes open while viewing a black screen. An additional 8 functional volumes recorded with the same parameters, but reverse phase encoding direction were collected. T1-weighted anatomical data were also acquired from each patient using a 3D multi-echo magnetization-prepared rapid gradient-echo (ME-MPRAGE) sequence with the following parameters: 176 slices, 1 mm isotropic, TR = 2520 ms, TE1 = 1.74 ms, TE2 = 3.6 ms, TE3 = 5.46 ms, TE4 = 7.32 ms, flip angle = 7°, FOV = 240 × 240, GRAPPA acceleration factor = 2.

2.5.2 Imaging data analysis—Preprocessing and denoising were performed as part of the larger project (see also Timmers et al., 2021). Preprocessing of the resting-state fMRI data included geometric distortion estimation and correction. From the pairs of images with reversed phase-encoding directions (distortions going in opposite directions), the susceptibility-induced off-resonance field was estimated using a method similar to that described in Andersson et al. (2003) (topup tool implemented in FMRIB Software Library [FSL]; Smith et al., 2004). Images were distortion corrected in the full resting-state dataset by using FSL's applytopup. Undistorted images were preprocessed in CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012) including the following steps: 3D head motion correction, segmentation into white matter (WM), grey matter (GM) and cerebral spin fluid (CSF), normalization to Montreal Neurological Institute (MNI) space and spatial smoothing (using a 6 mm full-width at half-maximum [FWHM] Gaussian kernel).

Denoising steps involved regression of motion parameters and their first derivatives (12 parameters) and WM/CSF noise components (derived by the anatomical component-based noise correction method, aCompCor; Behzadi et al., 2007; 2×5 parameters), linear trend removal, as well as simultaneous band pass filtering (0.005 – 0.1 Hz). Quality assurance was carried out to detect outliers, and two healthy controls were excluded from the analysis due to head movement (data with motion > 3 mm/degrees). First-level analysis was performed for estimation of bivariate correlation coefficients between the a priori defined regions-of-interest (ROIs) or seeds and the rest of the brain.

The anterior insula and the medial prefrontal cortex were used as ROIs. These seed locations were selected based on previous findings of resting-state functional connectivity changes in adult women with EAP (As-Sanie et al., 2016). The right anterior insula and the left medial prefrontal cortex ROIs were generated as spheres with a radius of 10 mm (peak MNI coordinates from As-Sanie et al., (2016): 34; 19; 0 and -26; 54; 4, respectively).

Functional connectivity between each ROI and the rest of the brain was tested with the seed-to-voxel approach in CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012). In the second-

level analyses, differences were assessed between patients and controls in the anterior insula and medial prefrontal gyrus functional connectivity using group as a between-subject factor. Main effects of group were examined at a cluster-level threshold of $p < 0.001$, and subsequent cluster-level false discovery rate (FDR) corrected $p < 0.05$. For significant findings, estimated bivariate correlation coefficients were averaged across the voxels of each cluster, extracted, and transformed using Fisher's z transformation for further analyses. To investigate the association between the resting-state functional connectivity results and the clinical measurements in the patient group (not across the entire sample), Pearson correlation was employed using SPSS. In this way, we aimed to assess whether the group results can be further explained by other clinical and psychological factors. In addition, independent of group differences, correlations of the resting-state functional connectivity in the relevant seeds with the clinical measurements were further explored in the patient group. Again, the significance level was set at a cluster-level threshold of $p < 0.001$, and subsequent cluster-level FDR corrected $p < 0.05$. Anatomical locations of the significant clusters were identified using the Harvard-Oxford cortical and subcortical structural atlases (Desikan et al., 2006). Results were visualized on the MNI 152 template brain provided in MRIcroGL software (<https://www.mccauslandcenter.sc.edu/mricrogl/>).

3. Results

3.1 Participants' characteristics

Out of the 28 participants included in this study (12 patients with EAP and 16 healthy controls), two controls had to be excluded for movement artifacts (criteria described above), and one patient for technical reasons resulting in a total of 25 participants ($M_{age}=16.8$ $SD=2.4$). Thus, the final sample consisted of 11 patients with EAP (13–21 years old, $M_{age}=17.1$, $SD=1.9$) and 14 age- and sex-matched healthy controls (13–21 years old, $M_{age}=16.6$, $SD=2.7$).

Clinical data of participants are shown in Table 1. Patients with EAP reported significantly higher levels of pain-related fear and functional disability, and marginally higher pain catastrophizing compared to healthy controls. Of note, on average, the patient cohort endorsed moderate levels of pain catastrophizing, fear of pain, and disability, and patients also endorsed mild to severe levels of pain severity in the past week. Furthermore, there were no significant differences between groups in anxiety and depressive symptoms. At the time point of the study all patients with EAP and 27% of the healthy controls used hormonal contraceptives. The rest of the controls were naturally cycling women (in this group the day of menstrual cycle at the time of the scan visit and the length of menstrual cycle were also assessed, see Table 1). In general, patients had an average pain duration of over 3 years (36.55 months; $SD \pm 32.61$) and the average number of painful days per month was 18.55 ± 11.77 days.

3.2 Functional connectivity results

Compared to healthy controls, patients with EAP showed significantly decreased resting-state functional connectivity between the right anterior insula and two clusters located in the right cerebellum (posterior lobe, crus I and crus II) and the left middle frontal gyrus (Table

2, Fig. 1). For the medial prefrontal gyrus seed, the comparison between the two groups revealed no significant findings.

Additionally, correlation analysis revealed that in patients with EAP, the functional connectivity strength between the right anterior insula seed and the right cerebellum was positively correlated with the average pain intensity ($r = 0.65$, $p = 0.03$) (Fig 2) but not with the other clinical and psychosocial factors (disease duration, pain catastrophizing, fear of pain, functional disability, anxiety and depression). Functional connectivity between the right anterior insula and middle frontal gyrus did not correlate significantly with these measures.

Independent of group differences, in patients with EAP, the functional connectivity of the right anterior insula showed negative correlation with fear of pain in the right superior frontal gyrus, and positive correlation with state anxiety in the left SMA, bilateral superior frontal gyrus and left middle frontal gyrus (Table 3, Fig 3). The functional connectivity of the left medial prefrontal cortex demonstrated negative correlation with state anxiety in the left precuneus cortex, and positive correlation with state anxiety in the left cerebellum (Table 4, Fig 4).

4. Discussion

This pilot study is the first, of our knowledge, to report brain alterations in adolescent and young women with EAP using resting-state fMRI. Here, we report two main findings. First, reduced right anterior insula connectivity was observed with the right cerebellum and left middle frontal gyrus/frontal pole in young women with EAP compared to healthy controls of similar age. Second, the functional connectivity pattern between the right anterior insula and cerebellum was associated with greater pain intensity in the patient group. These results indicate that functional brain changes connected to EAP are also present in a younger age group (13–21 years) and give further support for the involvement of CNS in endometriosis.

4.1 Decreased anterior insula - middle frontal gyrus functional connectivity in EAP

Evidence suggest that the anterior insula plays a pivotal role in acute and chronic pain, and mediates different aspects of pain (Lu et al., 2016). As part of the salience network, this region detects and integrates information about salience and mediates goal-directed cognitive control (Menon et al., 2020; Uddin, 2015). Our results revealed that in patients with EAP the right anterior insula demonstrated decreased functional connectivity with the left middle frontal gyrus, a region shown to be implicated in both the dorsal and ventral attentional networks (top-down and bottom-up controlled attention, respectively) (Corbetta et al., 2008; Fox et al., 2006; Vossel et al., 2014), and known to be affected in different pain conditions (including irritable bowel syndrome, fibromyalgia and migraine; Burgmer, Pogatzki-Zahn, Gaubitz, Stüber, et al., 2009; Hong et al., 2016; Szabo et al., 2019). Pain processing depends on bottom-up (e.g., stimulus intensity) and top-down effects (e.g., expectations). In the chronic pain state, these modulatory circuits seem to be disrupted contributing to the onset and maintenance of enhanced pain experience (Ossipov et al., 2010; Staud, 2013; Tracey & Mantyh, 2007).

Of particular importance, decreased GMV was also observed in the left middle frontal gyrus in adult women with EAP (As-Sanie et al., 2012) giving further support to the significance of this region in the development and maintenance of pain states in endometriosis. Crucially, the middle frontal gyrus is part of the dorsolateral prefrontal gyrus (DLPFC). Given that the DLPFC is generally associated with pain suppression and maintenance of pain inhibition (Freund et al., 2009; Lorenz et al., 2003; Seminowicz et al., 2018), particularly the left side (Seminowicz & Moayedi, 2017), it is reasonable to believe that the decreased connectivity between the middle frontal gyrus/DLPFC and the anterior insula may indicate altered pain modulation in EAP (Boggio et al., 2008; Lorenz et al., 2003; Sridharan et al., 2008). In line with this, the right anterior insula has a critical role in switching between network states (i.e., central executive network and default mode network), and it affects and projects to the central executive network, of which the DLPFC is a crucial part (Fox et al., 2005; Goulden et al., 2014; Seeley et al., 2007; Sridharan et al., 2008). Altered connectivity between these networks is frequently reported in chronic pain conditions (Androulakis et al., 2017; Becerra et al., 2014; Cottam et al., 2018; Ichesco et al., 2014; Russo et al., 2020).

4.2 Decreased anterior insula – cerebellum functional connectivity in EAP

Patients with EAP also showed reduced right anterior insula connectivity with the right posterior cerebellum (particularly, crus I and crus II) compared to controls. Although the cerebellum is commonly activated during nociceptive processing and it seems to have a dominantly inhibitory role in pain modulation (Mehnert & May, 2019; Moulton et al., 2010; Ruscheweyh et al., 2014), studies also reported cerebellar activations during affective and aversive-sensory stimulation (Borsook et al., 2008; Diano et al., 2016; Maleki et al., 2021; Moulton et al., 2011, 2014; Schraa-Tam et al., 2012; Silva et al., 2019; Stoodley & Schmahmann, 2009) leading to the proposed role of cerebellum in affective pain processing (Adamaszek et al., 2017). Notably, crus I and crus II (of lobule VII) could be a prominent cerebellar hub where emotional and cognitive information is gathered and sent to other brain regions (Adamaszek et al., 2017). Specifically, these cerebellar sub-regions have demonstrated overlapping activity between aversive emotional and painful heat stimulation (Moulton et al., 2011), and they seem to be functionally coherent with the salience network (Habas et al., 2009).

Taken together, our observation could be interpreted that the anterior insula is disrupted in terms of integrating and modulating signals from pain-related regions due to its diminished functional connectivity. Similarly, reduction in functional connectivity related to dysregulated pain inhibition was also observed among patients with fibromyalgia (often considered the prototypical centralized pain disorder) (Cifre et al., 2012; Flodin et al., 2014) and patients with various chronic pain conditions (Ikeda et al., 2018).

4.3 Relationship between pain intensity and functional connectivity, differences in adult vs. adolescent women with EAP

We found that the connectivity strength of the right anterior insula with the cerebellum increased with self-report pain intensity suggesting a link between heightened pain experience and greater coupling of brain areas implicated in physical, affective and cognitive-evaluative components of pain, and in the salience network (Adamaszek et al.,

2017; Craig, 2009; Habas et al., 2009; Moulton et al., 2010; Szabo et al., 2022). In line with our results, previous studies have shown that greater activation in the anterior insula is related to the magnitude of painful stimuli rating (Baliki et al., 2009; Coghill et al., 1999; Starr et al., 2009), and this region is central for the subjective evaluation of internal conditions/body states, such as pain (Craig, 2009). Although this finding could be attributed to the ongoing salient and painful sensations possibly underpinning central sensitization in patients with EAP, further studies with longitudinal design are needed to confirm whether this link between subjective pain intensity and changes in functional connectivity reflects either an adaptive mechanism or an atypical condition that predisposes young women to chronic pain.

Based on the present and previous results, we can conclude that brain changes related to the EAP may be represented differently in the developing brain. That is, in adult women increased anterior insula functional connectivity was found within regions of the medial prefrontal cortex (part of the default mode network) (As-Sanie et al., 2016), while we found decreased connections with the middle frontal gyrus and cerebellum. Connectivity differences between adult and younger patients with complex regional pain syndrome have also been reported before (Becerra et al., 2014; Bolwerk et al., 2013) suggesting a potentially important age related and developmental difference of the underlying brain mechanisms and connections (especially in the frontal areas) (Selemon, 2013; Uddin et al., 2011), or it could relate to the different manifestations of the symptoms in younger women with EAP (e.g., lesions often present differently; both cyclic and non-cyclic pelvic pain is common in adolescents) (Laufer, 2008; Laufer et al., 2003). During adolescence, repeated pain is likely accompanied by enhanced neuroplasticity in which networks of the brain, including those underlying pain processing, undergo significant development (for a review, see Spear, 2013). It should be also noted that the central executive network is not fully developed until adulthood (maturation of the prefrontal cortex is fully accomplished around the age of 25 years; Arain et al., 2013; Casey et al., 2008) suggesting that pain-related experiences might be dominated by emotionally-driven responses and the engagement of the salience network in a younger age group (Uddin et al., 2011). Recent evidence has also showed that in adolescent females (compared to adult women) pain-evoked activation was increased in limbic brain areas and in regions mainly involved in the bottom-up attentional mechanism and self-referential processing (Tong et al., 2022). This imbalance in the brain development could play an important role in the bottom-up and top-down processing of pain suggesting a less effective top-down control system during adolescence (as compared to adulthood) (Casey et al., 2008). Adolescents may process emotional distress and affective pain in similar areas of the brain. ‘Social pain’, the experience of pain resulting from interpersonal rejection or loss (Eisenberger, 2006, 2012), relies on some of the same brain regions that process physical pain including the anterior insula. The anterior insula seems to be involved in the distressing experience and affective component of pain and could be associated with physical and mental health problems (Cacioppo et al., 2013).

Lastly, independent of group differences, in patients with EAP, the functional connectivity of the right anterior insula showed positive correlation with state anxiety in the bilateral superior and left middle frontal gyrus, and in the left SMA. Besides the involvement of the middle frontal regions in pain (as discussed above), activation of the SMA is consistently

reported during pain processing in healthy controls and patients with fibromyalgia (Burgmer, Pogatzki-Zahn, Gaubitz, Wessoleck, et al., 2009; Cifre et al., 2012; Coghill et al., 1994; Qiu et al., 2006; Staud & Rodriguez, 2006), and it has been proposed that the SMA might be more involved in the affective function of pain (Qiu et al., 2006). In line with this, state anxiety was also related to enhanced functional connectivity between the left medial prefrontal cortex and left cerebellum (crus I and crus II) further supporting the cerebellar involvement in pain, and emotional and affective functions (Adamaszek et al., 2017; Moulton et al., 2011). Interestingly, the connectivity of the left medial prefrontal cortex showed negative correlation with state anxiety in the left precuneus (components of the default mode network) indicating altered functional connections underlying attentional processes and emotional states in young patients with EAP (Cavanna & Trimble, 2006; Saviola et al., 2020).

Although in adult patients with EAP (As-Sanie et al., 2016), functional connectivity was positively correlated with both clinical anxiety and depression, in our pilot study, patients did not show increased anxiety and depressive symptoms relative to controls but they did report higher levels of pain-related fear, catastrophizing, and functional disability, which could suggest an increased risk of developing mood disturbances later in life. Of note, fear of pain was associated with weakened functional connectivity of the anterior insula in the right superior frontal gyrus, implicating that pain-related fear may contribute to the diminished or ineffective pain inhibition in young women with EAP.

4.4 Limitations and future directions

First, since this was a pilot study, results must be interpreted cautiously due to the small sample size. Nevertheless, it seems that age-related alterations may occur with the endometriosis disease, however, future studies are needed to compare across different age groups (i.e., adolescents, young adults, and adult women with endometriosis). Second, while all patients used hormonal contraceptives, most of the healthy participants did not, and endogenous hormones may be potential mediators of brain states (N. Petersen et al., 2014). There does not seem to be consistency or consensus of what phase of the menstrual cycle is ideal for neuroimaging studies and adolescent participants may have variable cycle lengths (Hidalgo-Lopez et al., 2020; Otomo et al., 2020; Wang et al., 2021) making it difficult to ascertain cycle phase by day alone; a confirmation hormonal assay would be ideal (Masuda et al., 2016). Third, we only assessed resting-state (task-free) functional connectivity differences between patients with EAP and controls. Future studies should aim to include endometriosis patients without pain and patients with other types of chronic pain. In addition, no studies have explored brain responses to painful or other stressful stimuli in women with EAP. For example, offset analgesia (OA) is an increasingly used method to measure inhibitory pain mechanism (Derbyshire & Osborn, 2009; Yelle et al., 2009) and while previous studies do provide evidence for attenuated OA responses (i.e., a disproportionately large reduction in pain perception after a small decrease in temperature during noxious stimulation; Grill and Coghill, 2002) in patients with various chronic pain conditions, this is unknown in EAP (Lunde et al., 2020).

4.5 Conclusion

Our results support that endometriosis-related pain is likely due to dysfunction in the CNS pain regulatory system, an area of investigation understudied in this population. Since most women report symptoms of endometriosis during adolescence, and there is a risk of chronification of pain, this would be a crucial time to intervene (Sieberg et al., 2020). Also, studies need to further explore whether neural alterations are normalized by therapy or laparoscopic surgery. Detecting early “normalization” of atypical brain changes could be an important biomarker for predicting pain chronification, treatment response, and for developing centrally mediated treatments in endometriosis.

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Highlights

- Altered brain function in young patients with endometriosis-associated pain (EAP)
- Less functional connectivity between the right anterior insula and pain-related regions
- Anterior insula and cerebellum connectivity was linked to greater pain intensity
- Alterations in the pain regulatory pathways in endometriosis
- Endometriosis management should include centrally mediated treatments

Main Effect of Group: Patients with EAP > Controls

Seed region:
Right anterior insula

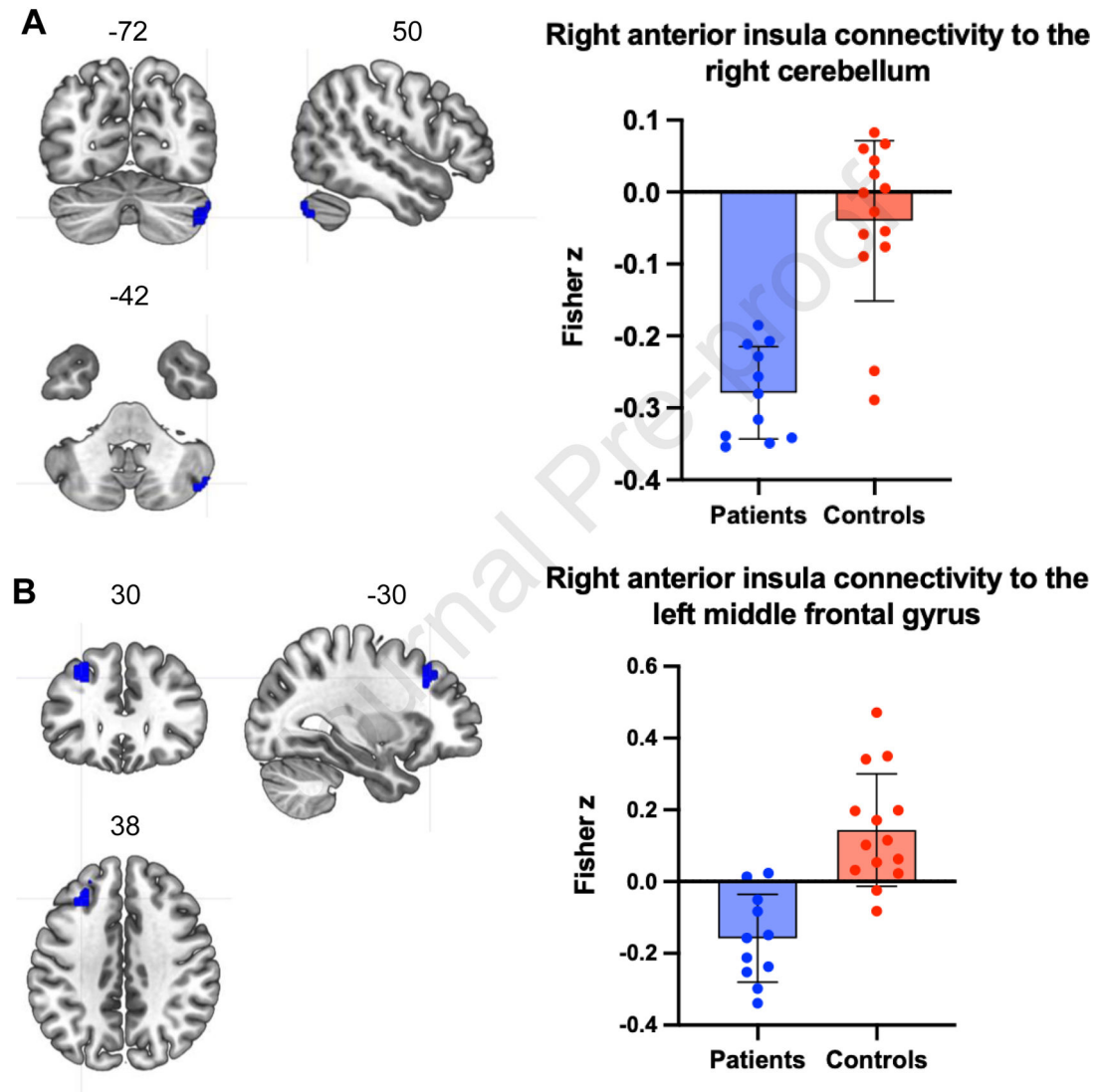
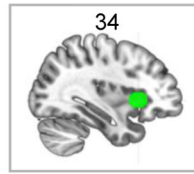


Figure 1.

Altered resting-state functional connectivity between the right anterior insula and the rest of the brain in patients with endometriosis-associated pain (EAP) compared to healthy controls. The right anterior insula demonstrated significantly decreased functional connectivity to the right cerebellum (crus I and crus II) (**A**), and left middle frontal gyrus (**B**) in EAP patients. Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at $p_{FDR} < 0.05$. Bar

graphs indicate average and individual Fisher's z -transformed connectivity values. Error bars represent standard error of mean.

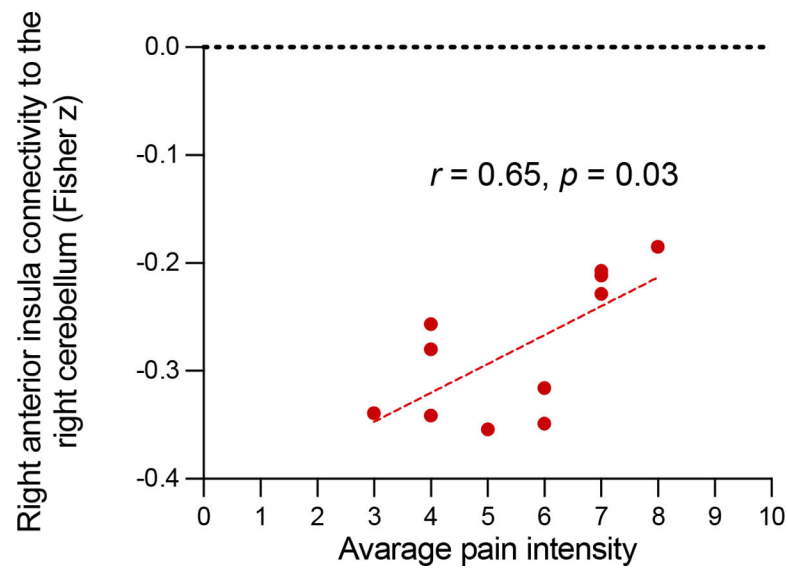
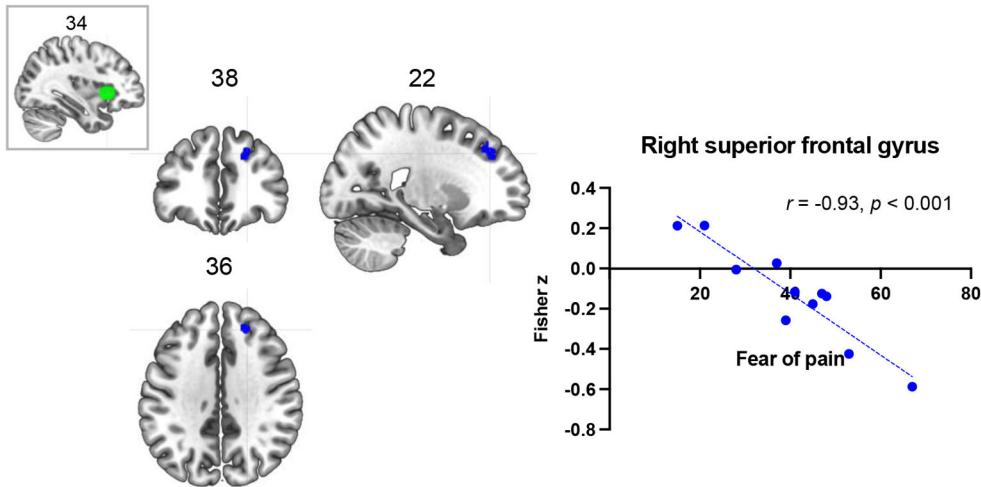


Figure 2.

In patients with endometriosis-associated pain (EAP), right anterior insula connectivity to the right cerebellum was positively correlated with average pain intensity. Connectivity values are Fisher's z -transformed.

A) Fear of pain

Seed: Right anterior insula



B) State anxiety

Seed: Right anterior insula

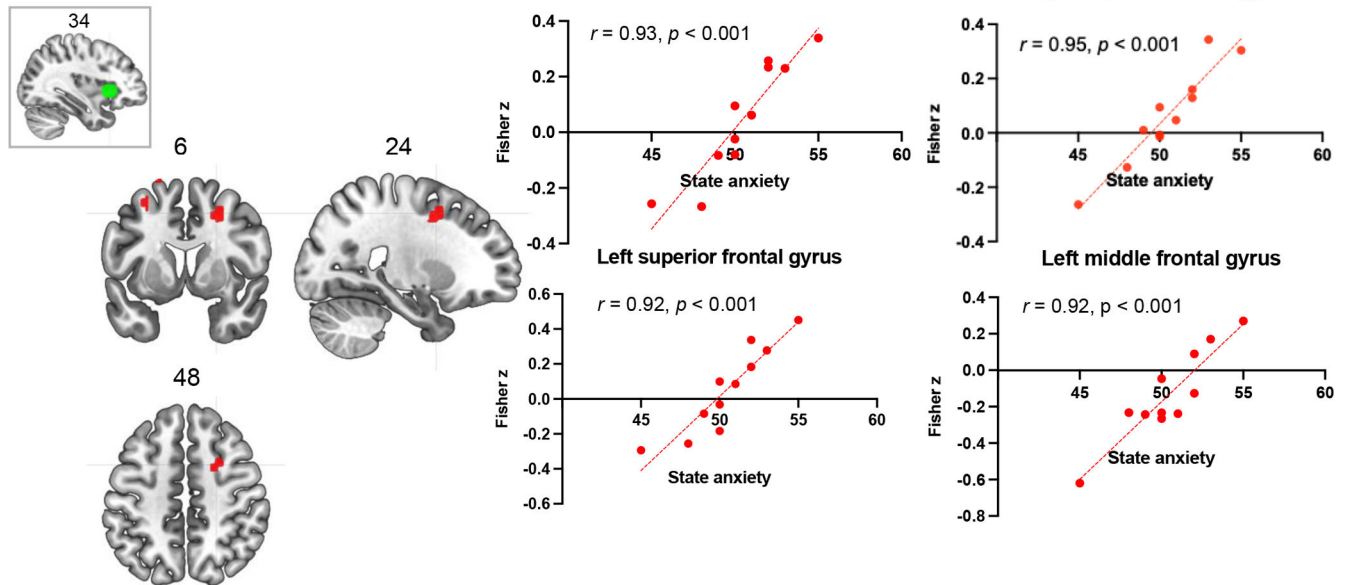


Figure 3.

In patients with endometriosis-associated pain (EAP), resting-state functional connectivity of the right anterior insula was negatively related to fear of pain in the right superior frontal gyrus (A), and positively related to state anxiety in the left supplementary motor area, bilateral superior frontal gyrus and left middle frontal gyrus (B). Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at $p\text{FDR} < 0.05$. Connectivity values are Fisher's z -transformed.

State anxiety

Seed: Left medial prefrontal cortex

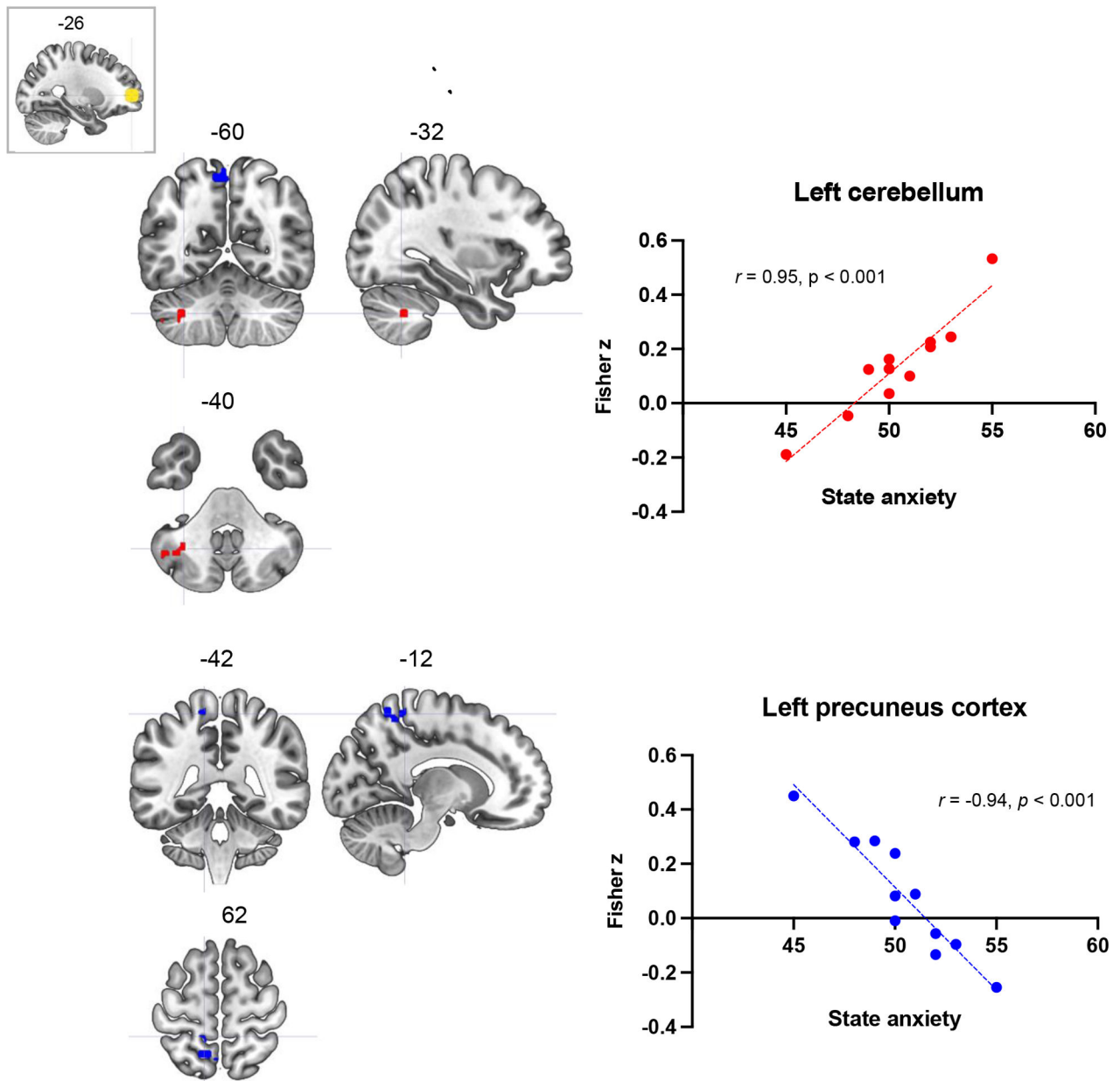


Figure 4.

In patients with endometriosis-associated pain (EAP), resting-state functional connectivity of the left medial prefrontal cortex was positively related to state anxiety in the left cerebellum (crus I and crus II), and negatively related to state anxiety in the left precuneus cortex. Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at $p\text{FDR} < 0.05$. Connectivity values are Fisher's z -transformed.

Table 1.

Demographics and clinical characteristics of the participant groups.

Subject group	Patients with EAP <i>n</i> = 11	Healthy controls <i>n</i> = 14	Test statistic	<i>p</i> value
Age (years)	17.1 ± 1.9 (13–21)	16.6 ± 2.7 (13–21)	<i>t</i> (23) = 0.45	0.65
PCS-C	17.9 ± 8.6 (0–34)	11.7 ± 7.1 (0–24)	<i>t</i> (23) = 1.97	0.06
FOPQ-C	40.1 ± 4.8 (15–67)	15.2 ± 8.7 (2–32)	<i>t</i> (23) = 5.26	< 0.001
FDI	13.2 ± 9.3 (1–33)	1.6 ± 2.7 (0–8)	<i>U</i> = 9.00	< 0.001
STAI-S-C	50.5 ± 2.7 (45–55)	48.4 ± 3.1 (41–52)	<i>t</i> (23) = 1.78	0.09
STAI-T-C	12.3 ± 8.4 (0–29)	12.4 ± 8.3 (1–32)	<i>t</i> (23) = 0.03	0.98
CDI-2	52.5 ± 7.6 (41–63)	47.9 ± 8.1 (40–63)	<i>t</i> (23) = 1.21	0.25
Pain severity (average pain in the last week, 0 to 10)	5.6 ± 1.6 (3–8)	–	–	–
Pain duration (month)	36.6 ± 32.6 (4–117)	–	–	–
Painful days per month	18.55 ± 11.77 (5–30)	–	–	–
Using hormonal contraceptives	11 (100%)	3 (27%)	$\chi^2 = 15.43$	< 0.001
Length of menstrual cycle (days) ^a	–	32.7 ± 7.6 (23–49)	–	–
Day of menstrual cycle (at the time of the scan) ^a	–	12.5 ± 10.8 (2–36)	–	–

Note. Data are expressed as mean ± *SD* (range) or number of patients (%). Continuous data were analyzed using the independent-sample *t*-test for parametric variables or the Mann-Whitney *U* test for nonparametric variables. Categorical data were analyzed using Chi-square (χ^2) test.

EAP, endometriosis-associated pain; PCS-C, Pain Catastrophizing Scale–Child version; FOPQ-C, Fear of Pain Questionnaire for Children; FDI, Functional Disability Inventory; STAI-S-C, State-Trait Anxiety Inventory for Children–State scale; STAI-T-C, State-Trait Anxiety Inventory for Children–Trait scale; CDI-2, Children’s Depression Inventory-2.

^aLength and day of the menstrual cycle are presented for healthy subjects not using any hormonal contraceptives (*n*=11).

The *p* values for test statistics that reached significance are bolded.

Table 2.

Brain regions showing decreased functional connectivity with the right anterior insula in patients with endometriosis-associated pain (EAP) compared to healthy controls.

Cluster	Cluster size	Peak MNI coordinates			Cluster p (FDR)	Cluster p -uncorr
		x	y	z		
Right cerebellum	153	50	-72	-42	0.012	0.0005
Left middle frontal gyrus/frontal pole	145	-30	30	38	0.012	0.0007

Note. Clusters are significant at $p\text{FDR} < 0.05$ following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.

Table 3.

Significant correlations in resting-state functional connectivity of the right anterior insula with fear of pain (negative) and state anxiety (positive) in patients with endometriosis-associated pain (EAP).

Cluster	Cluster size	Peak MNI coordinates			Cluster p (FDR)	Cluster p -uncorr
		x	y	z		
Fear of pain (negative correlation)						
Right superior frontal gyrus / frontal pole	80	22	38	36	0.036	0.0015
State Anxiety (positive correlation)						
Left supplementary motor area	75	−2	−10	62	0.029	0.0020
Right superior frontal gyrus / frontal pole	73	24	6	48	0.029	0.0023
Left superior frontal gyrus / frontal pole	68	−20	6	74	0.029	0.0030
Left middle frontal gyrus	68	−32	8	56	0.029	0.0030

Note. Clusters are significant at $p_{\text{FDR}} < 0.05$ following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.

Table 4.

Significant correlations in resting-state functional connectivity of the left medial prefrontal cortex with state anxiety (positive and negative) in patients with endometriosis-associated pain (EAP).

Cluster	Cluster size	Peak MNI coordinates			Cluster p (FDR)	Cluster p -uncorrected
		x	y	z		
State Anxiety						
Left cerebellum (positive correlation)	147	−32	−60	−40	0.029	0.000004
Left precuneus cortex (negative correlation)	157	−12	−42	62	0.001	0.000008

Note. Clusters are significant at $p\text{FDR} < 0.05$ following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.



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Quantitative sensory testing in a magnetic resonance environment: considerations for thermal sensitivity and patient safety

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Introduction: Quantitative sensory testing (QST) is often used to understand the perceptual basis of acute and chronic conditions, including pain. As the need grows for developing a mechanistic understanding of neurological pathways underlying perception in the basic and clinical sciences, there is a greater need to adapt techniques such as QST to the magnetic resonance (MR) environment. No studies have yet evaluated the impact of the MR environment on the perception of thermal stimuli. This study aimed to evaluate the differences in temperature sensitivity outside an MR environment and during an MRI scanning session. We hypothesized that there would be a difference in how participants reported their pain sensitivity between the two environments.

Methods: Healthy participants underwent thermal QST outside the MR scanning environment, where they were asked to rate the temperature of a noxious stimulus at which they perceived their pain to be 7/10, using a Likert scale ranging from 0 to 10. Participants repeated this procedure inside a 3.0 T MRI approximately 30 min later. We repeated our investigation in a clinical cohort of participants with a chronic pain condition.

Results: There were statistically significant changes of 1.1°C in thermal sensitivity between environments. This increase in pain threshold was found in healthy participants and replicated in the clinical cohort.

Discussion: Findings can be applied toward improving MR safety, the resolution of brain pathways underlying pain mechanisms, and to more broadly comment on the impact of the MR environment on investigations that integrate perception-influenced processes.

KEYWORDS

magnetic resonance imaging, thermal sensitivity, MR safety, quantitative sensory testing, pain

Introduction

The application of quantitative sensory testing (QST) in the magnetic resonance (MR) environment is the advancement of a well-studied technique into a novel environment that is promising for informing the mechanisms underlying cognitive processes. The MR environment is inherently complex, both in terms of the basic machinery and the impact

it can have on the human body. As higher magnetic field environments are emerging worldwide (1), it is critical to understand the impact of the MR environment on cognitive faculties. Exposing patients to the MR environment means exposure to unique thermal (e.g., continuous flow of dehumidified room temperature air through the MR bore) and psychological environments (2, 3) and the established impact of MR and changing MR fields on the human body (4). There is little information on applying QST in the MR environment, particularly concerning complex cognitive processes such as pain perception.

Applying QST in pain cognitive neuroscience has proved pivotal in detecting clinical changes and informing pain mechanisms. Thermal QST is a valuable tool used in pain research and can help detect pathophysiological mechanisms associated with neuropathic pain (5) and detect altered central pain processing (6, 7). QST is safe and has been used in adult and pediatric cohorts (8), making it an increasingly popular method of testing pain sensitivity in patients among clinicians and researchers. The application of QST has shown to be reliable over time, including research showing the stability of the technique over a 10-week period (9). The predictive value of QST for identifying persons at risk of developing chronic pain has also been explored, with some research supporting the use of QST in predicting persistent post-surgical pain (10, 11). The application of QST has notable potential in focused populations and should be investigated for its application in unique environments, such as the MR environment.

To date, there have been no studies evaluating changes in thermal pain sensitivity using QST-based approaches in the MR environment. This study aimed to explore the relationship between thermal sensitivity inside and outside the MR environment using a standard QST pain sensitivity protocol that required participants to rate their level of perceived pain using a presented Likert scale. We conducted our investigation in the context of a group of healthy female participants between the ages of 13 and 43 years and extended our findings to a clinical cohort of participants with chronic pain. Our clinical cohort was comprised of patients with surgically confirmed endometriosis, a chronic pain condition that impacts approximately 1 in 10 women of reproductive age (12). Findings are discussed in terms of the application of QST in MR environments and the broader impact of MR on cognitive neuroimaging.

Materials and methods

Participants and study recruitment

Sixty-one participants were recruited for the study, and 55 (aged 13–43 years; $M=27.60$, $SD=7.92$) were included in the data analysis. Participants were required to be between the ages of 12–44 on the day of the study visit, with the ability to speak sufficient English to complete study visit tasks (i.e., self-report questionnaires in English). The clinical cohort included patients with surgically confirmed endometriosis, verified by research staff.

Exclusion criteria were (1) inability to speak sufficient English to complete study visit tasks; (2) severe cognitive impairments; (3) patients with co-morbid medical and/or pain conditions that may potentially confound the data; (4) MRI exclusion criteria [e.g., metallic implants, claustrophobia, weight >350 lbs (limit of MRI table)]; (5) current use of opioid analgesics, which may confound pain data; (6) history of hysterectomy or oophorectomy; and (7) participants who are already in menopause, defined as the cessation of menses for 12 consecutive menses, unrelated to exogenous hormonal influences. Participants consented to the study after being screened for MRI compatibility and study eligibility by trained research staff. Six participants were excluded from the analysis due to withdrawal by self-request, positive drug screens, and equipment issues (see Figure 1).

Participants were female sex assigned at birth, most identified as female, with one clinical patient identifying as a transgender male and one as non-binary. Most participants identified as White (80%), with Asian being the second most prominent racial group (see Table 1). Participants were screened for birth control use and menstrual cycle history to minimize hormonal influences. All participants were either on hormonal birth control (i.e., combined birth control pill, hormonal intrauterine device (IUD), progesterone implant) or asked to come in between days 2 and 10 of their menstrual cycle, in which day 1 of the cycle was defined as the first day of their most recent period.

On the day of the study, participants were asked to report their pain levels from 0 (“no pain at all”) to 10 (“worst pain imaginable”). Healthy control participants reported pain scores of 0–2 ($M=0.18$, $SD=0.59$), while clinical participants reported average pain scores of 0–6 ($M=1.93$, $SD=1.81$). Participants were given a battery of psychological questionnaires, which included select PROMIS measures (anxiety and depression) (13, 14), the Pain Catastrophizing Scale (PCS) (15, 16), and the Fear of Pain Questionnaire (FPQ) (17, 18), with pediatric or adult versions administered accordingly.

Psychological measures

Anxiety and depression measures

Anxiety

The PROMIS Anxiety 8a—Adult v1.0 (13) and Anxiety 8a—Pediatric v2.0 (14) were used to evaluate anxious symptomatology. This eight-item measure evaluates feelings of anxiety experienced within the last 7 days. Each question on the anxiety PROMIS measure includes a five-point Likert scale, ranging in value from one (Never) to five (Always). Raw scores are summed from responses, and then *T*-scaled to the general population. A *T*-score of 50 ($SD=10$) represents the average score of the population. A higher PROMIS anxiety *T*-score represents more impaired functioning with a score of 60 or above being clinically elevated. Cronbach’s alpha of the adult sample was 0.939 and for the pediatric sample was 0.953, demonstrating excellent internal item reliability in measuring anxiety and depression.

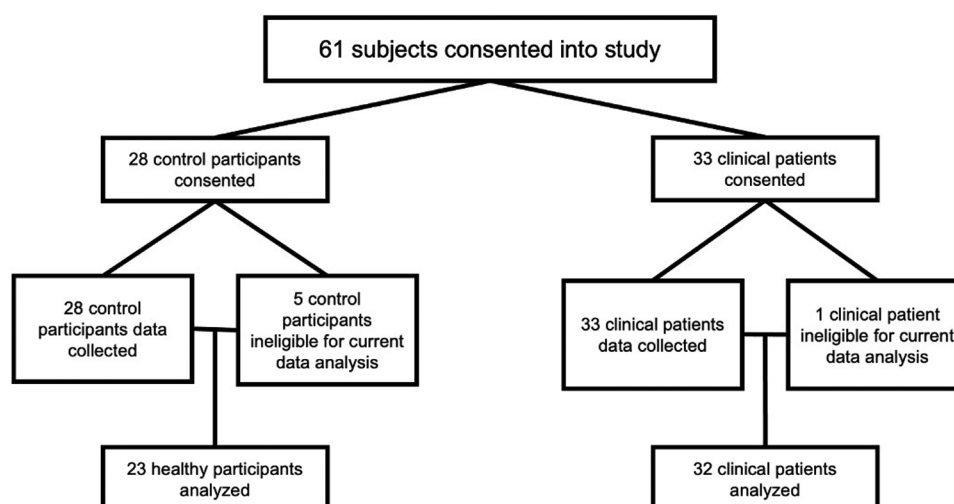


FIGURE 1

Participant analysis cohort breakdown. All participants are female sex assigned at birth and all clinical participants had surgically confirmed endometriosis.

TABLE 1 Demographic breakdown of healthy and clinical participants.

Demographics of clinical vs. control subjects		
	Clinical	Control
	(N = 32)	(N = 23)
Age		
Minimum	15.68	13.03
Maximum	43.10	41.78
Mean	27.92	27.16
SD	8.43	7.33
Gender identity		
Female	93.8%	100.0%
Ethnicity		
Non-Hispanic	93.8%	73.9%
Hispanic	6.2%	26.1%
Race		
White	96.9%	56.5%
Asian	3.1%	21.7%
Black or African-American	6.3%	4.3%
Native American/Alaskan	6.3%	0.0%
Other	0.0%	17.4%

Depression

The PROMIS Depression 8a—Adult v1.0 (13) and Depression 8a—Pediatric v2.0 (14) were used to evaluate depressive symptomatology. Participants self-reported depressive feelings experienced within the last 7 days. This measure is similar in question format and scoring methodology as the PROMIS anxiety measure. A higher PROMIS depression *T*-score also represents more depressive symptoms with a *T*-score of 60 or above being clinically elevated. Cronbach's alpha for the adult sample was 0.958. Cronbach's alpha for the pediatric sample was 0.913.

Pain measures

Pain catastrophizing

The PCS (15) was used to measure pain catastrophizing, a construct assessing pain-related worry (19). It is scored on a Likert style scale from 0 (Not at all) to 4 (All the time) and is scored by summing the responses. Along with a total score, the PCS possesses three subscale scores assessing rumination, magnification, and helplessness. A total score of 30 and above represents clinically relevant catastrophizing. The Pain Catastrophizing Scale for Children (PCS-C) (16) is the pediatric version of the adult PCS. The PCS-C assesses the same symptomatology of pain catastrophizing and is well-validated in the literature for assessing pain-related rumination, magnification, and helplessness in a pediatric cohort. The Cronbach's alpha for the adult sample was 0.950. Cronbach's alpha for the pediatric sample was 0.921.

Fear of pain

The FPQ (17) measures self-reported feelings of fear of different noxious stimuli and is divided into three subscales of severe, minor, and medical pain. The questionnaire shows good internal and test-retest reliability. The Cronbach's alpha for the adult sample was 0.945. The Cronbach's alpha for the pediatric sample was 0.940. The Fear of Pain Questionnaire, child version (FOPQ-C) (18) was developed for pediatric patients and is also a five-point Likert scale (0 = "strongly disagree"; 4 = "strongly agree") consisting of two subscales, fear of pain and avoidance of activities.

Thermal QST

The noxious thermal stimulus was administered using an fMRI-compatible Medoc TSA 2 (Medoc, Israel), with a 30 mm × 30 mm

thermode. The stimulus was applied on the medial and lateral sides of their non-dominant calf. Tested temperatures ranged from 32.0°C to 48.0°C, and the temperature rate of change was 13.0°C/s. Unless a task was being run, the thermode was kept at 32.0°C. The researcher would use a non-toxic pink highlighter to mark four spaces for thermal testing: two space medial and two spaces lateral on the non-dominant calf. The researcher would switch the space used during the threshold test for each trial in a circular, clockwise pattern from where the researcher started. The space (upper versus lower medial or lateral space) was pseudorandomized per participant.

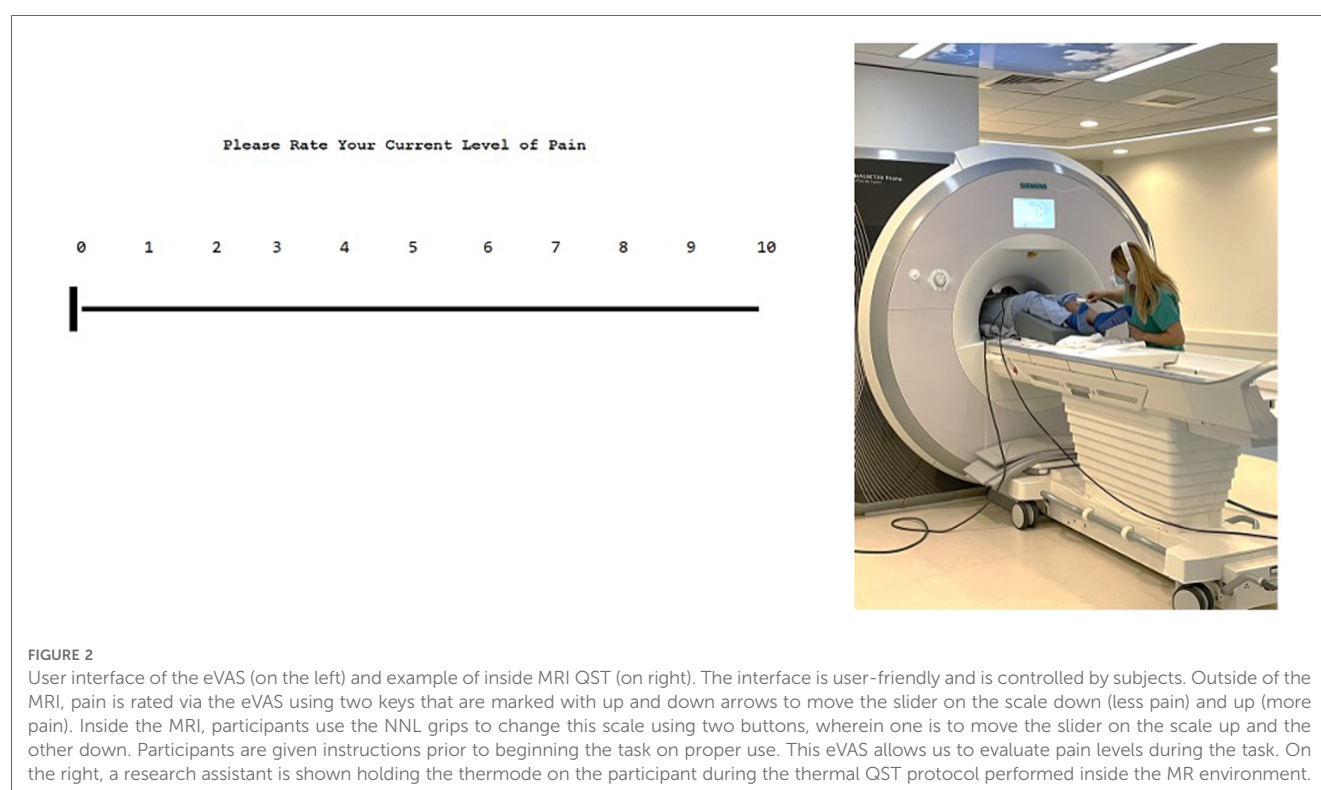
Outside of the MRI environment, in a controlled testing space, participants were instructed to rate the pain from the stimulus using the pain scale of 0 (“no pain at all”) to 10 (“the worst pain imaginable”). The temperatures of both testing environments, inside and outside the MR environment, were thermostatically controlled to be approximately 21°C. Participants were given a remote-control device connected to the Medoc that allowed them to cease temperature changes when they felt a 7 out of 10 (moderate to severe pain) pain level from the noxious stimuli. Temperature paradigms were performed online and coincident with participants rating their level of pain perception. Three trials (Trial 1, Trial 2, and Trial 3) were performed to find the participants’ individual 7 out of 10 (7/10) temperature, changing locations of the thermode on the calf in between each trial. The average 7/10 temperature was found from averaging all three trials. A thermal training paradigm was performed after finding the 7/10 temperature in preparation for further testing inside the MRI testing. All trials and averaged 7/10 temperature outside the MRI are referred to as the outside temperature thresholds.

MRI scanner protocol

Image acquisition was performed with a 3.0 T MRI (Siemens Prisma) scanner with a 64-channel head coil. A 7 min and 02 s T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE), a 3 min and 07 s T2-weighted anatomical images, and a 7 min and 19 s resting-state sequence were performed (total time: 17 min and 28 s sequence). Participants were given similar verbal instruction and rated their pain with grips connected to a Nordic Neuro Lab (NNL) system that allowed participant control on an electronic visual analog scale (eVAS) from 0 to 10 (see **Figure 2**). When the participant reached a 7, a trained researcher stopped the thermode from changing temperature manually. The researcher holding the thermode inside the MRI briefly removed the thermode to change locations on the calf, as was performed outside. Skin was briefly wiped with a towel to remove perspiration in between each trial. Three trials were performed, and mathematical averaging was done to determine an average 7/10 temperature. These 7/10 temperatures are referred to as inside temperature thresholds. Participants were not administered blankets or sheets for the duration of the study to reduce excess overheating.

Statistical analyses

Statistical analyses were performed using SPSS v. 24 (IBM, Armonk, NY, USA). Descriptive data were collected for demographics, emotional functioning, and thermal data. Shapiro–Wilk tests were used to examine normality. Fisher’s exact test



(chi-square test of homogeneity) was performed to examine racial breakdown proportions between cohorts. Normally distributed psychological data were compared with independent samples *t*-tests, while non-normally distributed data were compared via Mann–Whitney *U* tests. A related-samples Wilcoxon signed rank test was performed on the combined cohort data, as well as the separate clinical and control cohorts to evaluate whether there were differences between temperature threshold due to the MRI environment. We performed two-way ANOVA in order to explore an interaction effect between cohorts and MR environment. We calculated effect sizes using whole group data at 80% power and an alpha level of 0.05 to understand the effect of environment given our sample size.

Results

Control participants were aged 13–42 years ($M = 27.16$, $SD = 7.33$), while clinical participants were aged 16–42 years ($M = 27.92$, $SD = 8.43$). All participants were female sex assigned at birth. There were significant differences ($p < 0.01$) based on race between the control and clinical cohorts. About 97% of the clinical cohort identified as White, and 0% identified as Other; 57% of control participants identified as White, and 17.4% identified as Other (see [Table 1](#)). Both groups had similar proportions of minority populations (i.e., Black/African-American, Asian).

Anxiety *T*-scores of control participants ranged from 37.10 to 74.90 ($M = 51.88$, $SD = 9.83$), while *T*-scores of the clinical cohort

ranged from 37.10 to 73.00 ($M = 58.97$, $SD = 7.93$). Depression *T*-scores of control participants ranged from 37.10 to 72.60 ($M = 45.68$, $SD = 8.77$), while *T*-scores for the clinical cohort ranged from 43.20 to 73.60 ($M = 55.93$, $SD = 8.04$). Anxiety and fear of pain scores were normally distributed ($p > 0.05$), but depression and pain catastrophizing were not ($p < 0.05$). The clinical cohort endorsed greater symptomatology relative to healthy controls in anxiety, depression, and pain catastrophizing ($p < 0.005$). There were no significant differences between the groups in fear of pain. Anxiety, depression, and pain catastrophizing were statistically significantly different in between chronic pain and pain-free cohorts ($p < 0.01$), while fear of pain was not found to be statistically significant ($p = 0.56$) (see [Table 2](#)).

The temperatures of both testing environments were thermostatically controlled to be approximately 21°C. A paired-samples Wilcoxon signed rank test was performed on the combined (healthy and clinical) cohort data to evaluate whether there were differences in temperature threshold due to the MRI environment. This was performed for each trial and an averaged trial. Statistically significant results ($p < 0.005$) were found in each trial and in the average of all three trials (see [Table 3](#)). As shown in [Figure 1](#), for the combined cohort (healthy controls and clinical participants), there was a significant increase in temperature threshold inside of the MRI scanner for each trial and averaged data (trial 1: 1.5°C, $z = 3.14$; trial 2: 2.4°C, $z = 4.32$; trial 3: 0.4°C, $z = 3.11$; averaged: 1.1°C, $z = 4.36$).

Wilcoxon signed ranks tests were also performed within the clinical and control cohorts separately to determine if consistent differences inside and outside of the MRI were found in both

TABLE 2 Differences between clinical and control participants in psychological tests.

Normal data	Clinical			Control			Statistic	
	M	SD		M	SD		<i>t</i> (53)	<i>p</i>
Anxiety (<i>T</i> -score)	58.97	7.93		51.88	9.83		−2.957	0.005
Fear of pain	70.09	18.17		67.04	20.12		−0.587	0.56
Non-normal data	M	SD	Mean rank	M	SD	Mean rank	Test statistic	<i>p</i>
Depression (<i>T</i> -score)	55.93	8.04	17.46	45.68	8.77	35.58	4.149	<0.001
Pain catastrophizing scale	30.44	11.23	18.36	19.91	9.87	34.91	3.788	<0.001

TABLE 3 Related-samples Wilcoxon signed rank test to compare environments.

	Trial	<i>N</i>	Test statistic	<i>p</i> -value	Median	
					Outside MRI	Inside MRI
All participants	1	55	3.14	0.002	45.10	46.60
	2	55	4.32	<0.001	44.40	46.80
	3	55	3.11	0.002	45.50	45.90
	Averaged	55	4.36	<0.001	45.23	46.33
Clinical	1	32	2.28	0.023	45.75	46.50
	2	32	3.86	<0.001	44.60	46.90
	3	32	3.64	<0.001	45.80	46.45
	Averaged	32	4.03	<0.001	45.67	46.83
Control	1	23	2.05	0.040	45.00	46.90
	2	23	2.29	0.022	44.20	46.10
	3	23	0.76	0.445	44.20	44.90
	Averaged	23	1.98	0.048	43.70	46.23

TABLE 4 Independent samples Kruskal–Wallis H test to compare independent cohorts.

	Trial	N	df	Test statistic	p -value	Median	
						Control	Clinical
Outside MRI	1	55	1	0.29	0.864	45.00	45.75
	2	55	1	0.21	0.621	44.20	44.60
	3	55	1	0.77	0.379	44.20	45.80
	Averaged	55	1	0.04	0.851	43.70	45.67
Inside MRI	1	55	1	0.25	0.619	46.90	46.50
	2	55	1	2.30	0.129	46.10	46.90
	3	55	1	2.90	0.088	44.90	46.45
	Averaged	55	1	1.53	0.216	46.23	46.83

TABLE 5 Results of a two-way ANOVA evaluating the interaction effects between environment and cohort on 7/10 threshold during an averaged trial.

Evaluating the interaction effects between environment and cohort on 7/10 temperature						
Averaged						
Predictor	Sum of squares	df	Mean square	F	p	Partial η^2
(Intercept)	2,18,244.702	1	2,18,244.702	36,598.528	0	0.997
Environment	24.866	1	24.866	4.17	0.044	0.038
Cohort	4.365	1	4.365	0.732	0.394	0.007
Environment×Cohort	1.216	1	1.216	0.204	0.652	0.002
Error	632.1	106	5.963			

cohort types. Statistically significant results were found in most trials ($p < 0.05$), except trial 3 of the control participants. Each trial indicated an increase [trial 1 (clinical, A): 0.75°C, trial 1 (control, B): 1.90°C; trial 2 (A): 2.30°C, trial 2 (B): 1.90°C; trial 3 (A): 0.65°C, trial 3 (B): 0.70°C; averaged (A): 1.16°C, averaged (B): 2.54°C] in the 7/10 threshold inside compared to outside of the MRI scanner (see [Table 3](#)).

To determine if there were differences in temperature thresholds between control and clinical participants, a Kruskal–Wallis H test was performed. There were no statistically significantly different 7/10 thresholds between cohort types inside of the MRI and outside of the MRI ($p > .05$) (see [Table 4](#)).

ANOVA

We elected to perform a two-way ANOVA to explore an interaction effect between cohorts and MR environment. There was no significant interaction between the environment and cohort for temperature threshold using averaged trial data (see [Table 5](#) and [Supplementary Table 1](#)). There was no significant difference in temperature threshold between cohorts, $F(1,106) = 0.732$, $p = 0.039$, partial $\eta^2 = 0.007$. The marginal means for control and clinical participants were 44.95 ± 0.36 and 45.35 ± 0.31 , respectively, with a non-significant mean difference of -0.404 (95% CI, -1.34 to 0.53). There was a significant difference in environment, $F(1,106) = 4.17$, $p < 0.05$, partial $\eta^2 = 0.04$, that being inside of the MRI was associated with a mean temperature threshold increase of 0.96 (95% CI, 0.28 – 1.90), with unweighted marginal means for outside and inside of the MRI being 44.67 ± 0.334 and 45.63 ± 0.33 , respectively. Within the

combined cohort, nine individuals were higher outside the MR environment, 44 inside the MR environment, and two reached the maximum temperature threshold in both environments ([Figure 3](#)).

Discussion

A reliable change in thermal pain sensitivity was experienced by participants based on the testing environment. The ability of QST to inform patient diagnostics and delineate central mechanisms of pain perception and chronicity is contingent upon the accurate application of thermal stimuli. To date, QST has largely been performed in clinical or research settings outside of the MR environment ([20](#)); however, the application of QST in the MR environment is an emerging application of the technology. The MR scanner represents an ideal environment for studying neurocognitive processes with unique psychological stressors (e.g., claustrophobia), novel stimuli, and attributes of the physics of the MR environment itself. The findings from this investigation outline a reliable change in thermal sensitivity that was experienced when both healthy and clinical participants completed a QST thermal sensitivity protocol inside and outside of the MR scanning environment.

The MR environment can present as stressful to participants, which can be exacerbated in people with underlying anxiety. Therefore, we explored two behavioral based interpretations of the findings. First, it is possible that the findings observed in the current investigation reflect active or exacerbated psychological symptoms. Participants in this investigation are actively screened for any history of claustrophobia and psychological co-

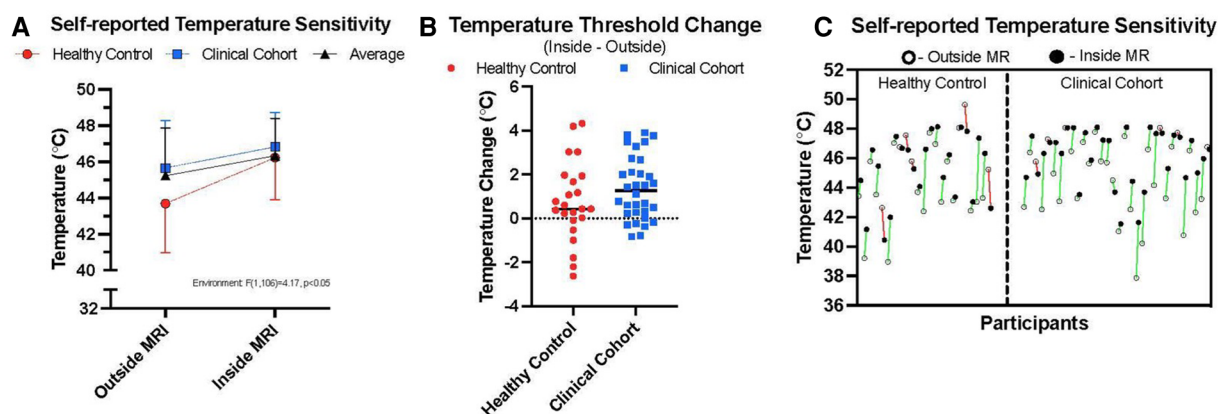


FIGURE 3

Thermal sensitivity. (A) outlines the average temperatures taken from median scores at which participants reported their 7/10 thermal sensitivity in the two environments, inside and outside of the MRI room. Healthy control data are presented alongside persons with chronic pain (clinical cohort) and averaged data across the two cohorts. (B) highlights the relative change between environments on an individual basis taking the difference between individual 7/10 thresholds between environments and a horizontal line plotting the median value for each cohort. (C) shows individual data points showing the relative change in thermal sensitivity ratings between the two environments for both cohorts (green = higher temperature sensitivities inside, relative to outside MR environment; red = lower temperature sensitivities inside, relative to outside the MR environment).

morbidities that would require clinical intervention, as the condensed volume of the MR bore can induce feelings of anxiety (21) and other undesirable psychological symptoms (22, 23). In our investigation, our healthy control cohort reported relatively normal anxiety levels, with only three individuals reporting levels higher than mild. Similar findings were observed for clinical depression (see Table 2). Notably, our clinical cohort endorsed more symptoms of anxiety, depression, and pain catastrophizing compared to the healthy controls, demonstrating the impact of chronic pain on psychological wellbeing (24). This finding is aligned with previous literature, in which anxiety and depression are observed in populations with chronic pain (25–28). Moreover, previous literature has identified pain catastrophizing as a psychiatric measure associated with lower thermal tolerance (29), as well as increased pain sensitization (30). Despite these differences, we observed similar thermal sensitivity changes between cohorts (approximately 1.1°C; see Table 3). We also performed a correlation analysis between the psychological measures and the temperature thresholds inside and outside of the MRI to observe whether psychological backgrounds are associated with differences in temperature threshold. No statistically significant results were found (see Supplementary Table 6). However, we recommend that extra vigilance be taken with individuals who report elevated psychological symptoms to ensure patient comfort.

Second, observed findings may be due to practice-related effects, as all participants received outside thermal sensitivity testing prior to being tested in the MR environment. Contradicting this hypothesis are observations that practice effects (on the order applied in our investigation) may increase thermal sensitivity (31). That is, practice may decrease the temperature at which a person identifies a 7/10 pain threshold. Indeed, we saw trends in the data to suggest this was present on a trial-to-trial basis (decreased temperatures required to produce

a 7/10) in this study (see Healthy Controls, Table 3); however, the change in environment was associated with a decrease in thermal sensitivity (higher temperatures required to produce a 7/10). Given that the MR environment is cooled, it would be expected that a person would require a lower temperature to induce a 7/10 as they accommodate to the environment—the reverse was observed. We note that a circulating, randomized, pattern of testing was performed to ensure that the exact same testing site was not used (see Materials and methods). As such, we suggest that the findings observed in this investigation likely do not pertain to the psychological nature of the MR scanning environment.

The MR environment has specific physics-based attributes that are known to impact the human body. As these have been known to produce thermal differences in human tissues, we explore their possible role in our findings. Radio-frequency pulses, used to produce the different imaging sequences, have established heating impacts (32, 33), leading to specific absorption rate (SAR) cut-offs established for scanning of human participants. SAR may cause heating in body tissues (34) as well as increases in skin temperature (35). These typically depend on the strength of the MR scanner (e.g., 3 vs. 7 T) and the length of the scanning sequence performed (36). As it pertains to this investigation, there was approximately a 30 min (anatomical scanning time + time of setup) delay between the testing of the two environments (see Supplementary MRI information). That is, between recording temperature sensitivity data outside of the scanner and reaching the point of the imaging paradigm inside the scanner, there were three different scanning sequences performed including an MPAGE (7 min; 02 s), T2 (3 min; 07 s), and resting-state blood oxygenation level dependent (BOLD) echo planar imaging (EPI) (7 min; 19 s) scan. This exposure to different magnetic field environments could, in theory, produce warming of the human body. This would be notable in the

context of changes in baseline operating of c-fiber pathways (37), the nerve fibers responsible for sending thermal nociceptive volleys throughout the nervous system to produce the perception of *pain*. Notably, prior work has shown that c-fiber pathways may act in response to changes in thermal stimuli, rather than to absolute temperature levels (31), suggesting that the local neuro-environment where recordings were made were unique in the two environmental conditions. As noted, we randomized the recording site between trials, so observations were most likely not the product of repeated administration of thermal stimuli from the MEDOC device in the same position, but the product of a more diffuse heating that modified the perception of the test stimulus across the multiple testing sites. We suggest that the impact of MR-based protocols on our participants may have impacted the mechanisms underlying pain perception.

An exploratory analysis was performed in which the main cohort was divided into a younger half ($n = 27$) and older half ($n = 28$). Most trials (2, 3, and averaged) showed statistically significant differences ($p < 0.05$) in 7/10 threshold temperature from inside and outside of the MRI scanner. The impact of the scanner environment was also explored after dividing the control and clinical cohorts into younger and older halves to identify age differences based on clinical cohort designation. No control cohorts showed statistically significant differences inside and outside of the MRI scanner when divided into younger and older halves ($p > 0.05$). However, clinical cohorts showed statistically significant differences inside and outside the MRI scanner for nearly all trials (except the older clinical cohort in trial 1). These follow-up analyses suggest that age did not impact current environment findings. At the overall cohort level, we continued to observe a 1°C difference between environments.

The presented findings have important implications for MR scanning in cognitive neuroscience. First, the issue of patient safety must be considered, particularly in the context of pediatric and special populations who cannot effectively communicate the presence or extent of pain. For these populations, there may be limited capacity to perform within-scanner thermal sensitivity testing based on abilities to understand instructions or behavioral limitations. These scenarios may present risk by applying thermal stimuli that is not proportionate to elicit an intended response. A significant risk factor for QST investigation is the possibility of thermal burns, which can be produced if the thermode is applied for too long, or at too high of a temperature. Given that findings from the current investigation reflect more thermal energy being needed to invoke the same level of pain stimulus as outside the scanner, there should be an abundance of caution as to how this metric is computed prior to application of noxious stimuli in the MR environment. Moreover, such stimuli need to be adjusted for application outside of the MRI if a person's 7/10 is only recorded inside of the MRI. Exposure to a within-scanner 7/10 is likely to exceed safety levels when performed outside of the MRI. Second, the use of QST for thermal sensitivity testing has important diagnostic and prognostic purposes and must be applied using strict criteria. Given that prior work on QST has noted standard

deviations of patient reporting on the order of 1°–2° (38), we feel that a 1° change in thermal sensitivity is significant. With this degree of change, it is possible that a person's 7/10 threshold or their maximum pain intensity may be missed or over expressed in current and/or future protocols. This has translational effects for subsequent analyses on the validity and reliability of brain function and structure observations that demand application of procedures validated outside of the scanner. Future research should integrate findings from this investigation either to introduce a correction factor or perform similar test–retest data to understand the impact of MR environment on their study findings. Third, and most broadly, observed changes in thermal sensitivity reflect a change in pain perception to the applied nociceptive stimulus (temperature). If the observed changes are a direct result of the scanning environment, the implications of findings extend beyond the pain sciences. That is, research into specific faculties such as executive function and memory are not independent of perception and should consider, alongside the findings of their own investigations, the physical impacts of the MR environment. This is especially notable given the desire to increase resolution with higher field MR environments.

The current investigation has important limitations. First, the study population was solely represented by participants who were biologically women at birth. Although we have no reason to suggest the presence of this finding would be absent in men, the strength of its effect or characteristics may differ. Second, our study cohort was of moderate size. To our knowledge, we are the first to investigate the impact of scanner environment on temperature sensitivity, so we were unable to calculate proposed effect sizes. However, we demonstrated our findings in two independent cohorts (overall group effect size of 0.47—see [Material and methods](#)), one of which presented with a chronic condition that included elevated levels of anxiety and depression. As shown in prior research (39), there is significant inter-subject variability in QST ratings. This should be kept in mind when interpreting study findings considering our smaller cohorts; however, having intra-subject data between the two environments will help increase reliability in findings. Our clinical cohort was disproportionally represented by persons identifying as White, which reflects a current disparity in access to medical care for minority populations (40). Finally, this investigation was performed under specific scanner sequence protocols using a 3 T Siemens MR scanner. If study findings were due to the physical environment of the scanner, then any changes to these, perhaps by including a higher SAR scan (e.g., diffusion-weighted vs. MPRAGE), may modify study findings. It will be of high interest to evaluate this process in future research and ultimately control or correct for its impact on study findings.

In conclusion, this investigation found a significant and reliable change in thermal sensitivity based on the MR scanning environment. We point out these findings to be significant as they pertain to patient safety, the evaluation and diagnosis of pain patients, and the evaluation of broader cognitive neuroscience research questions that are impacted by a patient's perception in the MR environment. Our answers to questions involving basic science and disease mechanisms are dependent

on the proper application of quantitative sensory testing in the MR environment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board—Boston Children's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

Study conception and design: SH, CS, and AK. Data collection: AK, GC, ES, and CL. Analysis and interpretation of results: AK, SH, and DZ. Draft manuscript preparation: AK and SH. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpain.2023.1223239/full#supplementary-material>

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