AWARD NUMBER: W81XWH-19-1-0560

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, Boston, MA

REPORT DATE: September 2021

TYPE OF REPORT: Annual report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE		*Form Approved OMB No. 0704-0188*
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering, and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**		
1. REPORT DATE September 2021	**2. REPORT TYPE** Annual	**3. DATES COVERED** 15Aug2020-14Aug2021
4. TITLE AND SUBTITLE Defining the Role for Descending Pain Modulation and Reward- Aversion Processes towards the Development of Chronic Pain in Endometriosis		**5a. CONTRACT NUMBER** W81XWH-19-1-0560
		5b. GRANT NUMBER
		5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) Dr. Christine Sieberg Dr. Scott Holmes		**5d. PROJECT NUMBER**
		5e. TASK NUMBER
		5f. WORK UNIT NUMBER
E-Mails: Christine.sieberg@childrens.harvard.edu; Scott.Holmes@childrens.harvad.edu		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **AND ADDRESS(ES)**		**8. PERFORMING ORGANIZATION REPORT NUMBER**

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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

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.

In respect to the COVID-19 pandemic, recruitment and data collection was delayed. However, we currently have recruited and tested 10 participants, with 11 participants on the schedule, and 11 more who have expressed interest and who are in the process of being scheduled. The research team has also published several papers related to the project and have three papers in preparation (two reviews; preliminary resting state data) during this reporting period and have attended various webinars and training related to the project. Additionally, Dr. Borsook (Partnering PI) retired from BCH and transitioned to the position of consultant for the current project. Dr. Holmes assumed Dr. Borsook's role on February 10th, 2021. Lastly, the imaging center at BCH has moved locations. The MRI aims of the current project will now take place at 2 Brookline Place, Boston, MA 02215.

In the report last year, the research team had proposed alternatives to counteract the setbacks that the project faced due to COVID-19, which included: **(1)** Partnering with other Harvard Medical School (HMS) affiliated hospitals to aid in recruitment. The research team has increased the number of partnering gynecological surgeons at HMS, thus increasing our recruitment pool for people with endometriosis. **(2)** Adopting another imaging modality (*i.e.,* fNIRS) that does not have as many COVID-related restrictions. All equipment has been obtained and the research team (RAs and Post-Doc) have been trained and data collection and preliminary analysis for this sub-aim have begun. **(3)** Exploring adding another research scanning site at one of the other HMS affiliated hospitals. Fortunately, the research is progressing well with recruitment and testing for fMRI and fNIRS so we have not needed to explore the addition of an extra scanning site at this time.

15. SUBJECT TERMS					
Pain; Endometriosis; Adolescent; fMRI; Age-related changes; Neurobiology					
16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	34	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

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I. **Introduction:**

a. The goal of this project is 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 fMRIs.

II. **Keywords**

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

III. **Accomplishments**

a. *Major goals.* The major goals of the project fall under 3 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.
iii. *Recruitment:* The recruitment goal for Aim 1 is 20 participants in each age group for Aim 1 (not including 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. See Table 1 for current recruitment status and distribution.

TABLE 1: Recruitment distribution for Aims 1 and 2. A total of n=23 individuals expressed interest in participating, however, they did not meet inclusionary eligibility criteria for this study.

MRI	**Healthy Controls**	**Endometriosis Patients**
Completed study	n=1	n=0
Scheduled for study visit	n=5	n=2
fNIRS	**Healthy Controls**	**Endometriosis Patients**
Completed study	n=6	n=3
Scheduled for study visit	n=3	n=1
Ineligible	n=15	n=8

b. *Recruitment of Research Assistant/Post-Doctoral Fellow:* An additional RA has been hired, as Ms. Lunde is a current Doctoral Candidate and does not require full funding. Ayeong Kim, BA has been hired as an RA who began working on the project in July 2021. Ms. Kim is funded from Dr. Sieberg's budget. She has previously worked with Dr. Borsook and Dr. Holmes as an undergraduate research intern during her senior year at Boston University. Throughout her time in the lab, Ms. Kim 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. Kim (both at 50% effort) to finish the project set up regarding the new COVID-19 challenges, new BCH imaging center, as well as fully train Ms. Kim in all QST and the fMRI procedures.

c. Training of new RA, Post-Doctoral Fellow, and student interns on QST and pain psychophysics: Ms. Lunde, Ms. Kim, 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.

d. *Milestones achieved for Aim 1, 2 and 3*

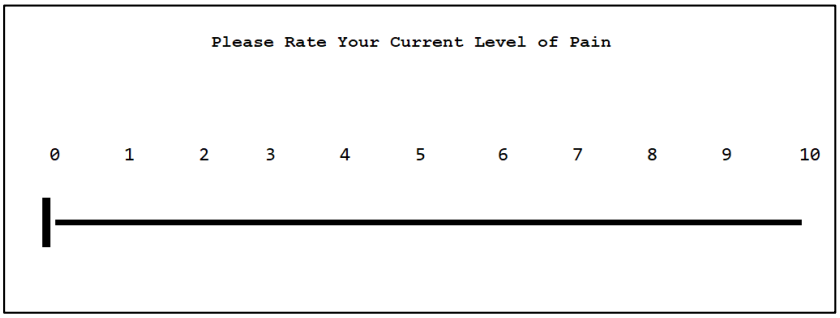
   i. Commentary on the use of Offset Analgesia (OA) to assess endometriosis-associated pain entitled: *Commentary: Novel use of Offset Analgesia to assess adolescents and adults with treatment resistant endometriosis-associated pain*. The manuscript, which was proposed to begin in month 6 of the grant was published in November 2020 (PMID:33204144) (Authors: Lunde, Szabo, Holmes, Borsook, & Sieberg).

   ii. A paper (in preparation) on pilot fMRI resting state and psychological data on a cohort of adolescent women with surgically confirmed endometriosis that will be submitted to *Pain* in October 2021. 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.

   iii. A second review paper (in preparation) will be submitted to the *Journal of Pain* in December 2021 on the topic of descending/endogenous analgesia in an fMRI setting for chronic pain conditions, with the proposal of a new theoretical model for assessing and understanding endometriosis-associated pain (Authors: Szabo, Lunde, Kim, Holmes, & Sieberg).

   iv. *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).* 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 the behavioral OA.



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

TABLE 2: *Demographics for preliminary sample*.

Race and ethnicity distribution	Healthy Controls (n=8)	Patients (n=3)
White, not of Hispanic origin	n=6	n=3
Asian, or Pacific Islander	n=2	n=0
Age	**Healthy Controls (mean; range)**	**Patients (mean; range)**
	22 years (20-24)	22 years (20-23)

TABLE 3: *Results for preliminary questionnaire data*. These values were calculated on SPSS. Perceived stress, depression, anxiety, and pain interference, as measured by the PROMIS measures, are T-scores where M=50, SD=10 and T=60 begins clinical elevation. Of note, this preliminary sample is not experiencing clinically elevated symptoms of depression, but some controls and patients are endorsing clinically elevated symptoms of anxiety. Interestingly, both healthy controls and patients with endometriosis are endorsing moderate to high levels of fear of pain. We have randomized the order of testing (*i.e.,* imaging/sensory tests first followed by self-report questionnaires & vice-versa). As the sample size increases, it will be interesting to further explore the role of fear of pain and anxiety on the OA response. Similarly, there is a range of catastrophizing scores (*e.g.*, a total score of >30 is clinically elevated). As literature has demonstrated (Roberts et al, 2006), there tends to be wide variability around the mean total catastrophizing score, even in healthy controls. We are excited to further explore the role of catastrophizing in the relationship of the OA response. Of note, the current sample has a wide range of perceived stress, which we will also continue to further explore with our larger sample.

Questionnaires	Healthy Controls			Patients		
Fear of pain (Child report)	n	Mean (SD)	Range	n	Mean (SD)	Range
	4	36 (22.46)	18-67	1	31*	31*
Fear of pain (Adult report)	4	71 (23.90)	42-93	1	65*	65*
Perceived Stress	8	49.01 (12.90)	33-67.6	3	54.63 (14.26)	38.70-66.20
Depression	8	46.85 (9.35)	37.10-58.80	2	59.7 (1.27)	57.90-59.70
Anxiety	8	54.16 (8.93)	37.10-67.70	3	55.13 (17.43)	37.10-71.90
Pain catastrophizing	8	12.63 (12.89)	1-36	2	22.5 (7.78)	17-28
Pain interference	8	22.8 (8.14)	40.70-63.50	3	50.13 (8.56)	40.70-57.40

*No SD could be calculated due to only one data point being available at this point in time.

TABLE 4*:* *Behavioral Offset Analgesia (OA) Preliminary Data from two controls and two endometriosis patients.* 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.

Questionnaires	Healthy Controls		Patients	
	Control 1	Control 2	Patient 1	Patient 2
First Trial	5	2	3	3
Second Trial	3	1	3	5
Third Trial	1	1	2	3
Fourth Trial	0	2	4	6

Mean eVAS change	2.25	1.5	3	4.25

FIGURE 2: *Graph of preliminary behavioral offset analgesia data from two controls and two endometriosis patients.* Controls are shown in the blue and orange lines, while endometriosis patients are shown in grey and yellow. The x-axis shows the trials over time, with 1 being the first trial of the thermal pain paradigm, and 4 being the final. The y-axis shows the offset analgesia value. This figure takes the data from Table 4, exemplifying how controls have an offset analgesia response that is expected of healthy, pain-free individuals, but endometriosis patients, who experience chronic pain, show an abnormal response and a lack of the expected offset analgesia effect. Endometriosis patients 1 and 2 show an increasing trend, which is not shown by controls. As we gain more data, we expect to continue to find these changes in the endometriosis cohort and better determine the trends we see in a chronic pain cohort when compared to healthy, pain-free controls.

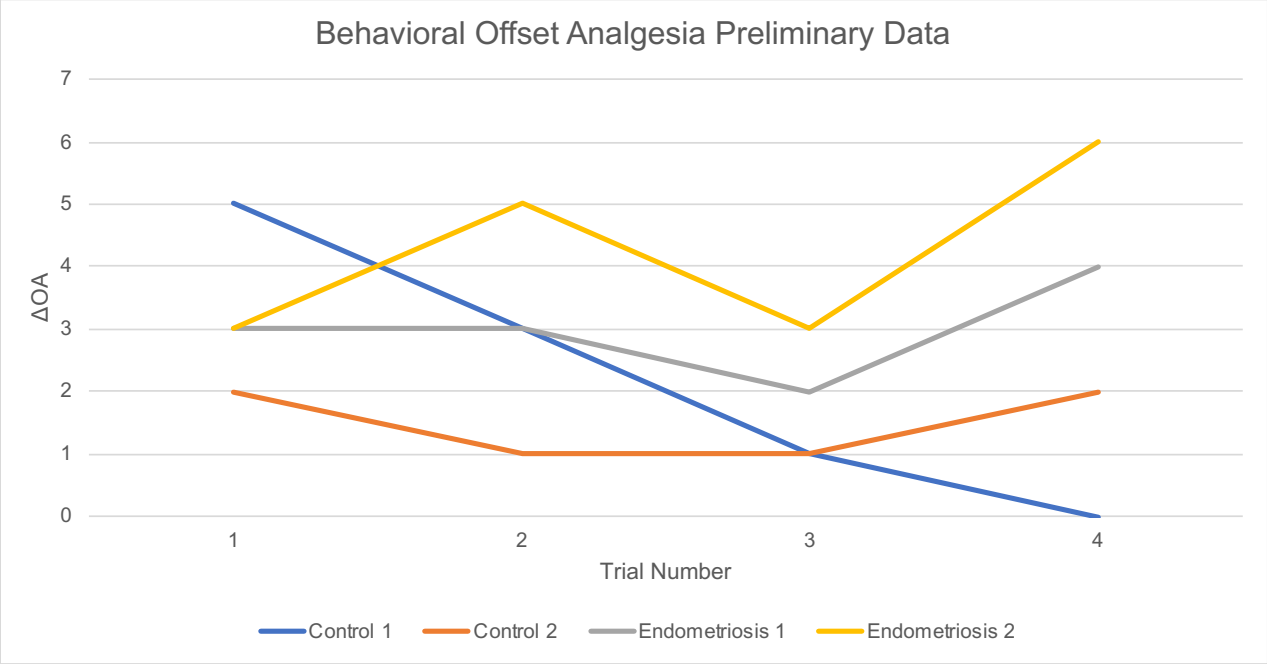


FIGURE 3: *Brain images from an exemplar participant* collected on the new Siemens PRISMA research scanner showing a normal T1-weighted image (top row), brain parcellation using Freesurfer (middle row), and their raw resting state fMRI (bottom row). Coronal, axial and sagittal images are presented from left to right.

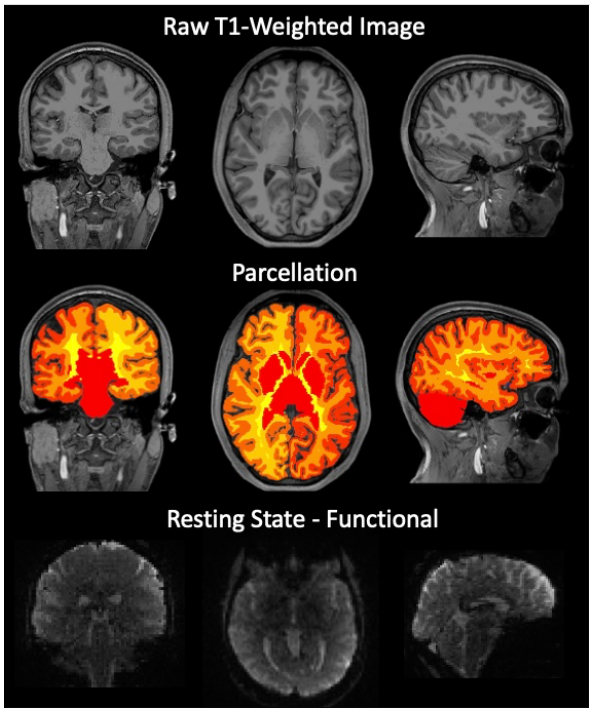


FIGURE 4: *Mean amplitude of low-frequency cortical fluctuations in one control participant and one participant with endometriosis* during 2 minutes of pressure pain stimulation (VAS 4/10). Amplitude of low-frequency fluctuations (ALFF) were calculated as the power of the hemodynamic signal at 0.01-0.1 Hz. Endometriosis participant when compared to control participant exhibited reduced amplitude of cortical signal in the prefrontal cortex and greater amplitude of cortical signal in the medial and right primary somatosensory cortex during ongoing painful stimulation. These findings are consistent with previous studies where decrease in ALFF of prefrontal cortex and increased ALFF of postcentral gyrus is observed in chronic neuropathic pain (PMID: 30588078) and chronic low-back pain (PMID: 30948036) populations. lPFC: lateral prefrontal cortex, mPFC: medial prefrontal cortex, S1: primary somatosensory cortex, mS1: medial primary somatosensory cortex.

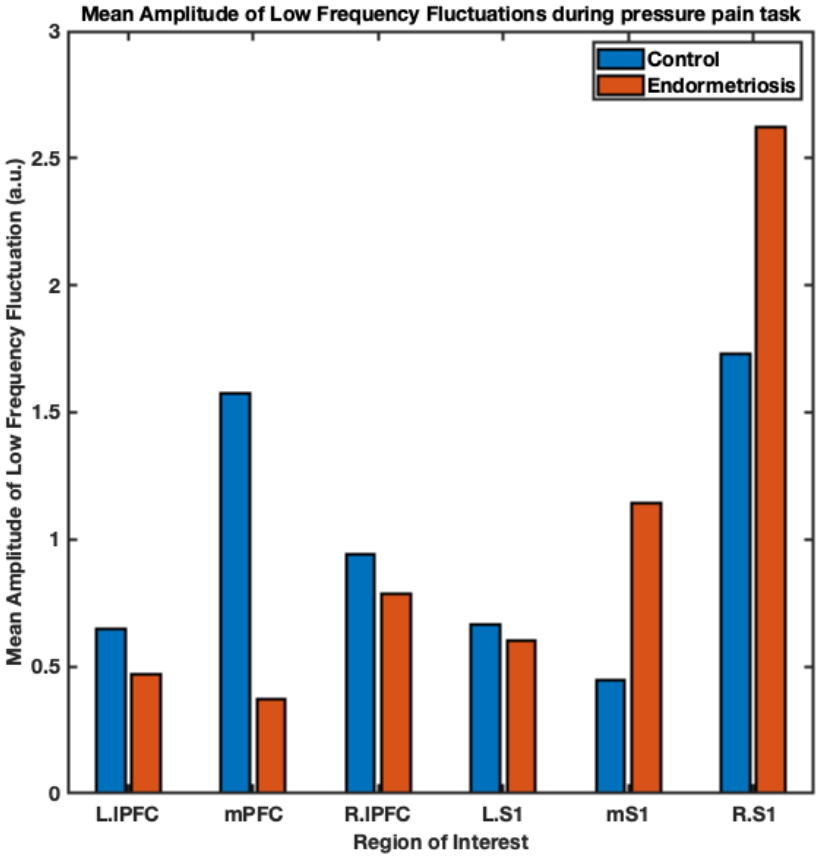
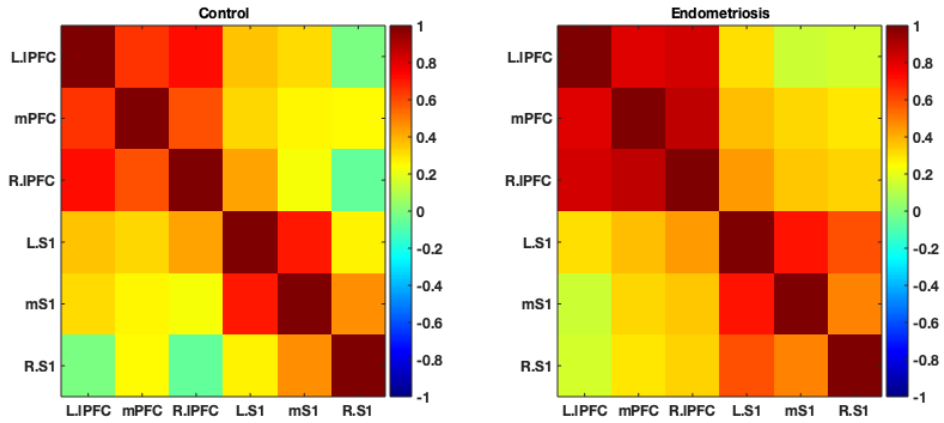


FIGURE 5: *Resting-state functional connectivity (RSFC) in one control participant and one participant with endometriosis.* RSFC was computed using a pair-wise Pearson's r correlation of six regions of interest. Endometriosis participant when compared to control subject demonstrated higher localized connectivity within both prefrontal cortex and somatosensory cortex. Color bar indicates the Pearson's r correlation i.e., strength of connectivity where hot and cold colors indicate positive connectivity. lPFC: lateral prefrontal cortex, mPFC: medial prefrontal cortex, S1: primary somatosensory cortex, mS1: medial primary somatosensory cortex.



For **Aim 3** (comparing brain mechanism in adolescent, young adult, and adult women with endometriosis to female patients with migraines), neuroimaging data will be obtained from our existing *Pain and Affective Neuroscience Center* (former *Center for Pain and the Brain*) database. Participants with migraine will be drawn from a larger study cohort including approximately 55 adolescents with migraine (25 females, 8–17 years old, *M* age=12.7 years, *SD*=2.9) and 48 young adult and adult women with migraine (35 females, 18–61 years old, *M* age= 39.7 years, *SD*=12.2). Overall, a sample size of *n*=20 for each of the age cohort will be used to compare structural and resting-state functional MRI data in these two patient groups.

vi. *Plan for next reporting period to accomplish goals:* During the next 6 months (now until Feb 2022), the research team plans to submit two manuscripts peer review journals and recruit 30 participants across both Aims 1 & 2. We also plan to test the remaining fNIRS participants and begin data analysis and manuscript preparation for the fNIRS pilot study.

IV. **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 on 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 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 form 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.

V. **Changes and Problems**

a. *Changes in approach and reasons for change:* Changes in project oversight often leads to a disruption in a project's proposed timeline. The research team has successfully managed the transition from Dr. Borsook to Dr. Holmes as he has been involved in the current project as a Co-Investigator since Spring 2020 (see previous progress report). Dr. Holmes has worked with Dr. Sieberg for over 3 years where they have collaborated on several successful projects.

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. During the delay, the research team published a manuscript related to the project and completed project setup for the fNIRS pilot sub aim. Within the Year 1 progress report, the research team had proposed three models.

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.

VI. **Products**

a. *Publications, conference papers, and presentations:*

i. *Journal publications:*

1. 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.

b. *Books or other non-periodical, one-time publications:* Nothing to report.

c. *Other publications, conference papers, and presentations:*
    i. Presentation by Dr. Szabo: Chronic nociceptive pain and central sensitization in two pain conditions: New daily persistent headache (NDPH) and endometriosis. Chronic/Acute Pain Research Meeting. Pain Division, Department of Anesthesiology, Critical Care and Pain Medicine. Boston Children's Hospital | Harvard Medical School

    ii. Presentation by Dr. Sieberg on Dr. Holmes' panel entitled: Understanding sex differences in pain in different end-organ systems: From nerve fiber integrity to pain perception for the United States Association for the Study of Pain 2020 Virtual Scientifc Meeting.

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.

VII. 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
    i. Research identifier: 0000-003-4077-9971
    ii. Nearest month person worked: 1
    iii. Contribution to project: Radiologist at BCH contracted to examine all MRI participants for incidental findings.
    iv. Funding support: 2% of effort Federal: US Department of Defense (Dr. Holmes' budget)

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

f. Post-doctoral fellow: Dr. Keerthana Karunakaran, no change

g. Research Assistant: Claire Lunde, no change

h. Research Assistant: Ayeong Kim
    i. Research identifier: 0000-0002-4568-9855
    ii. Nearest month person worked: 3
    iii. Contribution to project: She performs routine oversight of IRB protocols, recruit and enrolling study participants, coordinating scheduling of screening and scan session visits, ensuring patients complete required forms for enrollment, participate in MRI scanning the subjects, performing all necessary screening tests (*e.g.,* pregnancy tests), and collating imaging and non-imaging data (*e.g.,* pregnancy tests)
    iv. Funding support: Foundation: Innovative Medicine Initiative European Commission and Federal: US Department of Defense

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:*

VIII. Special Reporting Requirements

a. *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.

IX. **Appendices**

(1) Ayeong Kim's CV -- newly hired Research Assistant
(2) Dr. Amy Danehy's CV -- Radiologist at BCH contracted to examine all MRI participants for incidental findings.
(3) Published commentary in the Journal of Pain Research, titled: Commentary: Novel Use of Offset Analgesia to Assess Adolescents and Adults with Treatment Resistant Endometriosis-Associated Pain
(4) Abstract for manuscript in preparation, titled: Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: A pilot resting-state study
(5) Abstract for manuscript in preparation, titled: Descending Pain Modulation in the Clinic

Ayeong (Jenny) Kim

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EDUCATION

BA IN NEUROSCIENCE **MAY 2021**

BOSTON UNIVERSITY

- Major: Neuroscience, Minor: Psychology
- Relevant Coursework: Molecular & Cellular Biology, Immunology, Biochemistry, Organic Chemistry, Experimental Psychology, Introduction to MATLAB for Research, Principles of Neuroscience

RESEARCH EXPERIENCE

CLINICAL RESEARCH ASSISTANT **JULY 2021 - PRESENT**

BOSTON CHILDREN'S HOSPITAL

- Developed research skills by working on D.O.D. & N.I.H-funded studies analyzing psychological batteries, fMRI, MRI, and fNIRS imaging data using FreeSurfer, HOMER3 (MATLAB-based software). Conducted experiments using a variety of QST techniques related to thermal and pressure pain. Amended studies for BCH IRB approval.

RESEARCH INTERN **SEPTEMBER 2019 - DECEMBER 2020**

BOSTON CHILDREN'S HOSPITAL

- Established research skills by working on an N.I.H-funded study analyzing psychological batteries and evaluating fMRI/MRI imaging data. Reinforced patient recruitment skills, as well as patient data management on EPIC, RedCap, and Excel.

TEACHING EXPERIENCE

ACADEMIC MENTOR **JANUARY 2021 - PRESENT**

LA COLABORATIVA

- Spent 2-4 hours weekly supporting academic development and tutoring public high school students in Chelsea, MA in various subjects of chemistry, geometry, English, and French over Zoom.

LEARNING ASSISTANT **JANUARY 2019 - MAY 2019**

BOSTON UNIVERSITY NEUROSCIENCE DEPARTMENT

- Presented as Learning Assistant for NE102 (Introduction to Neuroscience) laboratory-focused course at Boston University under direction of Dr. Ryann Guayasamin. Strengthened interpersonal and teaching skills to undergraduate students, while enriching knowledge of course material prevalent to cellular and molecular neurobiology, including writing methodology. Helped students develop experiments for analysis.

WORK EXPERIENCE

CASHIER & PRIME SHOPPER **MAY 2020 - MAY 2021**

WHOLE FOODS MARKET

- Addressed diverse customers in a fast-paced setting, procuring excellent customer service skills. Learned cash-handling processes at register (POS), as well as time management skills while working part-time with full-time coursework at Boston University.

RESIDENT ASSISTANT **AUGUST 2019 - MAY 2021**

BOSTON UNIVERSITY RESIDENCE LIFE

- Grew community-focused leadership skills and mediation skills during trainings. Managed 24 residents and created community experiences via floor events and meetings. Served 24-hour on-call duties, helping with a variety of issues within residential student life.

PUBLICATIONS

NEUROBIOLOGY OF DISEASE **NOVEMBER 2020**

Holmes SA, Kim A, Borsook D. The brain and behavioral correlates of motor-related analgesia (MRA). Neurobiol Dis. 2021 Jan;148:105158. doi: 10.1016/j.nbd.2020.105158. Epub 2020 Nov 4. PMID: 33157210.

PRESENTATIONS

INTERNATIONAL SOCIETY OF PSYCHONEUROENDOCRINOLOGY **SEPTEMBER 2021**

"A pilot investigation examining systemic inflammation in pediatric chronic pain patients"

LEADERSHIP EXPERIENCE

PRESIDENT **SEPTEMBER 2019 - SEPTEMBER 2020**

Undergraduate Women In Science and Engineering (uWISE)

- Collaborated with a team to coordinate events and increased member growth by 100+ people. Moderated administrative tasks and deadlines with Student Activities Organization at BU.

VOLUNTEER WORK

- Acquired 200 hours of community service throughout high school to present and volunteered with Alternative Service Breaks program at Boston University in February 2018.

HONORS & AWARDS

- Dean's List– May 2020, January 2021, May 2021
- CPR Certified with completion of MA EMT course – 2020

SKILLS

INTERPERSONAL SKILLS

- Customer service experience and mediation and conflict training (Resident Assistant).
- Fluency in English, Korean, & French.

LAB TECHNIQES

- Experience performing PCR, histology staining, immunohistochemistry, brain surgery on rat subjects.
- Created data sets and basic programs with MATLAB and E-Prime. Data management with RedCap, Epic, Powerchart, Microsoft Excel. Experience utilizing SPSS, OsiriX, FreeSurfer for data analysis & retrieval.
- Explored investigation, methodology, and co-writing of publications.

Amy R. Danehy, MD
Harvard Medical School Curriculum Vitae

Date Revised: May 8, 2020

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Place of Birth: Nashville, TN

Education

08/1988-06/1992	Bachelor of Music	Vanderbilt University, Nashville, TN
08/1993-06/1994	Biology, Biology Graduate Program	Middle Tennessee State University, Murfreesboro, TN
08/1994-06/1998	Doctor of Medicine	University of Tennessee, Memphis, TN

Postdoctoral Training

06/1998-06/1999	Intern	Internal Medicine	University of Tennessee, Memphis, TN
07/1999-06/2003	Resident	Diagnostic Radiology	University of Tennessee, Memphis, TN
07/2003-06/2004	Fellow	Pediatric Radiology	Boston Children's Hospital, Boston, MA
07/2004-06/2005	Fellow	Pediatric Neuroradiology	Boston Children's Hospital, Boston, MA

Faculty Academic Appointments

07/2004-06/2005	Clinical Fellow	Radiology	Harvard Medical School, Boston, MA
10/2017-present	Assistant Professor	Radiology	Harvard Medical School, Boston, MA

Appointments at Hospitals/Affiliated Institutions

08/1993-06/1994	Graduate Teaching Assistant	Biology	Middle Tennessee State University, Murfreesboro, TN
08/2005-07/2006	Consulting Radiologist	Radiology	Brigham and Women's Hospital, Boston, MA
08/2005-present	Neuroradiology	Radiology	Boston Children's Hospital Boston, MA
01/2011-present	Attending Consulting Radiologist	Neuroradiology	Harrington Hospital, Boston, MA
10/2007-present	Director of Neuro Satellites	Neuroradiology	Boston Children's Hospital Boston, MA
08/2012-present	Medical Director of MRI Safety	Neuroradiology	Boston Children's Hospital, Boston, MA
07/2013-present	Director of Neuro CT	Neuroradiology	Boston Children's Hospital, Boston, MA

Professional Societies

11/2008-present	American College of Radiology	Member
04/2011-present	American Society of Neuroradiology	Member
04/2011-present	American Society of Pediatric Neuroradiology	Member
04/2007-present	The Society for Pediatric Radiology	Member
6/2017-7/2021	Society of Pediatric Radiology Quality and Safety Committee	Member

Report of Funded and Unfunded Projects

Funding Information

Efficacy of intravenous thrombolysis in children with acute thrombolytic stroke. Multicenter study. NIH grant accepted. Funded 2010, closed December 2013 (Rivkin, Orbach)

Current Unfunded Projects

Migraine Evolution: Evaluation of Pediatric Migraines using Multimodal Magnetic Resonance Imaging. (P.A.I.N. group)

Report of Local Teaching and Training

Teaching of Students in Courses

07/2006-present	Neuroradiology/Neurosurgery Conference Residents/Fellows/Faculty 1-3 hours a month	Boston Children's Hospital, Boston, MA
07/2006-present	Neuroradiology/Neuro-oncology Conference Residents/Fellows/Faculty 1-3 hours a month	Boston Children's Hospital, Boston, MA
07/2006-present	Neuroradiology/Neurology Conference Residents/Fellows/Faculty 1-3 hours a month	Boston Children's Hospital, Boston, MA

Formal Teaching of Peers (e.g., CME and other continuing education courses)

2007	CNS Congenital Malformations, MRI/CT Update	Harvard Medical School, Brigham and Women's Hospital, Boston, MA
2020	Hemodynamic Imaging in Children with Transient Neurologic Symptoms	National Radiology Technology Week

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

National

2007	Imaging of Salivary Gland Lesions in Children, American Society of Head and Neck Radiology meeting, Seattle, WA
2021	Imaging of Moyamoya Disease, American Society of Pediatric Neuroradiology meeting.

Report of Clinical Activities and Innovations

Current Licensure and Certification

11/2003	Diplomate, American Board of Radiology

06/2004	Massachusetts Board of Medicine, Full Registration
11/2006	Subspecialty Certification, Pediatric Radiology
10/2012	Subspecialty Certification, Neuroradiology
06/2015	Subspecialty Certification, MRI Safety Medical Director
04/2017	Maintenance of Certification, Pediatric Radiology

Practice Activities

08/2005-present	Evaluation of Neuroradiologic Imaging Studies	Radiology	Boston Children's Hospital, Boston, MA
08/2005-07/2006	Evaluation of ultrasound, cardiothoracic, and oncological imaging studies	Radiology	Boston Children's Hospital, Boston, MA
08/2005-072006	Evaluation of diagnostic imaging studies obtained in the BWH Neonatal Intensive Care Unit	Radiology	Brigham and Women's Hospital, Boston, MA
01/2011-present	Evaluation of diagnostic imaging studies	Radiology	Harrington Hospital, Southbridge, MA

Report of Scholarship

Publications

Peer reviewed publications in print or other media

1. Karimova EJ, Rai SN, Deng X, Ingle DJ, **Ralph AC**, Neel MD, Kaste SC. MRI of knee osteonecrosis in children with leukemia and lymphoma: Part 1, observer agreement. AJR Am J Roentgenol 2006 Feb; 186(2):470-476.

2. Karimova EJ, Rai SN, Ingle D, **Ralph AC**, Deng X, Neel MD, Howard SC, Pui CH, Kaste SC. MRI of knee osteonecrosis in children with leukemia and lymphoma: Part 2, clinical and imaging patterns. AJR Am J Roentgenol 2006 Feb; 186(2):477-482.

3. Lee EY, Mason KP, Zurakowski D, Waltz DA, **Ralph A**, Riaz F, Boiselle PM. MDCT assessment of tracheomalacia in symptomatic infants with mediastinal aortic vascular anomalies: preliminary technical experience. Pediatr Radiol 2008 Jan; 38(1):82-88.

4. Lee EY, Zurakowski D, Waltz DA, Mason KP, Riaz F, **Ralph A**, Boiselle PM. MDCT evaluation

of the prevalence of tracheomalacia in children with mediastinal aortic vascular anomalies. J Thorac Imaging 2008 Nov; 23(4):258-265.

5. Arrington DK, **Danehy AR**, Peleggi A, Proctor RM, Irons MB, Ullrich NJ. Calvarial defects and skeletal dysplasia in patients with neurofibromatosis Type 1. J Neurosurg Pediatr 2013 Apr; 11(4):410-416.

6. Silvera VM, **Danehy AR**, Newton AW, Stamoulis C, Carducci C, Grant PE, Wilson CR, Kleinman PK. Retroclival collections associated with abusive head trauma in children. Pediatr Radiol 2014 Dec; 44 Suppl 4:S621-31. Epub 2014 Dec 14.

7. Lehman LL, Watson CG, Kapur K, **Danehy AR**, Rivkin MJ. Predictors of Stroke After Transient Ischemic Attack in Children. Stroke 2016 Jan; 47(1):88-93. doi: 10.1161/STROKEAHA.115.009904. Epub 2015 Nov 10.

8. Hughes A, **Danehy A**, Adil E. Case 226: Oval Window Atresia. Radiology 2016 Feb; 278(2):626-631.

9. Cheng HH, Rajagopal S, McDavitt E, Wigmore D, Williams K, Thiagarajan, R, Grant PE, **Danehy A**, Rivkin, MJ. Stroke in acquired and congenital heart disease patients and its relationship to hospital mortality and lasting neurologic deficits. Pediatr Crit Care Med 2016 Oct;17(10):976-983.

10. Lee S, Mirsky DM, Beslow LA, Amlie-Lefond C, **Danehy AR**, Lehman L, Stence NV, Vossough A, Wintermark M, Rivkin MJ. Pathways for Neuroimaging of Neonatal Stroke. International Paediatric Stroke Study Neuroimaging Consortium and the Paediatric Stroke Neuroimaging Consortium. Pediatr Neurol 2017 Apr; 69:37-48.

11. Youssef AM, Ludwick A, Wilcox SL, Lebel A, Peng K, Colon E, **Danehy A**, Burstein R, Becerra L, Borsook D. In child and adult migraineurs the somatosensory cortex stands out … again: An arterial spin labeling investigation. Hum Brain Mapp 2017 May 31. (Epub ahead of print)

12. Harrar DB, Salussolia CL, Kapur K, **Danehy A**, Kleinman ME, Mannix R, Rivkin MJ. A Stroke Alert Protocol Decreases the Time to Diagnosis of Brain Attack Symptoms in a Pediatric Emergency Department. J Pediatr. 2020 Jan;216:136-141.e6. doi: 10.1016/j.jpeds.2019.09.027. Epub 2019 Nov 6.

13. Harrar DB, Salussolia CL, Vittner P, **Danehy A,** Sen S, Whitehill R, Chao JH, Bernson-Leung ME, Rivkin MJ.Stroke After Cardiac Catheterization in Children. Pediatr Neurol. 2019 Nov;100:42-48. doi: 10.1016/j.pediatrneurol.2019.07.005. Epub 2019 Jul 19.

14. Colon E, Ludwick A, Wilcox SL, Youssef AM**, Danehy A**, Fair DA, Lebel AA, Burstein R, Becerra L, Borsook D. Migraine in the Young Brain: Adolescents vs. Young Adults. Front Hum Neurosci. 2019 Mar 22;13:87. doi: 10.3389/fnhum.2019.00087. eCollection 2019.

15. Cheng HH, Rajagopal SK, Sansevere AJ, McDavitt E, Wigmore D, Mecklosky J, Andren K, Williams KA, **Danehy A,** Soul JS. Post-arrest therapeutic hypothermia in pediatric patients with congenital heart disease.
Resuscitation. 2018 May;126:83-89. doi: 10.1016/j.resuscitation.2018.02.022. Epub 2018 Feb 21.

16. Bernson-Leung ME, Boyd TK, Meserve EE, **Danehy AR**, Kapur K, Trenor CC 3rd, Lehman LL, Rivkin MJ. Placental Pathology in Neonatal Stroke: A Retrospective Case-Control Study. J Pediatr. 2018 Apr;195:39-47.e5. doi: 10.1016/j.jpeds.2017.11.061. Epub 2018 Feb 1.

17. Lehman LL, Beaute J, Kapur K, **Danehy AR**, Bernson-Leung ME, Malkin H, Rivkin MJ, Trenor CC 3rd.
Workup for Perinatal Stroke Does Not Predict Recurrence. Stroke. 2017 Aug;48(8):2078-2083. doi: 10.1161/STROKEAHA.117.017356. Epub 2017 Jul 13.

18. Lehman LL, Bruccoleri R, **Danehy A**, Swanson J, Mrakotsky C, Smith E, Orbach DB, Burstein R. Adverse effects of erenumab on cerebral proliferative angiopathy: A case report. Cephalalgia. 2021 Jan;41(1):122-126. Doi: 10.1177/033310240950484. Epub 2020 Aug 19.

19. Gallant SC, **Danehy AR**, Licameli GR. Adverse events in pediatric cochlear implant patients undergoing magnetic resonance imaging. Int J Pediatr Otorhinolaryngol. 2021 Jan;140:110547. Doi: 10.1016/j.ijporl.2020.110547. Epub 2020 Dec 3.

20. Choi JJ, Burton CS, **Danehy AR**, Voss SD. Neck CT angiography examinations for pediatric oropharyngeal trauma: diagnostic yield and proposal of a new targeted technique. Pediatr Radiol. 2020 Oct;50(11):1602-1609. Doi: 10.1007/s00247-020-04737-7. Epub 2020 Jul 3.

21. Jaimes C, Biaggotti D, Sreedher G, Chaturvedi A, Moore MM, **Danehy AR**. Magnetic resonance imaging in children with implants. Pediatr Radiol. 2021 May;51(5):748-759. Doi: 10.1007/s00247-021-04965-5. Epub 2021 Apr 19.

Narrative Report

As a Pediatric Neuroradiologist, I devote 85% of my time to clinical work and teaching; the remainder is allocated to administrative activities. I have made a concerted effort to develop the clinical and teaching skills essential to diagnosing and treating pediatric patients who present with either common or complex disorders. As a physician and a teacher, I emphasize clinical problem solving with a drive to make better and timely diagnoses while promoting teaching and discovery at all levels. I encourage trainees to develop clinical skills, encourage a drive for scientific inquiry, and to find excellence through both interpretive and research activities. I strive continually to refine CT neuro imaging methods, as the Director of CT Neuroimaging, to minimize radiation exposure and maximize quality of imaging. I have been the Medical Director of MRI since 2012 with my board certification obtained in 2015. I work diligently with the MRI safety officer to assure the safety of all personnel, patients, and family members who enter the magnetic field. I lead the MRI safety committee with monthly reviews of the safety of the MR environment, safety events or near misses, and to assure compliance with OSHA, CMA and Joint Commission standards. Lastly I work with the multidisciplinary stroke team to develop early stroke response protocols, weekly review of stroke cases for clinic, and evaluation of stoke events occurring in the hospital.

Journal of Pain Research

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COMMENTARY

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:
Journal of Pain Research

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Scott A Holmes[1,4]
David Borsook[1,4]
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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 worldwide[1] 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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http://doi.org/10.2147/JPR.S276135

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 Coghill[14] 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 suggested[31] 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, dorsolateral 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 EAP[41] and patients with dysmenorrhea[42] (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 syndrome[43] 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

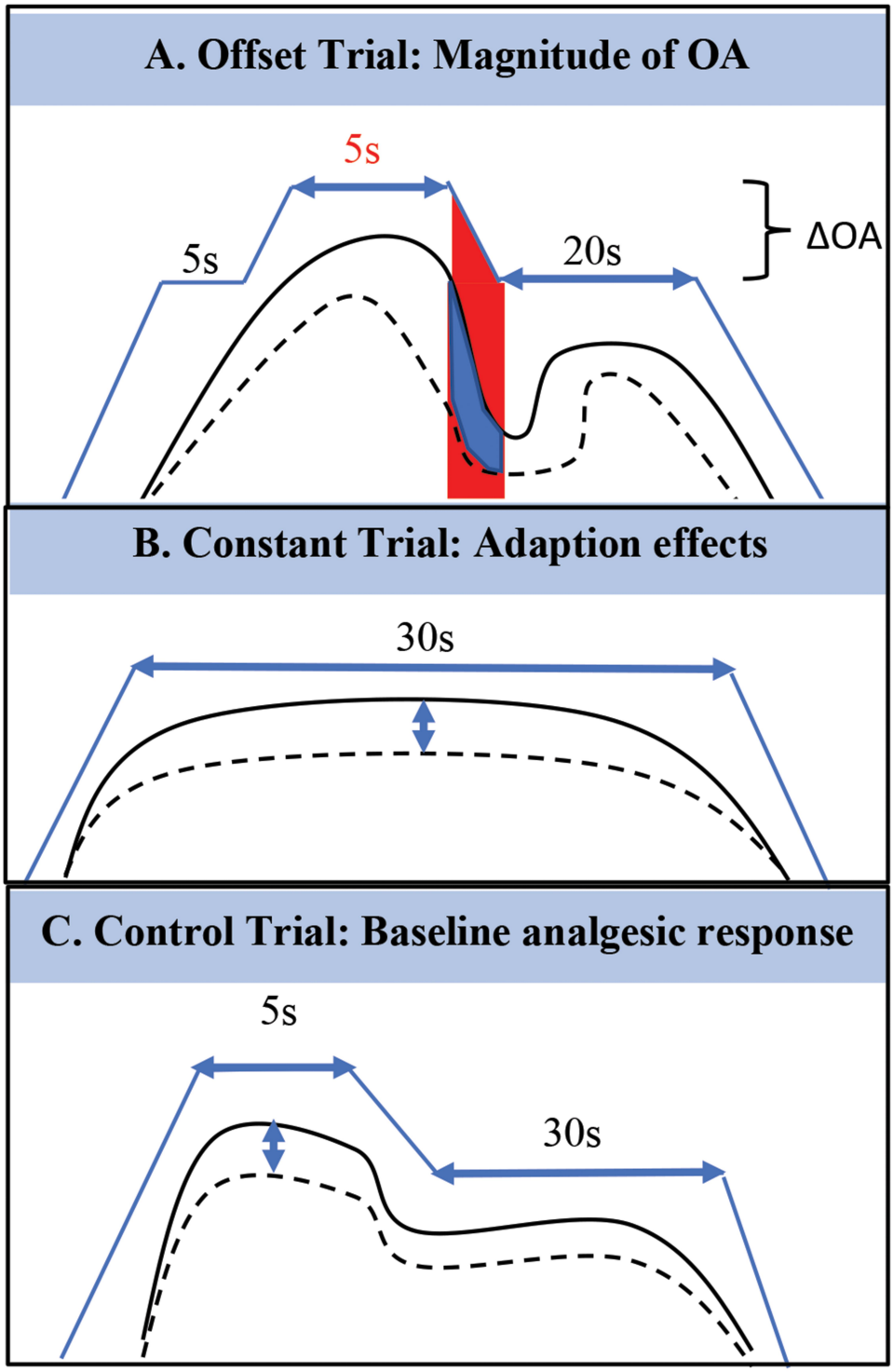

Figure 1 A commonly used 3-temperature OA paradigm includes Offset, Constant and Control trials. The x-axis represents time (seconds), with the y-axis representing temperature (Celsius). Participants continuously rate their pain using a visual analog scale (VAS) of 0–100. (**A**) The Offset Trial consists of individualized temperature 50/100 VAS for 5s, with a 10C increase for 5s, and ending with a decrease in 10C for 20s. (**B**) The Constant Trial consists of 30s at 20C below the 50/100 VAS. (**C**) The Control Trial consists of 5s at 50/100 VAS and then 30s at 320C. A 40s interval between each test is suggested. The redline below highlights the Offset Analgesia: a small decrease (10C) 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 (VASmax 5s) and the lowest VAS scores during the third temperature (VASmin 20s) in the Offset Trial: ΔOA=VASmax 5s – VASmin 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.

Funding

CBS and DB are Partnering PIs on a Peer Review Medical Research Program Investigator-Initiated Research Award from the United States Department of Defense (W81XWH19105060); CBS is also funded by a K23 Career Development Award from NIH (GM123372).

Disclosure

David Borsook reports personal fees from Redpin, outside the submitted work. The authors have no other potential conflicts of interest to disclose.

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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

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