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

PRINCIPAL INVESTIGATOR: Dr. Christine Sieberg

CONTRACTING ORGANIZATION: Children's Hospital Corporation

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: Endometriosis, a condition in which uterine tissue grows outside the uterus, is a debilitating disease, affecting millions of women, is the leading cause of chronic pelvic pain (CPP), and is often unresponsive to existing treatments. Unfortunately, women's reproductive health has lacked investigation in biomedical research; however, given that approximately 1 in 10 women worldwide have endometriosis this research is warranted. Further research on the biopsychosocial mechanisms contributing to endometriosis-associated pain is necessary to better inform treatment and prevention and is the goal of the current proposal. The research team has made significant progress in recruiting research participants, data collection, and data analysis. The recruitment goals have been delayed due to COVID-19; however, recruitment over the last reporting period has greatly improved and is expected to continue to improve. Specifically, we believe our pre-surgical cohort will increase during this next recruitment period as surgeries may not be canceled as often due to COVID-19. We currently have recruited and tested 107 participants, with 22 participants on the schedule. Many others have expressed interest and are currently undergoing eligibility screening. These participants are in the process of being scheduled by the project's Research Assistant. The research team has also submitted several poster abstracts related to the project and has manuscripts in preparation (one review and multiple data-driven manuscripts) during this reporting period. The research team has also attended various webinars and training related to the project. On August 5, 2022, a one-year no cost extension was approved. We are confident, given current recruitment and enrollment that with the extension, the research team will complete data collection, analyses, and manuscript preparation and submission. The Continuing Review at Boston Children's Hospital was approved on Sept 12, 2022.

15. SUBJECT TERMS

Pain; Endometriosis; Adolescent; fMRI; Age-related changes; Neurobiology

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I. **Introduction:**

a. This project aims to elucidate the factors contributing to chronic pelvic pain (CPP) associated with endometriosis and to understand the mechanisms that sustain or resolve chronic pain. The hypotheses to be studied are (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 versus those that do not and (2) there will be differences in brain circuit responsivity with age. The project's specific aims are to (1a) 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 versus healthy controls; (1b) correlate psychophysical measures (Quantitative Sensory Testing [QST] responses and psychological questionnaires) and brain changes with levels of Offset analgesia (OA); (2a) longitudinally compare brain metrics before and after surgery (structure and function) using functional Magnetic Resonance Imaging (fMRI) with the same subjective measures noted in Aim 1 (QST responses and psychological questionnaires) in young women (ages 12-25) presenting for surgery for endometriosis; (2b) correlate psychophysical measures with levels of OA; and (3) compare brain metrics of adolescents, young adults, and adult women with endometriosis in Aim 1 with female patients ages 12 to 44 with migraines in the existing databases who have undergone structural and fMRI.

II. **Keywords**

a. Pain; Endometriosis; Adolescent; fMRI; Age-related changes; Neurobiology; Central Sensitization; Quantitative Sensory Testing: Offset Analgesia

III. **Accomplishments**

a. *Major goals.* The project's major goals fall under three specific aims (see Introduction).

i. Within Aim 1 and 2, the major tasks to be completed during this reporting period included participant recruitment. Aim 3 will begin when participant recruitment is completed for Aim 1.
ii. *Enrollment:* This was proposed to begin in month six and cease in month 32. We began recruitment and testing in July 2021 due to COVID-related delays. During the current no-cost extension (NCE), the research team plans to complete study enrollment in April 2023.
iii. *Recruitment:* The recruitment goal for Aim 1 is 20 participants in each age group (not including the 10% attrition rate) in the three cohorts of women, all post-pubertal (ages 12-17;18-25; 26-44) with surgically confirmed endometriosis and healthy age-matched controls. The recruitment goal for Aim 2 is 90. See **Table 2** for current recruitment status and distribution

The remaining tasks that are included in the original SOW include:

1. Complete data collection for Aims 1 and 2 (Table 2).

2. We have finished data collection for the fNIRS pilot study (part of Aim 1), and we are now working to process and analyze the fNIRS data and questionnaires. Manuscript preparation has begun related to this pilot sub-aim.

3. Manuscript preparation and publication (Table 1). While we are waiting to complete data collection for Aims 1 and 2, we are currently working on a review paper on descending/endogenous analgesia in the fMRI setting and a data-driven manuscript on Aim 3, which utilizes an existing migraine cohort. Additionally, we are preparing a data-driven manuscript describing the relationship between pain sensitivity inside the MRI and outside the MRI environment. See Appendix for all abstracts of manuscripts under review or in preparation related to the current

project. A paper on pilot fMRI resting state and psychological data on a cohort of adolescent women with surgically confirmed endometriosis was revised and resubmitted to European Journal of Paediatric Neurology in Sept 2022. Drs. Sieberg & Szabo had access to this data from a larger chronic pain study that was conducted at BCH, and they are using this data to inform key regions of interest in the resting state analyses for the current project.

4. Ten abstracts have been submitted and accepted for national and international conference presentations. See Appendix for all accepted poster abstracts related to the current project.

a. Poster presentation at the International Symposium on Pediatric Pain 2022, entitled: Brain functional connectivity changes in adolescent and young women with endometriosis-associated pain: A pilot resting state MRI study.
b. Two abstracts were accepted and presented at the European Pain School by Dr. Ziyan Wu and Claire Lunde.
c. Poster Abstract accepted to Society for Neuroscience (SFN) 2022.
d. Three poster abstracts accepted to the International Association for the Study of Pain (IASP) 2022.
e. One poster abstract accepted and one invited talk to the International Pelvic Pain Society (IPPS) 2022.
f. One poster abstract and poster data-blitz presentation accepted to the Society for Functional Near-Infrared Spectroscopy (SFNIRS) 2022.

5. Boston Children's Hospital Department of Anesthesiology Trailblazer Award, entitled: Imaging central neurochemical alterations in adolescent women with endometriosis-associated pain (EAP): An exploratory proton MRS assessment. In Feb 2022, the grant was awarded to Dr. Edina Szabo, the postdoctoral fellow on this grant, with Dr, Christine Sieberg, Dr. Scott Holmes as Award mentors. The overall aim of this proposal, which is an extension of the current award, is to evaluate the extent to which changes in markers of neuronal viability (i.e., the levels of N-acetyl-aspartate [NAA], choline [Cho], and creatine [Cr]), and measures of energy demands (i.e., levels of γ-aminobutyric acid [GABA], and glutamate / glutamine [Glu/Gln]) are different in patients with EAP relative to healthy controls. In addition, metabolite changes in pain modulation regions are predicted to correlate with pain behavior and emotional functioning as measured by self-report in patients with EAP.

Dr. Sieberg was also invited to submit a DoD Expansion Award and submitted that grant in August 2022. The objectives of the proposal are to expand upon Aim 3 of the current 2018 PRMRP award to further elucidate how inflammatory biomarkers and brain metrics (e.g., fMRI resting state, structural data & evoked pain functional connectivity) may vary as a function of diagnosis (endometriosis only; migraine only; endometriosis +migraine; migraine/endometriosis free controls) and psychophysical functioning (e.g., emotions, stress, QST responses).

6. Dr. Sieberg completed three presentations involving the current award during the reporting period:
a. Endometriosis-associated pain: The path from clinical encounter to investigation
Oral presentation to the Tommy Fuss Center for Neuropsychiatric Diseases, Feb 2022
b. Reframing pain assessment and treatment in gynecology: Adolescents-adults
Department of Obstetrics & Gynecology/Invited Grand Rounds
NorthShore University Health System, Chicago, IL
c. 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

TABLE 1. Planned publications related to the current project.

Provisional title/topic	Target submission date
Topic: Brain response to Offset Analgesia during MRI and the age-related differences for patients and pain-free controls (Aim 2)	August 2023

Title: Exploring the Role of Childhood Trauma on Descending Pain Inhibition in People with Endometriosis using Functional Near-infrared Spectroscopy	November 2022
Topic: fNIRS resting state comparisons between patients and pain-free controls.	July 2023
Title: Endometriosis and Migraine: Exploring Structural Brain Alterations in Two Comorbid Pain Disorders (Aim 3)	August 2023
Title: Endometriosis and Migraine: Exploring Functional Brain Alterations in Two Comorbid Pain Disorders	April 2023
Title: Methodology paper: Comparing fnirs and MRI	November 2022
Topic: Cerebral endometriosis analysis from MRI data	July 2023
Title: Brain regions related to thermal pain differences during menstrual phases: CNS activation and pain perception in a pilot sample	Submitted June 2022 to Current Research in Neurobiology
Topic: Patient cohort resting state analysis using fNIRS and MRI data	August 2023
Title: Investigating thermal sensitivity changes in the context of an MRI scanner: Application of Quantitative Sensory Testing in mixed environments	November 2022
Title: Descending pain modulation in the clinic	December 2022

TABLE 2: Recruitment distribution for Aims 1 and 2.

fMRI			
	Pain-free Controls	**Endometriosis Patients**	**Total**
Completed Study Visit	30	35	65
Scheduled for Study Visit	2	15	17
Subjects currently active in study (Aim 2)	2	3	5
Subjects withdrawn at their own/family request	1	0	1
Subjects withdrawn by PI due to toxicity or adverse events	0	0	0
Subjects withdrawn by PI due to other reasons (e.g. pregnancy, lack of compliance)	2	0	2
Subjects lost to follow-up	0	1	1
Subjects no longer participating for other reasons. Specify reason	0	0	0
TOTAL	**37**	**59**	**96**
fNIRS			
	Pain-free Controls	**Endometriosis Patients**	**Total**
Completed Study Visit	20	22	42
Scheduled for Study Visit	1	4	5
Subjects currently active in study (Aim 2)	1	3	4
Subjects withdrawn at their own/family request	0	0	0

Subjects withdrawn by PI due to toxicity or adverse events	0	0	0
Subjects withdrawn by PI due to other reasons (e.g. pregnancy, lack of compliance)	0	0	0
Subjects lost to follow-up	0	1	0
Subjects no longer participating for other reasons. Specify reason	0	0	0
TOTAL	**22**	**30**	**52**

TABLE 3: Demographics for preliminary sample.

Race and ethnicity distribution	**Controls (n=48)**	**Endometriosis Patients (n=55)**
White, not of Hispanic origin	27	45
White of Hispanic Origin	2	2
Black/African American, not of Hispanic Origin	1	1
Black/African American of Hispanic Origin	2	1
Asian, or Pacific Islander	11	3
Native American	0	0
Other/Multiple	5	3
Age at study visit	**Controls (mean; range)**	**Endometriosis Patients (mean; range)**
	24.50; 29	27.46; 27

b. Recruitment of Research Assistant/Post-Doctoral Fellow: An additional RA has been hired to aid in participant recruitment and data collection. The previous RA, Ayeong Kim has reduced her funding to 50% as she has transitioned to a different NIH-funded project. Gabriela Comptdaer, MS has been hired as an RA and began working on the project in July 2022. Ms. Comptdaer was a master's student intern working on the current project before she was hired as an RA. Ms. Comptdaer is funded from Dr. Sieberg's budget. Throughout her time in the lab, Ms. Comptdaer has been trained in Quantitative Sensory Testing by Ms. Lunde, conducted a QST protocol in prior studies, fNIRS and MRI study visits, and has experience in participant recruitment along with data management and analysis. Ms. Lunde is working closely with Ms. Comptdaer to finish the project set up regarding the new BCH imaging center, fully train Ms.Comptdaer in all QST and the fMRI procedures, and begin analyzing the data for manuscript preparation.

Training of new RA, Post-Doctoral Fellow, and student interns on QST and pain psychophysics: Ms. Lunde, Ms. Kim, Ms. Comptdaer, and Dr. Szabo have completed extensive training for neuroimaging protocols at Boston Children's Hospital. They have completed 10 hours of shadowing MRI scans, completed all MRI training modules, programmed all new equipment, and created the REDCap project to collect all questionnaire data on an iPad. Miss Lunde has mentored and trained all student interns on QST and pain psychophysics.

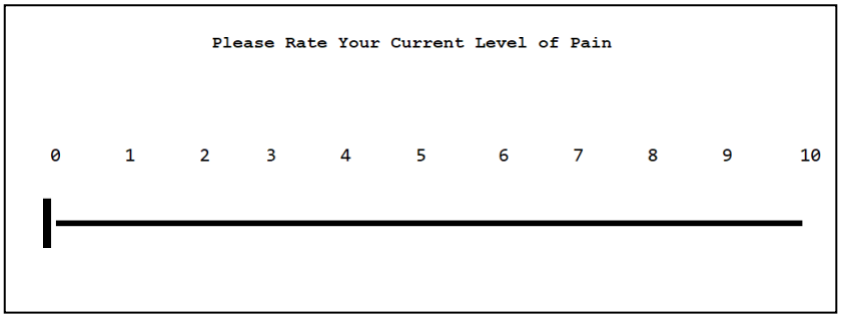
c. *Conduct experiments: brain imaging; QST and OA.* All equipment has been ordered and all training for the research team has been completed. We have established our novel MRI-based OA paradigm with the Department of Radiology. The user interface (*see Figure 1*) is very easy to use for subjects and is similar across MRI and fNIRS objectives to enable comparison of data after study completion between modalities. Completed mock fMRI, QST, and OA testing with the Department of Radiology at BCH has shown feasibility and safety.

FIGURE 1: *User interface of the electronic Visual Analogue Scale (eVAS) and Behavioral Offset Analgesia (OA) Preliminary Data.* The interface is user-friendly and is controlled by subjects via two keys that are marked with up and down arrows to move the slider on the scale down (less pain) and up (more pain), accordingly. This eVAS allows us to calculate behavioral OA.

Behavioral OA preliminary data for 14 participants with endometriosis and 14 pain-free controls. These values were calculated from pain scores during the offset portion of each pain condition. Each data point was taken at the same point in each trial, from the point at which the participants experienced the greatest pain and the lowest pain. Of particular interest, the patients experienced an increased response towards the end of the thermal pain trials (at fourth trial), while controls had a diminished or relatively constant response throughout.

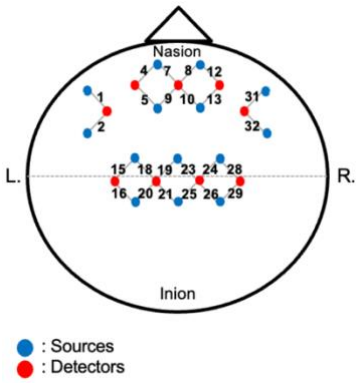
The magnitude of the behavioral OA response was calculated using the percentage of difference between the highest pain score during the second temperature (pain max 5s) and the lowest pain scores during the third temperature (pain min 20s) in the Offset Trial: ΔOA=pain max 5s – pain min 20s. A Constant Trial was included to rule out adaptation effects.

14 females with surgically confirmed endometriosis (mean age = 26.7 years, SD = 5.4) and 14 pain-free females (mean age = 22.6 years, SD = 4.2) have been recruited. T-tests showed participants with EAP showed an attenuated OA response, median: 77.1% vs. 43.8%, *(t(25) =.484, p=.05*



d. Reporting results to community of interest: For Aims 1 and 2, preliminary images from testing of OA paradigms (*See Figure 2*) show that we can obtain high-quality structural and functional brain imaging scans (*See Figure 3*) on this new research-grade MRI scanner.

FIGURE 2. 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).Resting-state functional connectivity (RSFC) will be computed using a pair-wise Pearson's r correlation of six regions of interest. Endometriosis participants, when compared to control



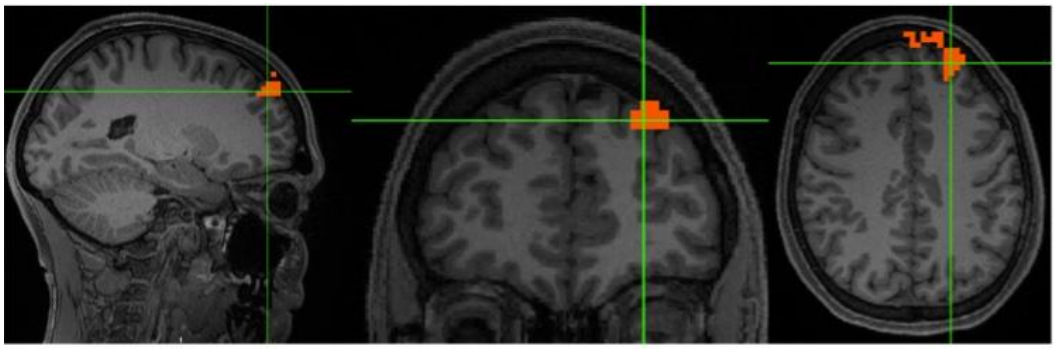
subjects, are expected to demonstrate higher localized connectivity within both the prefrontal cortex and somatosensory cortex.

TABLE 4. Preliminary questionnaire data.

- 15 females with surgically confirmed endometriosis (mean age = 26.7 years, SD = 5.7) and 14 pain-free females (mean age = 22.2 years, SD = 4.4) have completed the study.
- Mann-Whitney U Test showed there are differences in the Childhood Traumatic Events Scale, assessed using a validated burden score, between participants with EPA vs controls (U = 61.5, p = .057).

Group	**Average burden Score (range= 0-42)**	**Average quantity of traumas**
Controls	3.1 (SD=3.8)	0.9 (SD=0.7)
Endometriosis	6.4 (SD=5.5)	1.2 (SD=0.8)

FIGURE 3. Brain regions active during an offset analgesia paradigm relative to brain activity during a rest period. Participants are presented with a likert scale during the scan to measure strength of offset analgesia response. Preliminary findings using an exemplar participant showing brain activation in the frontal cortex during offset analgesia trials (relative to rest conditions).



Plan for the next reporting period to accomplish goals: During the next 6 months (now until Feb 2023), the research team plans to submit four manuscripts to peer-reviewed journals and recruit the remaining participants for both Aims 1 & 2. We also plan to complete data analysis and manuscript preparation for the fNIRS pilot study.

I. **Impact**

a. *Impact on the development of the principle discipline of the project:* This is the first study to explore the brain systems contributing to chronic pelvic pain (CPP) in women, adolescents to adults, with endometriosis. The results from this study will (1) enhance our understanding of the neurobiology of chronic pelvic pain (CPP); (2) provide a metric to follow patients with co-morbid endometriosis and CPP in the clinic; (3) potentially provide a metric for those who will chronify after surgery; (4) contribute to an understanding of 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.

b. *Impact on other disciplines:* This project has a goal of using the disease process as a basis for

new treatment approaches. While endometriosis can be treated by surgical excision of the lesions and/or hormonal treatment, sometimes combined with anti-inflammatory drugs, there is no cure and there are no existing treatments for the approximately 30% of women who report ongoing pain after surgical excision of the lesions. By understanding the neural underpinnings of the disease and risk factors for chronification, findings from the proposed project 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. New treatments are needed in the context of effective approaches. This is especially important in the current opioid epidemic with new research highlighting that 24% of Obstetrician/Gynecologists prescribe opioids for endometriosis-related pain. Additionally, this project will aid in the development of biomarkers for endometriosis. The current study utilizes a number of potential biomarkers that can be used to understand disease state, disease responsivity (progression, stasis or regression) or treatment effects.

c. *Impact on technology transfer*: The use of fNIRS is an innovative and novel technological tool for elucidating pain mechanisms in patients with endometriosis, as it has never been used in this population. The near-infrared imaging tool is used for testing cognitive functionality and neural communication and uses a specific technique for measuring NIR light absorbance in the blood of hemoglobin with and without oxygen and detects ongoing neural activity and connectivity. The use of fNIRS technology to assess the brain of patients with endometriosis may provide novel insights into therapeutic targets or appropriate individually tailored patient-oriented intervention strategies for the development of persistent endometriosis-associated pain.

d. *Impact on society beyond science and technology*: 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.

IV. **Changes and Problems**

a. Changes in approach and reasons for change: Nothing to report.

b. *Actual or anticipated problems or delays and actions or plans to resolve them:* The project recruitment targets have been delayed due to COVID-19. However, as the pandemic has become more controlled, recruitment over the last reporting period has greatly improved and is expected to continue to improve. In the previous annual report, we proposed three new models for planning to move forward during the COVID-19 pandemic. During the current reporting period, the research team successfully implemented all three models which has greatly increased our recruitment numbers.

i. *Model 1*: Connecting with neighboring Harvard affiliated hospitals (i.e., Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, and Massachusetts General Hospital) to increase our recruitment opportunities. Dr. Sieberg has contacted Dr. Maria Milcetic Comer, a Gynecological surgeon at Brigham and Women's Hospital, who will allow recruitment in her clinic. By collaborating with other surgeons (currently were only working in Dr. Laufer's clinic at BCH and BWH) we may increase the number of participants tested per week.

ii. *Model 2:* Due to the research imaging center with new scanners planned for the Spring of 2021, one possibility was to change the imaging site to another HMS affiliated hospital. Specifically, with this move, it was not ideal to begin testing participants on one scanner and then change during the course of the study. While there was delay to the opening of the new center, it did open in Summer 2021 and fortunately, the research team has been able to proceed with scheduling and testing MRI participants without having to move the scanning to another HMS affiliated hospital.

iii. *Model 3:* Switching from fMRI to Near Infrared Spectroscopy and Imaging (fNIRS). The research team did not switch to fNIRS, however, a sub-aim pilot study was added to the SOW. Including the pilot study using fNIRS has increased greatly flexibility (equipment is portable and can be completed in Dr. Sieberg's lab thus avoiding COVID related scheduling issues with the Radiology Department). It is also less expensive and does not require a $550 fee for each participant.

c. *Changes that had significant impact on expenditures:* Nothing to report.

d. *Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:* Nothing to report.

e. *Significant changes in use or care of human subjects:* Nothing to report.

f. *Significant changes in use or care of vertebrate animals:* Nothing to report.

g. *Significant changes in use of biohazards and/or select agents:* Nothing to report.

V. **Products**

a. *Publications, conference papers, and presentations:*
   i. *Journal publications:* See Appendix for accepted poster abstracts and abstracts of manuscripts in preparation and under review.
b. *Books or other non-periodical, one-time publications:* Nothing to report
c. *Other publications, conference papers, and presentations:* See Appendix for accepted poster abstracts and abstracts of manuscripts in preparation and under review.

d. *Website or other internet sites:* Nothing to report.
e. *Technologies or techniques:* Nothing to report.
f. *Inventions, patent applications, and/or licenses:* Nothing to report.
g. *Other products:* Nothing to report.

VI. Participant and Other Collaborating Organizations

a. PI: Christine Sieberg, no change
b. Co-PI: Dr. Scott Holmes, no change
c. Consultant: Dr. David Borsook, no change
d. Consultant: Dr. Amy Danehy, no change
e. Post-doctoral fellow: Dr. Edina Szabo, no change
f. Post-doctoral fellow: Dr. Ziyan Wu
   Research identifier: 0000-0003-4471-8906
   i. **Nearest month person worked: 9**
   ii. **Contribution to the project:** Expertise and time with MRI and fNIRS data analysis and

manuscript preparation.

iii. **Funding support:** 5% of effort Federal: US Department of Defense (Dr. Holmes' budget) and NIH R35 awarded to Dr. Sieberg

g. Research Coordinator: Claire Lunde, no change
h. Research Assistant: Ayeong Kim, no change
i. Research Assistant: Gabriela Comptdaer
    i. **Research identifier: 0000-0001-5021-0442**
    ii. **Nearest month person worked:** 3
    iii. **Contribution to project:** She performs routine oversight of IRB protocols, recruits and enrolls study participants, coordinates the scheduling of screening and study visits, and ensures patients complete the required forms for enrollment, performs all necessary screening tests (e.g., pregnancy tests), and collating imaging and non-imaging data (e.g., pregnancy tests).
    iv. **Funding support:** 95% of effort Federal: US Department of Defense (Dr. Sieberg's budget) and 5% NIH R35 awarded to Dr. Sieberg

i. *Change in the active other support of the PD/PI or senior/key personnel since the last reporting period:* Nothing to report.
j. *Organizations involved as partners:* Michigan State University and Brigham and Women's Hospital

VII. Special Reporting Requirements

Collaborative awards: Both Dr. Sieberg and Dr. Holmes (Partnering PIs are both responsible for each task to be completed at BCH where all participant testing will take place, as well as the analyses and manuscript preparation and publication.

VIII. Appendices

(1) Gabriela Comptdaer's CV: newly hired Research Assistant.
(2) Accepted poster abstracts.
(3) Manuscripts in under review and in preparation.

Gabriela Comptdaer

EDUCATION

Boston University Graduate Medical Sciences
Masters in Medical Sciences *May 2022*

- **Comptdaer, G.** (2022). The Impact of Acute Stress and Childhood Traumatic Events on Pain Sensitivity Among Adults with Chronic Low Back Pain [Master's Thesis, Boston University] Biobehavioral Pain Innovations Lab

Boston University College of Arts and Sciences
May 2020
Bachelor of Arts in Neuroscience, Minor in Biology

PUBLICTIONS

Rosato R, **Comptdaer G**, Mulligan R, *et al*. Increased focal internal carotid artery angulation in patients with posterior communicating artery aneurysms. *Journal of NeuroInterventional Surgery* Published Online First: 23 May 2020. doi:10.1136/neurintsurg-2020-015883

ABSTRACTS AND POSTERS

Comptdaer, G., Lunde, CE**.,** Meints, S., Edwards, R., Sieberg, CB. The impact of acute stress and childhood traumatic events on pain sensitivity among adults with chronic low back pain. International Association for the Study of Pain, Toronto, ON. August 2022

Wu, Z., Lunde, CE., Szabo, E., Karunakaran, KD., Kim, A., **Comptdaer, G**., Wolfson, A., Gagnon, H., Holmes, S., Sieberg, CB. Altered Resting-State Functional Connectivity Between Prefrontal and Somatosensory Cortex After Pain Response in Healthy Adults: A Pilot Functional Near-Infrared Spectroscopy Study. International Association for the Study of Pain, Toronto, ON. August 2022

Jotwani, ML., Lunde, CE., **Comptdaer, G.,** Gagnon, H., Wolfson, A., Wu, Z., Sieberg, CB. Utilizing fNIRS to explore the relationship between pain catastrophizing and neural activity in post-surgical pain: A pilot investigation. Society for Neuroscience, San Diego, CA. November 2022

MANUSCRIPTS IN PREPARATION

Comptdaer, G., Lunde, CE., Jotwani, ML., Dhaliwal, H., Silliman, E., Sieberg, CB. The Pain Experiences of University Students: The Role of Childhood Traumatic Events and Mental Health. Expected submission: September 2022

Comptdaer, G., Issenman, J., Lunde, CE., Meints, S., Edwards, R., Sieberg, CB., The Impact of Acute Stress on Sensory Perception among Healthy, Pain-free Adults and Adults with Chronic Low Back Pain. Expected submission: December 2022

RESEARCH EXPERIENCE

Biobehavioral Pain Innovation Lab, Boston Children's Hospital
Clinical Research Assistant *Jul 2022 - Present*

- Conducts clinical translational research on several IRB-approved, grant-funded projects under the mentorship of Dr. Christine Sieberg, PhD, EdM, MA

- Coordinates implementation of clinical research protocol investigating psychophysical and neural mechanisms contributing to chronic pelvic pain in adolescents and young adults with endometriosis.
- Leads participant recruitment and neuroimaging data collection utilizing both MRI and fNIRS methodologies, supports IRB approval, and collaborates in data analysis and manuscript preparation

Biobehavioral Pediatric Pain Lab, Boston Children's Hospital
Graduate Research Intern *Jul 2021 – May 2022*

- Supported clinical translational research on several IRB-approved, grant-funded projects under the mentorship of Dr. Christine Sieberg, PhD, EdM, MA
    - Assisted in participant recruitment, neuroimaging data collection, and data organization
- Collaborated with research collaborators at the Brigham and Women's Hospital to complete a graduate thesis entitled "The Impact of Acute Stress and Childhood Traumatic Events on Pain Sensitivity Among Adults with Chronic Low Back Pain".

Laboratory of Behavioral Neuroscience, Boston University
Undergraduate Research Assistant *Jan 2020 – Mar 2020*

- Conducted research investigating the molecular, pharmacological, and behavioral determinants of extinction memory enhancement in cocaine-addicted rats under the supervision of Dr. Kathleen Kantak, PhD.
- Assisted in surgical implantation of intravenous catheters, performed post-operative care, and subsequent infusions and injections on rats.
- Established a long history of cocaine self-administration in rats, and subsequently implemented extinction training strategies.

Cerebrovascular Hemodynamics Laboratory, Tufts Medical Center
Research Intern *May 2018 – Aug 2019*

- Performed research analyzing the morphological characteristics of cerebral arteries in patients with aneurysms under the supervision of Dr. Adel Malek.
- Analyzed cerebral aneurysms from angiographic data using Amira 3D visualization and MeshLab
- Performed statistical analysis in JMP and contributed to the writing and reviewing process of the publication in the Journal of NeuroInterventional Surgery.

TEACHING EXPERIENCE

Boston University School of Medicine, GI and Nutrition Module (MED MS146)
Tutor *Mar 2022 – Apr 2022*

- Acted as a tutor for the GI and Nutrition module offered as part of the first year medical school curriculum.
- Led one-on-one tutoring sessions with students to review lecture material and walk through practice problems.

Boston University School of Medicine, Graduate Medical Sciences
Teaching Assistant *Mar 2022 – May 2022*

- Acted as a teaching assistant for the "Introduction to Biomedical Information" (GMS MS640) offered to Masters of Medical Science students.
- Led CV workshops for students in the course, providing an outline and guidance for creating an effective CVs.
- Read and gave feedback on the "Mini-Thesis" that students in the course produced in preparation for their thesis projects.

Boston University School of Medicine, Graduate Medical Sciences
Teaching Assistant and Tutor *Sep 2021 – Dec 2021*

- Acted as a teaching assistant for the "Biochemistry and Cell Biology" course (GMS BI751) offered as part of the graduate medical science curriculum.
- Led weekly review sessions in which the TAs reviewed material covered in lecture in the past week and discussed practice problems
- Ran weekly tutoring sessions with four college senior students in the EMSSP track offered at BUSM

Boston University Department of Neuroscience
Learning Assistant *Jan 2019 – May 2019*

- Acted as a learning assistant for "Introduction to Computational Models of Brain and Behavior", where students learned computational models through the programming language MATLAB.
- Led laboratory sections of around 20 students covering lecture material and answering questions

CLINICAL EXPERIENCE

Fallon Ambulance Services
Emergency Medical Technician *Feb 2020 – Jul 2020*

- Worked collaboratively with emergency service personnel in responding to pre-scheduled transfers and 911-dispatched calls.
- Provided efficient and immediate pre-hospital care to the critically ill and injured, and transported patients to medical facilities.

Hospital General de La Ciudad de Mexico
Intern *Jul 2016*

- Shadowed Dr. Gabriel Medrano in the rheumatoid section of the hospital, seeing both inpatients and outpatients.
- Observed treatment and follow-up care of several patients diagnosed with lupus, rheumatoid arthritis, and systemic sclerosis.

Gap Medics
International Medical Student Shadow
Jul 2015

- Shadowed different doctors in several hospitals and clinics in Kilimanjaro, Tanzania for three weeks.
- Witnessed several surgeries such as amputations, circumcisions, and caesarian sections, and several cases of kerosene burns and wound debridement.
- Assisted with over seven births during optional night shifts in the labor and delivery ward.

LEADERSHIP AND VOLUNTEERING EXPERIENCES

Massachusetts Department of Children and Families
Foster Care Review Community Volunteer *Jul 2020 – Present*

- Acted as a part of the review panel, where cases concerning children who had been placed in foster care were reviewed, and decisions regarding future placement were made.

Harvard Medical School, Medical Portuguese
Volunteer Teacher *Sep 2020 – Dec 2020, Sep 2021 – Dec 2021*

- Led weekly sessions in which Harvard Medical School students implemented newly learned vocabulary to simulated patient interactions fully in Portuguese

Boston Medical Center
Pediatrics Play Space Volunteer *Jun 2019 – Aug 2019*

- Volunteered at the outpatient pediatric clinic entertaining children before and after their doctors' appointments.

Global Programs, **Boston University**
International Peer Mentor & International Peer Mentor Leader *Apr 2018 – Nov 2019*

- Mentored a group of 3 incoming international students to Boston University during the Summer of 2018 and into the Fall semester.
- Accepted *International Peer Mentor Leader* position
    - Organized and partook in interviewing of new incoming International Peer Mentors
    - Arranged and assisted in events that supported the international community at Boston University.
    - Mentored a group of 15 International Peer Mentors in their roles.

ADDITIONAL WORK EXPERIENCE

Center for Career Development and Educational Resource Center, Boston University
Student Desk Assistant *Sep 2019 – Mar 2020*

- Served as a liaison between the Center for Career Development (CCD) and Educational Resource Center (ERC) and current Boston University students.
- Managed the front desk of both offices; checking students in for appointments, interviews, or events, and answering any questions about services the CCD/ERC offers.

Westduin Armonea Retirement Home
Nursing Assistant
Jul 2017

- Assisted elderly residents at a retirement home in Belgium during meal times and helped with maintenance of residential areas.
- Managed common area bar serving refreshments to residents and guests.

SKILLS AND TRAINING

Languages:

- English and Portuguese (Native)
- Spanish (Fluent)
- French (Intermediate)
- Mandarin (Intermediate)

Technical:

- EMT-Basic Certification - National Registry of Emergency Medical Technicians, 2019, 2021
- Health Care Provider CPR, American Heart Association, 2020, 2022

Research:

- Experienced in SPSS, MATLAB, Python, and R
- Proficient in Microsoft Excel, Word, PowerPoint
- CITI Training Certification: good Clinical Practice (FDA Focus), Biomedical Responsible Conduct of Research
- Trained in using PowerChart, EPIC, and Hound Dog databases

Manuscript under review for European Journal of Paediatric Neurology, submitted August 2022

Title: Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: A pilot resting-state study

Abstract

Endometriosis is a debilitating disease and the leading cause of chronic pelvic pain. Alterations in brain functional connectivity have been previously reported in adult women with endometriosis-associated pain (EAP), however, it is still unknown if similar patterns of changes exist in adolescents. In this pilot study, resting-state fMRI scans were obtained from 11 adolescent and young women with EAP and 14 healthy controls. Using a seed-to-voxel approach, we investigated functional connectivity between the anterior insula, the medial prefrontal cortex and the rest of the brain. Furthermore, the resulting functional connectivity differences were correlated with clinical characteristics including disease duration, pain intensity, and different psychosocial factors (pain catastrophizing, fear of pain, anxiety and depression). 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. Besides, functional connectivity between the right anterior insula and the right cerebellum (particularly, Crus I and Crus II) was positively associated with pain intensity levels. This pilot study is the first to report functional alterations in adolescent women with EAP. Our results are relevant not only for understanding the brain characteristics underlying EAP at younger age, but also enhancing future pain treatment efforts through supporting the potential role of central sensitization in endometriosis.

Keywords: endometriosis, resting-state fMRI, anterior insula, dorsolateral prefrontal gyrus, cerebellum, young women

Manuscript under review for Current Research in Neurobiology, submitted June 2022
Title: Brain regions related to thermal pain differences during menstrual phases: CNS activation and pain perception in a pilot sample

Abstract

While sex differences have been reported in animal and human pain studies, there remains disagreement on how the menstrual cycle influences experimental pain sensitivity. The disagreement may be explained by (1) a lack of standardized operational definitions and methods for identifying menstrual cycle phases in research, (2) the varied methods of assessing experimental pain, (3) the location on the body used in the application of painful stimuli, and (4) the measurement of different pain outcomes (e.g., thresholds vs. tolerances). The current study used functional magnetic resonance imaging (fMRI) and thermal stimuli to test the hypothesis that hormonal changes during the menstrual cycle will be associated with a change in thermal pain thresholds, particularly during times of low estrogen. Within-participant comparisons of fMRI following noxious thermal stimuli applied to the hand were included for 10 females (mean age=22.4 years, SD= 2.6 years; range=21-38 years) during their mid-follicular phase (days 6-8) and their mid-luteal phase (days 19-23) of their cycle. All menstrual phases were confirmed with blood samples analyzed for estradiol and progesterone levels. Non-noxious (41°C) and noxious (46°C) thermal stimuli were applied to the participants' dorsum of their left-hand outside and inside the MRI setting. While differences were not observed using subjective pain ratings, a difference in cerebral activation during the mid-follicular phase compared to mid-luteal was observed. During the mid-luteal phase, these differences included increased activation in traditional pain regions (insula, thalamus, primary somatosensory cortex). Our results suggest that females may process acute thermal pain stimuli differently during the phases of their menstrual cycle. A network of regions involved in pain processing may be modulated by the specific influences of a hormonal milieu, and such differences defined in healthy participants may have implications for altered responses in analgesic measures and disease processes.

Keywords: Menstrual cycle; Experimental pain; fMRI; Central Nervous System

Manuscript in preparation to be submitted in December 2022

Title: Descending Pain Modulation in the Clinic

Abstract

Pain perception is based on both nociceptive signals and their modulation by the central nervous system. Growing evidence suggests that dysregulation or decreased efficiency of the descending pain modulation system may facilitate pain and promote pain chronification which places a significant burden on the healthcare systems. This review aims at summarizing data on the descending pain pathways by identifying the underlying brain regions and networks, describing measures that can be effectively applied to evoke and assess this pain modulation effect, and discussing potential (prognostic and predictive) biomarkers which may help detect treatment outcomes/post-treatment pain state in patients at the clinic. Studies are also reviewed in terms of different disease models and distinguishing patient groups with different types of chronic pain using neuroimaging findings. Assessing and understanding the descending component of pain is of importance in a clinical setting, since it could provide guidance for developing future therapeutic approaches to the management of chronic pain.

Keywords: chronic pain, pain modulation, assessment, clinical practice

Manuscript under review for Current Research in Neurobiology, submitted June 2022
Title: Brain regions related to thermal pain differences during menstrual phases: CNS activation and pain perception in a pilot sample

Abstract

While sex differences have been reported in animal and human pain studies, there remains disagreement on how the menstrual cycle influences experimental pain sensitivity. The disagreement may be explained by (1) a lack of standardized operational definitions and methods for identifying menstrual cycle phases in research, (2) the varied methods of assessing experimental pain, (3) the location on the body used in the application of painful stimuli, and (4) the measurement of different pain outcomes (e.g., thresholds vs. tolerances). The current study used functional magnetic resonance imaging (fMRI) and thermal stimuli to test the hypothesis that hormonal changes during the menstrual cycle will be associated with a change in thermal pain thresholds, particularly during times of low estrogen. Within-participant comparisons of fMRI following noxious thermal stimuli applied to the hand were included for 10 females (mean age=22.4 years, SD= 2.6 years; range=21-38 years) during their mid-follicular phase (days 6-8) and their mid-luteal phase (days 19-23) of their cycle. All menstrual phases were confirmed with blood samples analyzed for estradiol and progesterone levels. Non-noxious (41°C) and noxious (46°C) thermal stimuli were applied to the participants' dorsum of their left-hand outside and inside the MRI setting. While differences were not observed using subjective pain ratings, a difference in cerebral activation during the mid-follicular phase compared to mid-luteal was observed. During the mid-luteal phase, these differences included increased activation in traditional pain regions (insula, thalamus, primary somatosensory cortex). Our results suggest that females may process acute thermal pain stimuli differently during the phases of their menstrual cycle. A network of regions involved in pain processing may be modulated by the specific influences of a hormonal milieu, and such differences defined in healthy participants may have implications for altered responses in analgesic measures and disease processes.

Keywords: Menstrual cycle; Experimental pain; fMRI; Central Nervous System

Poster Abstract accepted to IASP 2022
Title: Exploring the Role of Childhood Trauma on Descending Pain Inhibition in People with Endometriosis using Functional Near-infrared Spectroscopy

Authors: Claire E Lunde[1,2,3], Ziyan Wu[2,3], Edina Szabo[2,3], Keerthana Karunakaran[2,3], Ayeong Kim[2,3], Scott A Holmes[2], David Borsook[4], Christine B Sieberg[2,3,5]

[1]Nuffield Dept of Women's and Reproductive Health, Univ. of Oxford, UK
[2]Pain & Affective Neuroscience Center, Boston Children's Hospital, Boston, US
[3]Biobehavioral Pediatric Pain Lab, Department of Psychiatry & Behavioral Sciences, Boston Children's Hospital, Boston, US
[4]Massachusetts General Hospital, Boston, US
[5]Department of Psychiatry, Harvard Medical School, Boston, US

Presenting Author
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Background & Aims. Endometriosis is one of the most common chronic gynecological diseases affecting 10-15% of women in their reproductive years and 70% of people with chronic pelvic pain. Approximately 62% of adults in the US report at least one childhood trauma, which is associated with an increased risk of chronic pain and gynecological complications in adulthood. Both chronic pain and childhood trauma have been shown to alter pain modulation. Offset analgesia (OA) is form of endogenous pain inhibition and has been found to be attenuated in chronic pain populations but has yet to be measured in people with endometriosis-associated pain (EAP). The aim of the study was to explore the role of childhood trauma and descending pain inhibition (assessed using OA) in people with EAP using functional near-infrared spectroscopy (fNIRS).

Methods. A 3-temperature OA paradigm (Offset, Control, and Constant Trials) using heat stimuli was applied to the left forearm while hemodynamic signals were measured bilaterally over the frontal and somatosensory cortex. The magnitude of the behavioral OA response was calculated using the percentage of difference between the highest pain score during the second temperature (pain max 5s) and the lowest pain scores during the third temperature (pain min 20s) in the Offset Trial: *ΔOA=pain max 5s – pain min 20s.* A Constant Trial was included to rule out adaptation effects. Participants also completed the Childhood Traumatic Events Scale (CTES) to assess the presence and impact of historical traumatic events that occurred prior to the age of 17. Once data collection is complete (Spring 2022), resting state and OA response functional connectivity will be computed using pair-wise Pearson's r correlation of regions of interest: lateral prefrontal cortex, medial prefrontal cortex, primary somatosensory cortex, and medial primary somatosensory cortex. T-tests will be used to assess statistically significant differences in hemodynamic responses during resting state and OA. fNIRS and behavioral data will be compared using a partial correlation analysis, controlling for CTES burden score.

Results. 9 females (desired sample size is 15) with surgically confirmed endometriosis (mean age = 25 years, SD = 5.54) and 15 pain-free females (mean age = 22 years, SD = 3.46) have been recruited. Preliminary analyses indicate that participants with EAP show an attenuated OA response, (median: 18.1% vs. 31.8%, $p = 0.032$). A one-way ANOVA revealed a statistically significant difference in CTES burden score between the groups ($F(1, 20) = 9.67$, $p = .006$).

Conclusion. An attenuated OA response found in participants with EAP may indicate a lack of ability to modulate changes in pain perception. The EAP cohort reported a higher CTES burden score, indicating childhood trauma may be moderating the effect. This is the first study to assess brain function, endogenous pain inhibition, and the role of childhood trauma in people with EAP using fNIRS. Results may help describe the role of the prefrontal

and somatosensory cortex during OA, and the impact of childhood trauma on the OA response in people with and without EAP.

Relevance for Patient Care. This new approach may allow for identifying meaningful subgroups of patients with EAP, develop better preclinical models, and thus ultimately lead to more effective treatment.

CBS and SAH are Partnering PIs on a Peer Review Medical Research Program Investigator-Initiated Research Award from the United States Department of Defense (W81XWH19105060)

Poster Abstract accepted to IASP 2022 - Financial aid award at the 2022 IASP World Congress on Pain

Title: Endometriosis and Migraine: Exploring Structural Brain Alterations in Two Comorbid Pain Disorders

Edina Szabo, Ayeong Kim, Claire E. Lunde, Stacey Missmer, Scott A. Holmes, David Borsook, Christine B. Sieberg

Background: Research has revealed a relationship between endometriosis and migraine headaches (Jenabi & Khazaei, 2020). Individuals living with endometriosis are nearly twice as likely to experience migraine attacks as those without endometriosis (Yang et al., 2012). Besides shared genetic and hormonal mechanisms (Adewuyi et al., 2020), specific alterations in the central nervous system (central sensitization) could be a contributing factor to the comorbid pain in both conditions. The aim of the present study was to utilize brain magnetic resonance imaging (MRI) structural data to compare patients with surgically confirmed endometriosis to patients with migraine.

Methods: In this cross-sectional study, structural T1-weighted MRI brain images were acquired with a 3T scanner. Cortical thickness and subcortical volume were estimated using the FreeSurfer software package. Group differences were investigated utilizing the mri-glmfit tool and a vertex-specific general linear model.

Results: Preliminary data of our ongoing study (so far, we included n=12 patients with endometriosis and n=12 patients with episodic migraine, between the ages of 20-38 years) showed that individuals with endometriosis displayed decreased cortical thickness in the bilateral superior frontal gyrus, right caudal middle frontal gyrus, and right inferior frontal gyrus (pars orbitalis) compared to patients with migraine. Whereas an increase in cortical thickness was detected in regions including the bilateral inferior parietal lobe and left precentral sulcus (corrected for multiple comparisons using a cluster-wise threshold of $p < 0.05$ with Monte Carlo simulations). In addition, increased volume was observed in the left thalamus in endometriosis compared to patients with migraine.

Conclusion: The brain areas that differed when comparing patients with endometriosis to those with migraine have been previously reported to play a prominent role in the pain modulation system. Interestingly, the alterations in these regions (including the dorsolateral prefrontal gyrus and thalamus) are connected to increased pain sensitization and might implicate ineffective inhibitory mechanisms in this patient group with endometriosis. To further determine the similarities and differences in brain structure and function and to evaluate their specificity for each pain disorder, we plan to recruit more patients and include healthy controls. These findings could provide preliminary data for future studies exploring the use of centrally driven treatment options and methods of migraine treatments for endometriosis-associated pain.

References

Adewuyi, E. O., Sapkota, Y., Auta, A., Yoshihara, K., Nyegaard, M., Griffiths, L. R., Montgomery, G. W., Chasman, D. I., & Nyholt, D. R. (2020). Shared Molecular Genetic Mechanisms Underlie Endometriosis and Migraine Comorbidity. *Genes,* 11(3), 268. https://doi.org/10.3390/genes11030268

Jenabi, E., & Khazaei, S. (2020). Endometriosis and migraine headache risk: A meta-analysis. *Women & Health*, 60(8), 939–945. https://doi.org/10.1080/03630242.2020.1779905

Yang, M.-H., Wang, P.-H., Wang, S.-J., Sun, W.-Z., Oyang, Y.-J., & Fuh, J.-L. (2012). Women with endometriosis are more likely to suffer from migraines: A population-based study. *PloS One*, 7(3), e33941. https://doi.org/10.1371/journal.pone.0033941

Poster Abstract accepted to IASP 2022

Title: Thermal Sensitivity Changes in the Context of an MRI Scanner: Application of Quantitative Sensory Testing in Mixed Environments

Authors: Ayeong (Jenny) Kim, BA, Edina Szabo, PhD, Claire E. Lunde, BS, BA, Christine B. Sieberg, PhD, Scott A. Holmes, PhD

Presenting Author
Dr. Christine B Sieberg

Background & Aims: Magnetic resonance imaging (MRI) is often used for clinical and research purposes and has generally been considered safe. However, specific absorption rate (SAR) is an important consideration when assessing the response to thermal stimuli during an MRI. This study aimed to explore the relationship between pain sensitivity inside the MRI as well as outside the MRI environment. As pain is a subjective experience that can be affected by elevations in psychological health and sex differences, such as anxiety and depression (Brandl et al., 2022), we also assessed both physical and psychological health, and utilized an all-female cohort (Wiesenfeld-Hallin, 2005).

Methods: 17 healthy adults, ages 21 – 41 years old (M = 29.35, SD = 6.26) were recruited from the Greater Boston Area. Subjects were screened for major health conditions and MRI eligibility by research staff and provided written consent. All subjects identified as female (100%), and the majority identified as non-Hispanic white (70.6%). All subjects rated their pain on the day of the study as 0 out of 10, and were on hormonal birth control, or between days 2 and 10 of their menstrual cycle. The battery of psychological questionnaires included selected PROMIS measures (anxiety and depression).

The noxious thermal stimuli was administered using an fMRI-compatible Medoc TSA 2. Thermal testing was first performed in a controlled testing space by trained research staff. Participants were instructed to rate pain using the pain scale of 0 (no pain at all) to 10 (the worst pain imaginable) when rating the pain from the temperature being applied via 30x30mm thermode on the medial and lateral sides of their non-dominant calf. Temperatures that were tested ranged from 32.0°C to 48.0°C, and the temperature rate of change was 13.0°C/sec. Participants were instructed to stop the temperature from increasing when they felt that the pain reached a 7 out of 10 (7/10). Three trials were performed to find the average 7/10 temperature for each participant. The same procedure was performed approximately 30 minutes later inside the MRI (after acquiring T1 and T2-weighted anatomical images and a 7-minute resting-state period). Participants rated pain with an electronic visual analogue scale (eVAS) from 0-10.

Results: All participants in the cohort experienced no clinical elevation on anxiety and depression PROMIS measures (T-score > 60). The average 7/10 scores reported inside and outside of the MRI were statistically significantly higher inside the MRI environment ($t = -2.17$, $p < .05$). Participants reported a higher 7/10 threshold temperature inside the MRI during the fMRI sequence (Min outside = 44.37°C, Min inside = 45.15°C).

Conclusions: The current study shows that there may be a significant difference in thermal sensitivity when participants are exposed to an MRI scanning environment. However, more research is needed to understand the effects of MRI on noxious thermal pain perception. Our results are limited due to the smaller sample size. Future studies should evaluate differences in environmental temperature inside versus outside the MRI environment and account for the differences in study findings and applied noxious stimuli.

The research was approved by the Institutional Review Board at Boston Children's Hospital.

Relevance for Patient Care

The findings of this study can be applied to identifying greater considerations for SAR and MRI safety. As QST is often conducted in the MRI, it's important to understand how temperature, both localized to testing site and core body temperature, may be affected inside of the MRI environment.

Poster Abstract accepted to IPPS 2022

Title: Endometriosis and Migraine: Exploring Structural Brain Alterations in Two Comorbid Pain Disorders

Edina Szabo, Ayeong Kim, Claire E. Lunde, Stacey Missmer, Scott A. Holmes, David Borsook, Christine B. Sieberg

Background: Research has revealed a relationship between endometriosis and migraine headaches (Jenabi & Khazaei, 2020). Individuals living with endometriosis are nearly twice as likely to experience migraine attacks as those without endometriosis (Yang et al., 2012). Besides shared genetic and hormonal mechanisms (Adewuyi et al., 2020), specific alterations in the central nervous system (central sensitization) could be a contributing factor to the comorbid pain in both conditions. The aim of the present study was to utilize brain magnetic resonance imaging (MRI) structural data to compare patients with surgically confirmed endometriosis to patients with migraine.

Methods: In this cross-sectional study, structural T1-weighted MRI brain images were acquired with a 3T scanner. Cortical thickness and subcortical volume were estimated using the FreeSurfer software package. Group differences were investigated utilizing the mri-glmfit tool and a vertex-specific general linear model.

Results: Preliminary data of our ongoing study (so far, we included n=12 patients with endometriosis and n=12 patients with episodic migraine, between the ages of 20-38 years) showed that individuals with endometriosis displayed decreased cortical thickness in the bilateral superior frontal gyrus, right caudal middle frontal gyrus, and right inferior frontal gyrus (pars orbitalis) compared to patients with migraine. Whereas an increase in cortical thickness was detected in regions including the bilateral inferior parietal lobe and left precentral sulcus (corrected for multiple comparisons using a cluster-wise threshold of $p < 0.05$ with Monte Carlo simulations). In addition, increased volume was observed in the left thalamus in endometriosis compared to patients with migraine.

Conclusion: The brain areas that differed when comparing patients with endometriosis to those with migraine have been previously reported to play a prominent role in the pain modulation system. Interestingly, the alterations in these regions (including the dorsolateral prefrontal gyrus and thalamus) are connected to increased pain sensitization and might implicate ineffective inhibitory mechanisms in this patient group with endometriosis. To further determine the similarities and differences in brain structure and function and to evaluate their specificity for each pain disorder, we plan to recruit more patients and include healthy controls. These findings could provide preliminary data for future studies exploring the use of centrally driven treatment options and methods of migraine treatments for endometriosis-associated pain.

References

Adewuyi, E. O., Sapkota, Y., Auta, A., Yoshihara, K., Nyegaard, M., Griffiths, L. R., Montgomery, G. W., Chasman, D. I., & Nyholt, D. R. (2020). Shared Molecular Genetic Mechanisms Underlie Endometriosis and Migraine Comorbidity. Genes, 11(3), 268. https://doi.org/10.3390/genes11030268

Jenabi, E., & Khazaei, S. (2020). Endometriosis and migraine headache risk: A meta-analysis. Women & Health, 60(8), 939–945. https://doi.org/10.1080/03630242.2020.1779905

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Poster Abstract accepted to IPPS 2022
Title: Do people with endometriosis-associated pain in adulthood report more adverse childhood events?

Authors: Claire E Lunde[1,2], E. Szabo,[2] A. Kim[2], SA Holmes[2], K. D Borsook[3], CB Sieberg[2,4]

[1]Nuffield Dept of Women's and Reproductive Health, Univ. of Oxford
[2]Pain & Affective Neuroscience Center, Boston Children's Hospital
[3]Biobehavioral Pediatric Pain Lab, Department of Psychiatry and Behavioral Sciences
[3]Massachusetts General Hospital
[4]Harvard Medical School

Background & Aims. Endometriosis is one of the most common chronic gynecological diseases affecting 10-15% of women in their reproductive years and 70% of people with chronic pelvic pain. Approximately 62% of adults in the US report at least one childhood trauma, which is associated with an increased risk of chronic pain and gynecological complications in adulthood. Chronic pain, childhood stress, and resilience have been shown to impact pain perception in adulthood but have yet to be measured in people with endometriosis-associated pain (EAP). Resilience is important to measure in addition to stress or trauma as the mechanisms associated with stress-related psychopathology are expected to differ significantly from those associated with resilience. The aim of the study was to describe the experience of childhood stress, resilience, and trauma in people with surgically confirmed endometriosis.

Methods. Participants with endometriosis (n=37) and pain-free controls (n=40) completed two questionnaires: Childhood Traumatic Events Scale (CTES) and the Connor-Davidson Resilience Scale (CD-RISC). T-tests were used to compare the groups.

Results. While both groups endorsed an average of two childhood traumatic events (avg of 2 for both groups), those with endometriosis reported significantly higher burden score indicative of a greater perceived impact of the event. There were no significantly differences between groups on resiliency scores, although both groups endorsed moderate overall resiliency (possible range is 0-40; mean score and SD for controls = 21.8 (4.5) vs EAP participants = 21.1 (5.4). Those with endometriosis (mean age = 27.9 years, SD = 7.3) vs pain-free participants (mean age = 25.6 years, SD = 6.5) showed a statistically significant difference in average CTES burden score: 6.8 (5.2) vs 10.2 (7.6) ($t(50) = -1.8, p = .03$). No significant difference between groups were found for the measure of resilience (CD-RISC).

Conclusion. Further research with a larger sample size and mixed-methodologies are needed to further elucidate the relationship between EAP, trauma, and resiliency. However, these findings highlight the importance of trauma-informed care and positive psychology for those with EAP.

Poster Abstract and Poster Datablitz Presentation accepted to SFNIRS 2022

Title: Assessing inhibitory pain mechanisms and neural activity in patients with endometriosis-associated pain

Authors: Claire E Lunde[1,2,3], Edina Szabo[2,3], Ziyan Wu[2,3], Keerthana Karunakaran[2-4], Ayeong Kim[2,3], Scott A. Holmes[2], David Borsook[4,5], Christine B. Sieberg[2,3,5]

[1]*Nuffield Dept of Women's and Reproductive Health, Univ. of Oxford*
[2]*Pain & Affective Neuroscience Center, Boston Children's Hospital*
[3]*Biobehavioral Pediatric Pain Lab, Department of Psychiatry and Behavioral Sciences*
[4]*Massachusetts General Hospital*
[5]*Harvard Medical School*
Presenting author email: claire.lunde@spc.ox.ac.uk

Abstract: Endometriosis is one of the most common chronic gynecological diseases affecting 10-15% of individuals in their reproductive years and 70% of people with chronic pelvic pain. This study explores inhibitory pain mechanisms in people with endometriosis-associated pain (EAP). fNIRS was used to assess descending pain inhibition via an Offset Analgesia (OA) paradigm in 14 females with surgically confirmed endometriosis and 14 pain-free females. EAP participants showed attenuated OA responses, suggesting a decreased ability to modulate changes in pain perception. fNIRS data analysis is ongoing and is expected to show increased functional connectivity in brain regions involved in pain processing.

Introduction: Endometriosis is a debilitating and incurable condition affecting approximately 10–15% of all people of reproductive age (1 in 10 people globally), 20–50% of all people with infertility, and 25–70% of people and adolescents with chronic pelvic pain or dysmenorrhea. Despite these treatments, approximately 30% of patients report no improvement in pain after surgery, and many other patients frequently report recurring endometriosis-associated pain (EAP) without evidence of recurrent disease. Multiple mechanisms contribute to EAP, specifically peripheral and central pain drivers, including brain and psychophysical changes, which can either be inductors or protectors against pain development. Alterations of central pain inhibitory and reward systems might be associated with pain chronification. Offset analgesia (OA) is a psychophysical test of endogenous pain inhibition characterized by a disproportionately large reduction in pain perception after a small decrease in temperature during noxious thermal stimulation. An attenuated OA response is consistently found in patients with chronic pain, indicating a lack of ability to modulate changes in pain perception. Still, it has yet to be measured in people with EAP and, to our knowledge, has not been assessed via fNIRS.

Methods: A 3-temperature heat stimuli OA paradigm was applied to the left forearm while hemodynamic signals were measured bilaterally over the frontal and somatosensory cortex. Participants also completed 10-minutes of resting state hemodynamic signal measurement. The magnitude of the behavioral OA response (*ΔOA=pain score max – pain score min during offset trial*) was calculated by the percentage of difference for four OA trials. fNIRS data processing is in progress. Resting-state and OA response functional connectivity will be computed using pair-wise Pearson's r correlation of regions of interest. T-tests will be used to assess statistically significant differences in hemodynamic responses during resting state and OA. The research plan was approved by the Ethical Committee of Boston Children's Hospital.

Results: 14 females with surgically confirmed endometriosis (mean age = 26.7 years, SD = 5.4) and 14 pain-free females (mean age = 22.6 years, SD = 4.2) were included in analyses. T-tests showed participants with EAP had an attenuated OA response, median: *77.1% vs. 43.8%, ($t(25) = .484$, $p = .05$)*. fNIRS results are expected to show increased functional connectivity in brain regions involved in pain processing, such as the medial prefrontal cortex, anterior insula, cingulate gyrus, thalamus, and putamen.

Conclusion: Results may help describe the role of the prefrontal and somatosensory cortex on the OA response in people with and without EAP. The magnitude of OA could be a valuable index to distinguish the 30% of patients with persistent EAP after treatment. This new approach may allow for identifying meaningful subgroups of patients with EAP, developing better preclinical models, and thus ultimately lead to more effective treatment.

US Department of Defense award to CS & SH supported the research.

Poster Abstract accepted to SFN 2022
Does offset analgesia vary as a function of childhood trauma and resilience?

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Background & Aims. Endometriosis is one of the most common chronic gynecological diseases affecting 10-15% of women in their reproductive years and 70% of people with chronic pelvic pain. Approximately 62% of adults in the US report at least one childhood trauma, which is associated with an increased risk of chronic pain and gynecological complications in adulthood. Both chronic pain and childhood stress and resilience have been shown to alter pain modulation but has yet to be measured in people with endometriosis-associated pain (EAP). Resilience is important to measure in addition to stress or trauma as the neural mechanisms associated with stress-related psychopathology are expected to differ significantly from those associated with resilience. The aim of the study was to explore the role of childhood traumatic evets and resilience on descending pain inhibition in people with EAP using functional near-infrared spectroscopy (fNIRS).

Methods. A 3-temperature offset analgesia (OA) paradigm, a form of endogenous pain inhibition, using heat stimuli was applied to the left forearm while hemodynamic signals were measured bilaterally over the frontal and somatosensory cortex. The magnitude of the behavioral OA response (*ΔOA=pain score max – pain score min during offset trial*) was calculated by the percentage of difference for four OA trials. Participants also completed the Childhood Traumatic Events Scale (CTES) and the Connor-Davidson Resilience Scale (CD-RISC). fNIRS data processing is in progress. Resting-state and OA response functional connectivity will be computed using pair-wise Pearson's r correlation of regions of interest. T-tests will be used to assess statistically significant differences in hemodynamic responses during resting state and OA. fNIRS and behavioral data will be compared using a partial correlation analysis, controlling for CTES burden score and resilience. The research plan was approved by the Ethical Committee of Boston Children's Hospital.

Results. 14 females with surgically confirmed endometriosis (mean age = 26.7 years, SD = 5.4) and 14 pain-free females (mean age = 22.6 years, SD = 4.2) have been recruited. T-tests showed participants with EAP showed an attenuated OA response, median: 77.1% vs. 43.8%, *(t(25) =.484, p=.05*). T-tests showed there were statistically significant difference in average CTES burden score: 22.6 (4.2) vs 26.7 (5.4) (*t(25) =-1.7, p=.05*). No significant difference between groups were found for the measure of resilience (CD-RISC).

Conclusion. Results may help describe the role of the prefrontal and somatosensory cortex during OA, and the impact of adverse events and resilience during development on the OA response in people with and without EAP. This new approach may allow for the identification of meaningful subgroups of patients with EAP, develop better preclinical models, and thus ultimately lead to more effective treatment.

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Invited Oral Presentation by Dr. Sieberg at the International Pelvic Pain Society Convention – October 2022

Title: Elucidating the neural underpinnings of co-morbid endometriosis and migraine: A pilot fMRI investigation

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Introduction: Endometriosis and migraines are highly comorbid. Patients with endometriosis are twice as likely to experience migraine attacks as those without; however, it is unclear as to why. Migraine may parallel disease phenotypes in endometriosis in that it is a visceral pain that is intermittent in nature, involves inflammation, and can chronify. This study utilized fMRI to investigate resting state functional connectivity and structural data to compare patients with both endometriosis and migraine to those with endometriosis or migraine only.

Methods: Using the right anterior insula as a seed region, group differences in resting state functional connectivity between 12 patients with endometriosis and 5 patients with both endometriosis and migraine were compared. Group differences in cortical thickness were compared between the comorbid group and 12 patients with migraine only.

Results: Significantly decreased functional connectivity in the right anterior insula was observed in patients with both diseases in the left pallidum, part of the basal ganglia, compared to patients with endometriosis only. Decreased cortical thickness was detected in patients with both diseases in the left superior frontal gyrus compared to patients with migraine only.

Conclusions: The functional connectivity results are consistent with previous research showing a relationship between migraine and basal ganglia structures, implicating altered reward and affective pain processing. Patients with both diseases exhibited reduced cortical thickness in the left superior frontal gyrus, part of the dorsomedial prefrontal cortex, a key area for nociceptive modulation, when compared to patients with migraine only. This suggests alterations in cognitive inhibitory control processes, including descending pain modulation.

Presentation presented European Pain School 2022
Exploring the role of childhood trauma on pain modulation for people with endometriosis

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Background & Aims. Endometriosis is one of the most common chronic gynecological diseases affecting 10-15% of women in their reproductive years and 70% of people with chronic pelvic pain. Approximately 62% of adults in the US report at least one childhood trauma, which is associated with an increased risk of chronic pain and gynecological complications in adulthood. Both chronic pain and childhood trauma have been shown to alter pain modulation but has yet to be measured in people with endometriosis-associated pain (EAP). The aim of the study was to explore the role of childhood trauma and descending pain inhibition in people with EAP using functional near-infrared spectroscopy (fNIRS).

Methods. A 3-temperature offset analgesia (OA) paradigm, a form of endogenous pain inhibition, using heat stimuli was applied to the left forearm while hemodynamic signals were measured bilaterally over the frontal and somatosensory cortex. The magnitude of the behavioral OA response (ΔOA=pain score max – pain score min during offset trial) was calculated by the percentage of difference for four OA trials. Participants also completed the Childhood Traumatic Events Scale (CTES). Once data collection is complete (Spring 2022), resting state and OA response functional connectivity will be computed using pair-wise Pearson's r correlation of regions of interest. T-tests will be used to assess statistically significant differences in hemodynamic responses during resting state and OA. fNIRS and behavioral data will be compared using a partial correlation analysis, controlling for CTES burden score. The research plan was approved by the Ethical Committee of Boston Children's Hospital.

Results. 9 females (desired sample size is 15) with surgically confirmed endometriosis (mean age = 25 years, SD = 5.54) and15 pain-free females (mean age = 22 years, SD = 3.46) have been recruited. Preliminary analyses indicate that participants with EAP show an attenuated OA response, (median: 18.1% vs. 31.8%, $p = 0.032$). A one-way ANOVA revealed a statistically significant difference in CTES burden score between the groups ($F(1, 20) = 9.67$, $p = .006$).

Conclusion. Results may help describe the role of the prefrontal and somatosensory cortex during OA, and the impact of childhood trauma on the OA response in people with and without EAP. This new approach may allow for the identification of meaningful subgroups of patients with EAP, develop better preclinical models, and thus ultimately lead to more effective treatment.

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Presentation presetned European Pain School 2022
Altered resting-state functional connectivity between prefrontal and somatosensory cortex after pain response in healthy adults: A pilot functional near-infrared spectroscopy study

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Background & Aims. The neurobiological underpinnings associated with chronic pain are unclear, however, the novel use of technology, such as functional near-infrared spectroscopy (fNIRS) can provide insight. fNIRS is a non-invasive technique, which allows for the measurement of brain tissue oxygenation levels by absorbing and scattering near-infrared light at a particular wavelength (Chen W.L. et al. 2020). This pilot study aims to establish the validity of investigating pain-related brain activation and functional connectivity using fNIRS, and examine the effects of pain response in brain functional properties.

Methods. 9 female healthy young adults (mean age = 22 years, SD = 1.73 years) are included in this pilot sample (data collection ongoing). Experimental design included a 10-mins resting-state, a 3-temperature offset analgesia (OA) paradigm (Offset, Constant and Control) with heat stimuli applied to the left forearm, and 3 short resting periods (40 seconds each) between and after the OA sub-paradigms. fNIRS data from 6 regions of interest (ROIs), including lateral prefrontal, medial prefrontal and lateral primary somatosensory cortices in both hemispheres were obtained. Brain activations during long (10-mins) and short (40-seconds) resting period and pair-wise functional connectivity (FC) between the 6 ROIs were calculated. Paired-sample t-tests were implemented between long and short resting periods. The study was approved by the Ethical Committee of Boston Children's Hospital.

Results. Participants showed significantly reduced FC between the left and right lateral prefrontal cortices ($t = -2.399$, $p = .043$) as well as between right medial prefrontal cortex and left lateral primary somatosensory cortex ($t = -2.312$, $p = .050$) during after-pain modulation resting period relative to the long resting-state.

Conclusion. Results of this pilot study indicate that fNIRS is a valid non-invasive neuroimaging technique for evaluating cerebral oxygenation changes. The reduced FC within the prefrontal cortex and between prefrontal and somatosensory cortices may suggest a significant effect of pain responses of these brain regions. Data collection is ongoing and the larger sample size will afford further investigation to verify the findings of this pilot study and also extend to a larger study utilizing fNIRS to better understand endometriosis-associated pain.

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Reference

Chen W.L. et al., 2020. Functional Near-Infrared Spectroscopy and Its Clinical Application in the Field of Neuroscience: Advances and Future Directions. Front Neurosci. 14(724).