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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 (PI) and Dr. David Borsook (Partnering PI)

CONTRACTING ORGANIZATION: Children's Hospital Corporation

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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, which is warranted given that approximately 1 in 10 women worldwide have endometriosis. 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 respects to the COVID-19 pandemic, while recruitment and data collection have been stalled, the research team has used this time to publish several papers related to the project, including the publication of the project's first review paper, with another currently under review and three papers in preparation (two reviews; preliminary resting state data) along with attending various webinars and trainings related to the project. Currently due to COVID-19, research imaging has limits. During this time the research team has been discussing alternatives to counteract the setbacks that the project is currently facing. Recent discussion includes the following ideas: Reaching out to Harvard Medical School (HMS) affiliated hospitals to aid in recruitment, adopting another imaging modality (*i.e.*, fNIRS) that does not have COVID-related restrictions, and exploring adding another research scanning site at one of the other HMS affiliated hospitals.

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

KEYWORDS

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

ACCOMPLISHMENTS

- c. *Major goals.* The major goals of the project fall under 3 specific aims.
 - i. **Specific Aim 1:** Brain metrics & psychophysics in adolescent, young adult & adult women with surgically confirmed endometriosis vs. healthy controls.
 - ii. Within Aim 1, the first major task completed was project set up, which was proposed to be completed within months one through four, at both Dr. Sieberg and Dr. Borsook's site.
- d. *Local Institutional Review Board approval:* Proposed to be completed within months 1-2. Approval was obtained in month 2 (April 8th, 2019), at Dr. Sieberg's site.
- e. *Purchase equipment for Offset Analgesia (OA) paradigm:* Proposed timeline for completion was during month one, at Dr. Borsook's site. The Medoc TSA 2 Neurosensory Analyzer was ordered and arrived to BCH (Waltham) on February 10th, 2020, programmed, and approved for use during the MRI brain scan by the MRI safety committee. A Hokanson E20 Rapid Cuff Inflation System was purchased and delivered to BCH Waltham on April 22nd 2020. Lastly, an E-Prime license was purchased for designing the graphical interface during the fMRI.
- f. *DoD HRPO Submission:* HRPO protocol was submitted on May 28th, 2019 and approved on July 2nd, 2019. Additionally, a HRPO Approval Memorandum stating the U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements on February 3rd, 2020.

- g. *Recruitment of Research Assistant/Post-Doctoral Fellow:* The RA and post-doctoral fellow have been hired. Claire Lunde, BA. BS the Research Assistant (RA) began October 2019 and Edina Szabo, PhD, the post-doctoral fellow began Jan 7th, 2020. Of note, Ms. Lunde is on Dr. Sieberg's budget while Dr. Szabo is on Dr. Borsook's. Ms. Lunde worked previously with the PI, Dr. Sieberg, on another grant and has extensive experience with administering Quantitative Sensory Testing (QST), a critical component of the current project. As part of her previous RA position, Ms. Lunde attended a training session for the German Research Network on Neuropathic Pain (DFNS), which aims to characterize the somatosensory phenotype of patients with neuropathic pain. She completed the standardized QST training, which will be used during this protocol. Ms. Lunde has experience in IRB preparation and maintenance, patient recruitment, and record keeping of study data. She is currently performing routine oversight of IRB protocols, will begin recruitment and enrollment of study participants in the coming weeks, and will coordinate scheduling of screening and scan session visits, ensure patients complete required forms for enrollment, participate in MRI scanning the subjects, collate imaging and non-imaging data on internal computers as well as appropriate backups and aid in processing biological samples (e.g., pregnancy tests). Dr. Szabo completed her PhD in psychology at Eötvös Loránd University in Hungary in November 2019. She has extensive experience in neuroimaging and has authored or co-authored 18 peer-reviewed publications in this area. She has been assisting Drs. Borsook and Holmes in setting up the imaging protocols to be used in this study, will oversee the neuroimaging components of data collection, and assist with data analyses. In addition, Natalie Cuccia, BS has been hired as a RA who began working on the project in August 2020. Ms. Cuccia is on Dr. Sieberg's budget. She has previously worked in Dr. Sieberg's lab as an undergraduate research intern during senior year at Simmons University. Throughout her time in the lab, Ms. Cuccia has been trained in Quantitative Sensory Testing by Ms. Lunde, conducted a QST protocol in prior studies, and has experience in participant recruitment along with data management and analysis. Ms. Lunde is currently a full-time doctoral student and has reduced her effort on the project. She is working with Ms. Cuccia (both at 50% effort) to finish project set up in regards to the new COVID-19 challenges, as well as train Ms. Cuccia in QST and the fMRI procedures.
- h. *Training of new RA, Post-Doctoral Fellow, and Student Interns on QST and Pain Psychophysics:* Ms. Lunde and Dr. Szabo have completed the 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. Ms. Lunde has mentored and trained all of Dr. Sieberg's graduate and undergraduate student interns on QST and pain psychophysics. Prior to hire, Ms. Cuccia has been trained on QST and pain psychophysics. Ms. Cuccia will begin training for neuroimaging protocols at BCH when BCH Radiology Department has certified their COVID-19 re-entry procedure (TBD).
- i. The second major tasks to be completed within Aim 1 are participant recruitment and enrollment.
- i. *Recruitment & Enrollment:* Recruitment has been postponed due to regulations of BCH and the State of Massachusetts, which is currently in a State of Emergency due to the current COVID-19 pandemic. In response, BCH prepares to reopen with an increase of clinical visits by expanding various safety measures to ensure the safety of patients and staff members on site. By following the guidelines provided by the CDC and the Massachusetts Department of Public Health throughout the pandemic, BCH has developed policies as a precaution. These policies include, but are not limited to: a universal mask policy, clinical care social distancing procedures, departmental staggering, staff symptom screening, and e-work when possible to limit in person

interaction. As of August 26, 2020 BCH, has extended the work from home order, when possible, until June 2021. Please refer to the Appendix D for specifics regarding BCH COVID-19 re-entry policies. In order to account for recruitment time lost, recruitment rates have been calculated and goals have been altered. In previous studies within the PAIN Group, an average of 84 participants are recruited per year for fMRI studies. While clinical research within the Radiology Department just re-opened, there are COVID-related restrictions such as the number of people allowed in the scanning area. A backlog of studies, due to COVID-19, is also anticipated to slow recruitment. Additionally, a new research imaging facility with new scanners is set to open at BCH in the Spring 2021. Unfortunately, it is not ideal to switch scanners during a study as there can be a risk of reliability if multiple scanners are being used throughout the duration of the study. This potential move may delay the anticipated recruitment start date. This would require approximately 3 scans per week through July 2023 to stay on target with the proposed recruitment goal of testing 187 participants and scanning 243.. All BCH COVID-19 policies are listed in the Appendix.

j. *Milestones achieved for Aim 1:*

- i. HRPO approval: HRPO protocol was submitted on May 28th, 2019 and approved on July 2nd, 2020. Additionally, a HRPO Approval Memorandum stating the U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements on February 3rd, 2020.
- ii. Review paper on mechanisms of endometriosis-associated pain: Drs. Sieberg, Borsook and Ms. Lunde published this review, entitled, *Endometriosis and pain in the adolescent-striking early to limit suffering: A narrative review*, in December 2019 in the journal *Neuroscience and Biobehavioral Reviews* (PMID: 3186211)
- iii. 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, has been submitted to the *Journal of Pain Research* and is currently under review (Authors: Lunde, Szabo, Holmes, Borsook, and Sieberg).
- iv. A second review paper (in preparation) will be submitted to the *Journal of Pain* in December 2020 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, Holmes, Cuccia, Sieberg, and Borsook).
- v. A paper (in preparation) on pilot fMRI resting state and psychological data on a cohort of young women with surgically confirmed endometriosis that will be submitted Fall 2020.
- vi. *Conduct experiments: brain imaging; QST and OA*. All equipment has been ordered and all training for the research team has been completed (except for Ms. Cuccia). A mock fMRI, QST, and OA test was previously scheduled for March 14 2020 but was cancelled due to COVID-19 but will be rescheduled for Sept or Oct 2020.

k. *Accomplishment under major goals:*

- i. *Opportunities for training and professional development:* Dr. Sieberg, Dr. Szabo, Dr. Borsook and Miss Lunde attended a talk and training by Dr. Robert Coghill on the use of Offset Analgesia (OA) in a MRI environment. Dr. Coghill is an expert pain researcher, specifically, in how the nervous system evaluates and constructs an experience of sensory components of pain, including perceived intensity and location. Additionally, the research team often attends relevant seminars and workshops, such as the recent *Pain Research Forum* virtual seminar on the impact and influence of descending modulatory controls.
- ii. *Reporting results to community of interest:* Nothing to report
- iii. *Plan for next reporting period to accomplish goals:* During the next reporting period (6 months: Sept 2020-Feb 2021), the following will be on-going or completed:
 1. Dr. Sieberg and Dr. Borsook (among others on the project) will co-author a review paper on the use of descending pain modulation in the clinic.
 2. Participant recruitment and enrollment was projected to begin in month 6 and conclude in month 32. The new projection for the recruitment will conclude in July 2023 (month 48). It was planned to recruit 66 endometriosis participants (including 10% attrition rate), who will be female patients with surgically confirmed endometriosis, as well as 66 healthy aged matched controls. For Specific Aim 2, 55 females (accounting for 10% attrition rate) presenting for surgery for endometriosis will be recruited and undergo 2 brain scans. Due to the COVID-19 pandemic, goals have been altered accordingly. During the next reporting period (6 months) September 2020- February 2021 the following will be on-going or completed:
 1. Patient recruitment will be underway along with a new detailed plan determined by BCH and the research team.
 2. A mock scan/test run will be completed (*i.e.*, brain imaging, QST, OA)
 3. Continue monitoring and conducting quality improvement.

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 surgically 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 responsiveness (progression, stasis or regression) or treatment effects and may have implications for understanding other chronic pain conditions. For example, in our 3rd aim, we will compare brain metrics of adolescents, young adults, and adult women with endometriosis in Aim 1 with female patients ages 12-44 with migraines in our existing databases who have undergone structural and functional MRIs. Migraine may parallel disease phenotypes to endometriosis in that it is a visceral pain that is intermittent in nature in its episodic form, involves inflammation, and it can chronify. We will compare the data from Aim 1 with existing data we have on age, brain metrics, and psychophysics in patients with migraines. Aim 3 will provide preliminary data for future planned research exploring the use of medications (e.g., triptans) for the treatment of migraines for the treatment of endometriosis.

- c. *Impact on technology transfer*: Nothing to report.
- 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.

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*: As of August 28th, 2020, The Emergency Management Team at BCH has approved reentry for experimental imaging, however, scheduling issues, imaging back-logs, and logistics have not been determined. In response to COVID-19, the research team has discussed the following 3 models as options for moving forward that would allow for more flexibility (but allowing us to address all the aims of the grant) as the foreseeable future is unpredictable:
 - 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 we are 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 anticipated new research imaging center with new scanners planned for the Spring of 2021, one possibility is to change the imaging site to another HMS affiliated hospital. To add an another site, the research team would need to submit to the IRB at BCH, a reliance IRB to new site, submit to HRPO, and add a subcontract for the new hospital (unless it is BWH as a sub-contract already exists. Dr. Borsook is an affiliated faculty member at Massachusetts General Hospital as well as McLean Hospital so exploring these hospitals in addition to BWH is worthwhile.

- iii. *Model 3: Switching from fMRI to Near Infrared Spectroscopy and Imaging (fNIRS).* fNIRS is a spectroscopic method that uses light in the near-infrared region of the electromagnetic spectrum. Near-infrared light (700-1000 nm) penetrates superficial layers (e.g., skin, subcutaneous fat, skull) and is either absorbed by chromophores (oxy- and deoxyhemoglobin) or scattered within the tissue. Similar to fMRI, fNIRS has been shown to be involved in pain processing. fNIRS data from previous projects from the Pain Group show that the fNIRS approach is an objective measure/indicator of pain/nociception that can be measured accurately and reproducibly. Dr. Borsook is an expert in fNIRS and formed this program of research at BCH. He has offered his equipment for this project. Switching testing modalities would increase flexibility (equipment is portable and can be done in Dr. Sieberg's lab thus avoiding scheduling issues with the Radiology Department). It is also less expensive and would not require a \$550 fee for each participant. Additionally, we believe that we could address the aims with the use of this technology. See attached summary of full description of fNIRS and comparison to fMRI.
- c. *Changes that had significant impact on expenditures:* None 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.

PRODUCTS

- a. *Publications, conference papers, and presentations:*
- i. *Journal publication:* Sieberg, CB, Lunde, C., & Borsook, D. Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review, *Neuroscience and Biobehavioral Reviews*, 2020, Jan: 108: 866-876. (PMID: 3186211)
 - ii. *Journal publication:* Lunde, CE., Szabo, E., Holmes, SA., Borsook, D., and Sieberg, CB. Commentary: Novel use of Offset Analgesia to assess adolescents and adults with treatment resistant endometriosis-associated pain (Currently under review, *Journal of Pain Research*)
 - iii. *Presentations:* Dr. Sieberg gave the following invited presentation as part of a symposium on Biological Influences on Adolescent Pain: Sex, Stress, and Inflammation at the International Symposium on Pediatric Pain in Basel, Switzerland in June 2019: *Chronic Pelvic Pain in Adolescents with Endometriosis: The Role of Psychophysical and Inflammatory Factors in the Development of Central Sensitization*
 - iv. *Books or other non-periodical, one-time publications:* Nothing to report.
 - v. *Other publications, conference papers, and presentations:* Nothing to report.
- b. *Website or other internet sites:* Nothing to report.
- c. *Technologies or techniques:* Nothing to report
- d. *Inventions, patent applications, and/or licenses:* Nothing to report.
- e. *Other products:* Nothing to report.

PARTICIPANT AND OTHER COLLABORATING ORGANIZATIONS

a. PI

Name:	Dr. Christine Sieberg
Project Role:	PI
Researcher Identifier:	0000-0003-1696-0340

Nearest month person worked:	9
Contribution to project	Dr. Sieberg is the Principal Investigator on the project. She is responsible for the coordination and execution of clinical aspects of the project at Boston Children's Hospital. She contributed to study design, and will contribute to data collection and statistical analyses. She is also managing IRB related processes that are carried out for all clinical aspects of the project and that clinical coverage is on site for each subject scan. She has also contributed to manuscript preparation.
Funding Support:	

b. Co-PI

Name:	Dr. David Borsook
Project Role:	Co-PI
Researcher Identifier:	0000-0001-9825-0064
Nearest month person worked:	12
Contribution to project	Dr. Borsook is the partnering PI on the project. Together with Dr. Sieberg, he oversees the project and integrates the clinical (oversight of clinical recruitment and patient coverage) and fMRI components. He is responsible for helping with the drafting and finalizing of all manuscripts.
Funding Support:	

c. Post-doctoral fellow

Name:	Dr. Edina Szabo
Project Role:	Post-doctoral PAIN Group Fellow
Researcher Identifier:	0000-0003-4087-5373
Nearest month person worked:	12
Contribution to project	She oversees the day to day project as it relates to patient flow, fMRI imaging and works with the RA (Claire Lunde) to ensure that the imaging and data collection are carried out appropriately. She is responsible for acquiring the data in collaboration with Dr. Borsook and Dr. Sieberg. In addition, is primarily responsible for the overall data analysis and will contribute to writing up results for future publications.
Funding Support:	Federal: US Department of Defense

d. Research Assistant

Name:	Ms. Claire Lunde
Project Role:	Research Assistant
Researcher Identifier:	0000-0001-5423-7677

Nearest month person worked:	12
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 (<i>e.g.</i> , pregnancy tests), and collating imaging and non-imaging data (<i>e.g.</i> , pregnancy tests). Additionally, Claire will train all new hires for the project.
Funding Support:	Foundation: Innovative Medicine Initiative-European Commission Federal: US Department of Defense

e. Research Assistant

Name:	Ms. Natalie Cuccia
Project Role:	Research Assistant
Researcher Identifier:	0000-0001-6483-9946
Nearest month person worked:	1
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 (<i>e.g.</i> , pregnancy tests), and collating imaging and non-imaging data (<i>e.g.</i> , pregnancy tests).
Funding Support:	Federal: US Department of Defense

- a. *Change in the active other support of the PD/PI or senior/key personnel since the last reporting period:* Dr. Jaymin Upadhyay has left the PAIN Group and has been replaced on this project by Dr. Scott Holmes, a faculty member in the PAIN Group. His work focuses on delineating pain pathways in pediatric cohorts and determining factors that predispose patients to elevated and prolonged pain responses. This replacement was approved by Stephanie Davis (DoD Grant Management Specialist) on 7/22/2020. No modification of the award was made and all documents were filed as a reference. Additionally, Dr. Amy Danehy has been added at 2% effort as a Radiologist to examine all brain scans for incidental findings, a requirement for any imaging protocol at BCH.

b. *Organizations involved as partners:*

A. Brigham and Women's Hospital

Organization name:	Brigham and Women's Hospital
Location of organization:	Boston, MA, US

Partner's contribution to the project	Collaboration with Dr. Marc Laufer (Co-PI)
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B. University of Michigan

Organization name:	University of Michigan
Location of organization:	Ann Arbor, MI, US
Partner's contribution to the project	Collaboration with Dr. Stacey Missmer (Co-PI)

SPECIAL REPORTING REQUIREMENTS

- c. *Collaborative awards:*
 - i. A duplicate report was submitted for Dr. David Borsook (Co-PI).

APPENDICES

- d. *Curriculum vitae:* Natalie Cuccia (Research Assistant)
- e. *Curriculum vitae:* Claire Lunde (Research Assistant)
- f. *Curriculum vitae:* Edina Szabo
- g. Biographical Sketch: Dr. Scott Holmes
- h. Published review paper titled: *Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review*
- i. Manuscript commentary titled: *Commentary: Novel use of Offset Analgesia to assess adolescents and adults with treatment resistant endometriosis-associated pain.* Currently under review at the Journal of Pain Research
- j. Boston Children's Hospital COVID-19 Policies
- k. Psychological questionnaires included in study protocol
- l. Boston Children's Hospital Institutional Review Board project approval letter
- m. Project narrative submitted in grant application
- n. Description of fNIRS and comparison to fMRI

Natalie Cuccia

Education

Simmons University, Boston, MA

Bachelors of Science in Neuroscience, Minor in Nutrition

May 2020

Experiences

Boston Children's Biobehavioral Pediatric Pain Lab

Clinical Research Assistant

August 2020-Current

Undergraduate Research Assistant

August 2019-May 2020

- Responding to Scientific Review comments/resubmission
- Programmed and launched Redcap for various projects
- Trained in Quantitative Sensory Testing (QST)
- Working with QST machinery (Medoc), Pressure Algometer, Von Frey
- Testing participants,
- Collecting data
- Data entry and coding using SPSS
- Flagging and recruiting participants in clinical settings using PowerChart and Epic

Boston Healthcare for the Homeless*

Jan 2020-March 2020

Undergraduate Intern

- Creating and implementing healthy interventions
- Educating Part-time residents on chronic disease prevention
- Creating a safe place for confidential conversation
- Acting as the liaison between Simmons students and Healthcare for the Homeless

Simmons University Psychology

Sep 2019-May 2020

Undergraduate Research Assistant

- Running Clinical Personality Research Study
- Working ECG machinery and Biopac software
- Collecting, analyzing, and interpreting data using SPSS
- Participant Recruitment

Neuroscience Liaison Executive Board Member

Sep 2019-May

2020

Head of Public Relations & Social Media Coordinator

- Attending/participating in weekly E board meetings and monthly liaison meetings
- Posting on various social media platforms, creating posters promoting on campus events
- Acting as the liaison between students and faculty to strengthen department relationship
- Active student mentor
- Acting as the liaison between Simmons students and Healthcare for the Homeless

Head Start Internship

Jan 2018-May

2018

Undergraduate Student Teacher

- Designing healthy intervention programs for preschoolers and their families
- Planning and coordinating with classroom teacher
- Student teaching in a bilingual classroom.

**Internship ended early due to Covid-19*

Recognitions

Simmons University Department of Psychology Honorable Recognition 2020

Curriculum Vitae

Name: Claire Elizabeth Lunde (she/her)

EDUCATION

University of Oxford Expected Completion Date: October 2022

St. Peters College
Oxford, England

- Candidate for Doctor of Philosophy in Women's and Reproductive Health
 - Medical Sciences Division
 - Supervisors: Dr. Katy Vincent, Dr. Elaine Fox, Dr. Christine Sieberg

American University

Graduated May 2018

Washington, DC

- Bachelor of Science, Public Health
- Bachelor of Arts, Psychology

Eastern Washington University

May 2012-2014

Cheney, WA

- Tested into Running Start program during Junior and Senior year of high school
- Completed 50+ credits, 47.57 credit hours transferred to American University

PUBLICATIONS

Sieberg, CB, **Lunde, CE.**, & Borsook, D. Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review, *Neuroscience and Biobehavioral Reviews*, 2020, Jan: 108: 866-876. (PMID: 3186211)

Lunde, CE., Sieberg, CB. Walking the Tightrope: A Proposed Model of Chronic Pain and Stress. *Frontiers Neuroscience*. March 2020. (PMID: 32273840)

Pielech, M., **Lunde, CE**, Becker, S., Vowles, K., and Sieberg, CB. Co-morbid chronic pain and opioid misuse in youth: Knowns, unknowns, and implications for behavioral treatment. *American Psychologist*. April 2020. (In press)

Lunde, CE., Szabo, E., Holmes, S., Borsook, D., & Sieberg, CB. Commentary: Novel use of Offset Analgesia to assess adolescents and adults with treatment resistant endometriosis-associated pain, *Journal of Women's Health Issues*. Currently under review.

Lisenbee, J., **Lunde, CE.**, Shih S., Dahl, A., Series 1: A Guide to Preconception Health Considerations. *Society of Behavioral Medicine: Healthy Living* (sbm.org/healthy-living). Currently under review.

MANUSCRIPTS IN PREPARATION

Updated: July 2020

Lunde, CE., Madraswalla, M., Cuccia, N., & Sieberg, CE. Systematic review: Prepartum, intrapartum, and postpartum physical and psychological predictors of negative vaginal childbirth experiences for mothers with low-risk pregnancies. *Expected submission: July 2021*

Lunde, CE., Demetriou, L., Cox, E. Evans, E., Zondervan, K., Becker, C., Garbutt, K., Invitti, A., Martinez-Burgo, B., Kvaskoff, M., Fox, E. & Vincent, K. Determining the impact of the COVID-19 pandemic on the physical and mental health of people with endometriosis. *Expected submission: September 2020*

Lunde, CE., Sieberg, C., Silva, K., Borsook, D., Ullrich, N., Manley, P., & Moulton, E. The long-term impact of cerebellar tumor resection on executive functioning, anxiety, and fear of pain: Mixed methodology. *Expected submission date: September 2020*

Lunde, CE., Fox, E., Sieberg, CB, and Vincent, K. Endometriosis and childhood trauma: A review. *Expected submission date: December 2020*

Szabo, E., **Lunde, CE.,** Holmes, S., Sieberg, CB., Borsook, D. Review of descending/endogenous analgesia in fMRI setting: Proposed model for endometriosis-associated pain. *Expected submission date: December 2020*

Sieberg, CB., **Lunde, CE.,** Olsen, H, Meints, S., Lunde, C. DiVasta, A., Missmer, S., Sethna, N. Abdominal normative values of quantitative sensory testing in healthy males and females. *Expected submission date: October 2020*

Lunde, CE., Spiegel, B., Gordon, C., & Sieberg, CB. Narrative review: Rethinking biological sex and gender in women's reproductive health - what do transmen need? *Expected submission date: October 2020*

ABSTRACTS AND POSTERS

Lunde, CE. Spreading suicide: A systematic analysis of suicide as a contagion among adolescents and young adults. College of Arts and Sciences 27th Annual Robyn Rafferty Mathias Student Research Conference, Washington, DC.

Murani, K., **Lunde, CE.,** Gunthert, KC., & Juliano, LM. The effects of daily caffeinated energy drink use and caffeine abstinence on sleep among young adults. Poster presentation at the Society of Behavioral Medicine's 39th Annual Meeting and Scientific Sessions, New Orleans, LA

Lunde, CE., Wong, Shafrir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Missmer, Coles, & Sieberg. Examining pain, psychosocial, and sensory factors in adolescents and young women with endometriosis. Society of Behavioral Medicine's 40th Annual Meeting and Scientific Sessions, Washington, DC

Lunde, CE., Wong, Shafrir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Coles, Missmer, & Sieberg. Helplessness, heightened pain sensitivity, and lower health-related quality of life associated with endometriosis-related pain in adolescents and young women. Boston Children's Hospital Program for Research Assistant Development and Achievement Grand Rounds, Boston, MA

Lunde, CE., Wong, Shafrir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Coles, Missmer, & Sieberg. Lower health-related quality of life associated with endometriosis-associated pain. Fenway Psychology Research Conference. Boston, MA

Lunde, CE., Wong, Shafrir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Coles, Missmer, & Sieberg. Heightened pain sensitivity associated with endometriosis-associated pain when compared to general abdomen pain sensitivity among males and females. Harvard Medical School, Department of Psychiatry. Boston, MA

Updated: July 2020

Lunde, C., Sieberg, C., Silva, K., Ullrich, N., Manley, P., & Moulton, E. Long-term impact of cerebellar mass resection on executive functioning, anxiety, and fear of pain: mixed methodology. Organization for Human Brain Mapping. June 2020

ORAL PRESENTATIONS:

Presented research at the College of Arts and Sciences 27th Annual Robyn Rafferty Mathias Student Research Conference. **Lunde, CE.** Spreading suicide: A systematic analysis of suicide as a contagion among adolescents and young adults. College of Arts and Sciences 27th Annual Robyn Rafferty Mathias Student Research Conference American University; April 2018

Presented research poster at Society of Behavioral Medicine's 39th Annual Meeting and Scientific Sessions. Murani, K., **Lunde, CE.,** Gunthert, KC., & Juliano, LM. Poster: The effects of daily caffeinated energy drink use and caffeine abstinence on sleep among young adults. Poster presentation at the Society of Behavioral Medicine's 39th Annual Meeting and Scientific Sessions. New Orleans, LA; March 2018

Presented research at the Program for Research Assistant Development and Achievement Grand Rounds: **Lunde, CE.,** Wong, Shafir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Coles, Missmer, & Sieberg. Helplessness, heightened pain sensitivity, and lower health-related quality of life associated with endometriosis-related pain in adolescents and young women. Boston Children's Hospital; December 2018

Invited to present preliminary project results at Boston Center for Endometriosis Research Team Meeting. Study title: Examining pain, psychosocial, and sensory factors in adolescents and young women with endometriosis. Boston Children's Hospital; February 2019

Presented research at Fenway Psychology Research Conference. **Lunde, CE.,** Wong, Shafir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Coles, Missmer, & Sieberg. Lower health-related quality of life associated with endometriosis-associated pain. Emmanuel College; March 2019

Presented research poster at Society of Behavioral Medicine's 40th Annual Meeting and Scientific Sessions. **Lunde, CE.,** Wong, Shafir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Missmer, Coles, & Sieberg. Abstract and poster: Examining pain, psychosocial, and sensory factors in adolescents and young women with endometriosis. Washington, DC; March 2019

Presented research at Harvard Medical School, Department of Psychiatry, 2019 Research Day. **Lunde, CE.,** Wong, Shafir, DiVasta, Smith, Huntley, Olsen, Dhole, Mosher, Missmer, Coles, & Sieberg. Heightened pain sensitivity associated with endometriosis-associated pain when compared to general abdomen pain sensitivity among males and females. Harvard Medical School; April, 2019

Frequently present recent research articles in Journal Clubs at Boston Children's Hospital and the University of Oxford

Will present abstract at the #WeAreAllInThis Together COVID-19 Journal Club. **Lunde, CE.,** Sieberg, CB., Silva, K., Ullrich, N., Manley, P., & Moulton, E. Long-term impact of cerebellar mass resection on pain processing, and cognitive and emotional sequelae: mixed methodology. August 2020

RESEARCH EXPERIENCES

Nuffield Department of Women's and Reproductive Health
Medical Sciences Division; University of Oxford, Oxford, England
Mentors: Dr. Katy Vincent

May 2020 – Present

Updated: July 2020

- Study Title: Determining the impact of the COVID-19 pandemic on the physical and mental health of people with endometriosis
 - Funding: None
 - Specific Aims:
Identify how the COVID-19 pandemic has impacted the access to healthcare and symptom management regimes for those with endometriosis. The impact of the pandemic has been assessed by specific questions assessing access to healthcare/treatments and change in symptoms.
 - Survey received +7200 responses in 5 different languages from +35 countries.
 - Role: **Primary Investigator as DPhil Student;** created survey; data collection; data management, data analysis, manuscript preparation

Center for Pain and the Brain

Feb 2019-Present

Department of Pediatric Oncology; Department of Anesthesiology
Dana-Farber Cancer Institute; Boston Children's Hospital, Boston, MA
Mentors: Dr. David Borsook, Dr. Eric Mouton, & Dr. Christine Sieberg

Project:

- Study Title: The Impact of Cerebellar Mass Resection on Pain Processing
 - Funding: National Institutes of Health (NIH): R21CA185870
 - Specific Aims:
 1. Define the short and long-term perceptual impact of posterior cerebellar damage on affective responses to noxious stimuli using quantitative sensory testing.
 2. Define the short and long-term functional and structural impact of posterior cerebellar damage on cortical and subcortical networks related to pain processing, using structural MRI, functional MRI, and diffusion tensor imaging.
 - Role: **Clinical Research Coordinator;** data management, data analysis, medical chart review, literature review, manuscript preparation

Biobehavioral Pediatric Pain Lab

July 2018-Present

Departments of Psychiatry, Anesthesiology, Perioperative, and Pain Medicine
Boston Children's Hospital; Boston, MA
Mentors: Dr. Christine Sieberg, Dr. Katy Vincent

Projects:

- Study Title: Translational Research in Pelvic Pain (TRiPP): Deep Phenotyping of Women with Endometriosis-associated Pain and Bladder Pain Syndrome
 - Funding: IMI-2 European Commission
 - Specific Aims:
 1. To develop tools that allow the stratification of chronic pelvic pain patients on the basis of the underpinning pathophysiological mechanisms.
 2. To develop refined preclinical models of Endometriosis Associated Pain and Bladder Pain Syndrome to allow rapid, efficient and relevant screening of novel therapeutic compounds with a high chance of clinical success.
 - Role: **Clinical Research Assistant;** coordinating IRB, obtaining/maintenance of equipment, multi-site coordination, recruitment, and data collection
- Study Title: Examining pain, psychosocial, and sensory factors in adolescents and young women with endometriosis.
 - Funding: Boston Center for Endometriosis and Marriott Foundation Investigator Award
 - Specific Aims:
 1. To categorize patients with endometriosis as either showing no/low central sensitization (CS) or high CS based on responses derived during Quantitative Sensory Testing (QST), and examine differences in clinical and psychosocial characteristics between these two groups.

Updated: July 2020

2. To identify sensory thresholds of the 4 abdominal quadrants in a healthy sample of adolescent and young adult women to both establish QST norms for the pelvic region and to have a comparison group to the women in our study.
- o **Role: Clinical Research Assistant**; coordinating IRB, overseeing undergrad and grad student interns; manuscript and grant preparation, participant recruitment, conducting QST, and database management.
- **Study Title:** Defining the Role for Descending Pain Modulation and Reward- Aversion Processes towards the Development of Chronic Pain in Endometriosis
 - o Funding: US Department of Defense
 - o **Specific Aims:**
 1. 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.
 - o **Role: Clinical Research Assistant**; coordinating IRB, manuscript and grant preparation, participant recruitment, conducting QST, fMRI training, and database management.

Behavioral Pharmacology and Health Promotion Lab

May 2017-May 2018

Department of Psychology

American University; Washington, DC

Mentors: Dr. Laura Juliano, Kristina Murani, Dr. Tommy Gunawan

Projects:

- **Study Title:** Placebo mechanisms underlying smoking behavior and relapse processes
 - o Funding: National Institute of Health (5RO1DA033235-03)
 - o **Specific Aims:**
 1. Employ Balanced Placebo Design and 10-day cessation smoking model to examine smokers' reactions to lapse cigarettes.
 2. Examine smokers' subjective, cognitive, and behavioral reactions to smoking while varying expected and actual nicotine does as well as the length of prior abstinence
 - o **Role: Undergraduate Research Assistant**; Participant recruitment, implementing study procedure, data management and analysis
- **Study Title:** Factors that influence caffeine physical dependence and withdrawal
 - o Funding: American University Psychology Master's thesis
 - o **Specific Aims:**
 1. Investigate the effects of caffeinated energy drinks and caffeine abstinence on sleep functioning among light caffeine users we utilized a 6 week, within-subjects design.

Updated: July 2020

2. Show a direct causal link between caffeinated energy drink consumption and poor sleep among young adults.
- o **Role: Undergraduate Research Assistant;** participant recruitment, conducting protocol, database management and organization, and data analysis

District of Columbia Food Policy Council

Jan 2018-May 2018

Washington, DC

Mentors: Laine Cidlowski; David Guyott; Dr. Jolynn Gardner

Project:

- **Executive Report Title:** Long and short term solutions for food access and food policies in DC.
 - o **Funding:** American University Public Health Capstone
 - o **Objective:** I helped to produce an Executive Report on food access and policy in DC, specifically in Wards 7 and 8. In summary, this report contained information on the successful and unsuccessful initiatives and policies undertaken in DC and other cities within the U.S. The conclusion of the project recommended long and short term initiatives that could be implemented by the DC Food Policy Council and are supported by the team's findings.
 - o **Role: Undergraduate Research Intern;** extensive literature review, community outreach, and manuscript preparation

Re-issuance of *RFK: His Words for Our Times*

June 2017-Sept 2017

Washington, DC

Mentor and Author: Richard Allen

Project:

- **Book Title:** *RFK: His Words for Our Times*
 - o **Objective:** I assisted in providing updated research on the Kennedy Family and all administrative duties for the re-issuance of *RFK: His Words for Our Times*, a celebration of Kennedy's life. In honor of the fiftieth anniversary of Robert Kennedy's legacy, I also helped to thoroughly edit and update this classic volume. The book includes a collection of his most famous speeches, accompanied by commentary from notable historians and public figures such as John F. Kennedy, Lyndon Johnson, Martin Luther King, Jr., and Cesar Chavez, among others. The tightly curated collection also includes commentary about RFK's legacy from major historians and public figures, among them Barack Obama, Bill Clinton, Eric Garcetti, William Manchester, Elie Wiesel, and Desmond Tutu.
 - o **Role: Research Assistant;** lead communicator, fact checking, and editing

American Association of Suicidology

Jan 2017 -May 2017

Washington, DC

Mentors: Dr. Amy Kulp; Sara Lycett

Project:

- Produced a variety of fact sheets, brochures, statistical reports, and resources for public and professional communities
- Assisted in the set-up of major conferences of research presentations and panels, training workshops, and interactive webinars.
- **Role: Undergraduate Research Intern;** Fact checking, manuscript editing, and administrative duties

SUPERVISION

Research Assistant at Boston Children's Hospital

2020 -Present

Biobehavioral Pediatric Pain Lab

Masters in Medical Sciences at Boston University

2020 -Present

Supervision team for 2 students; Boston Children's Hospital

Updated: July 2020

Masters in Medical Sciences at Boston University Supervision team for 2 students; Boston Children's Hospital	2019 -2020
BS in Neuroscience at Simmons College, final year internship Supervision team for 2 students	2019 -2020
Masters in Medical Sciences at Boston University Supervision team for 2 students; Boston Children's Hospital	2018 -2019
BS in Neuroscience at Simmons College, final year internship Supervision team for 2 students	2018 -2019

RESEARCH SKILLS

Analysis Tools

- SPSS
- RStudio
- GingerALE

Clinical Research

- Epic (electronic medical records system)
- PowerChart (electronic medical records system)
- REDCap (web-based data collection analysis software)

Scientific Writing

- Microsoft tools: Word, Excel, PowerPoint
- Reference software: Mendeley, EndNote, Zotero

Mentored Reviewer for the Following Journals:

- Journal of Pain
- Journal of Clinical Pain

Assisted with Grant Submissions

- Department of Defense
- National Institute of Health

LEADERSHIP EXPERIENCES

Program for Research Assistant Development and Achievement (PRADA)

Boston Children's Hospital; Boston, MA

A service-oriented learning community for research assistants and coordinators offering opportunities for education, professional development, networking, and community engagement.

- **Role: Program Co-Director;** Foster collaboration and communication among the PRADA Executive Board, consisting of ~30 research assistants and coordinators throughout the enterprise who coordinate PRADA programming, and a senior research faculty advisor. Design and administer program evaluation surveys and analyze, interpret and present results. Oversee annual program budget of \$5,000 and maintain records of all financial transactions. **Nov 2019 – Present**
- **Role: Grand Rounds Chair;** Organize and support hospital wide Grand Rounds; implement committee to review and accept research abstracts; host Grand Rounds event: August 2019 **March 2019 - Feb 2020**
- **Role: Pre-Med Co-Chair;** Organize year-round seminars, workshops, and lunches that coincide with the medical school application cycle in an effort to help members reach their education goals **Oct 2018 - Feb 2020**

Delta Gamma Fraternity

2016 - 2017

Updated: July 2020

American University; Washington, DC

- **Role: Director of Crews;** Coordinated and evaluated the effectiveness of the chapter's personnel structure

American University Juniors

2014 - 2015

American University; Washington, DC

- **Role: Founder and Director;** Program for youths to aid in closing the education gap in DC. Partnered with local non-profit to provide college advice to underprivileged youths in DC. Created courses for elementary, middle and high school students: Science, Geography, Art, and Business Etiquettes.

TEACHING EXPERIENCE

Biology 110 Laboratory Course

2015 - 2016

American University; Washington, DC

- **Role: Teachers Aid;** Assisted undergraduate Pre-Med students with Biology lab procedures and exams

Tutor

2016-2018

American University; assisted students with writing courses and essay submissions

HONORS/AWARDS/SCHOLARSHIPS

Graduate Student Award: St. Peter's College

February 2020

University of Oxford, Oxford, England

Dean's List

Spring 2017, Fall 2017, Spring 2018

American University; Washington, DC

Meritorious Abstract Award

April 2018

Society of Behavioral Medicine's 39th Annual Meeting and Scientific Sessions; New Orleans, LA

- Murani, K., **Lunde, CE.**, Gunthert, KC., & Juliano, LM. The effects of daily caffeinated energy drink use and caffeine abstinence on sleep among young adults.

Community Service Wonk Award

August 2014

Center of Diversity and Inclusion

American University; Washington, DC

Sisters Giving to Sisters Scholarship

2017 and 2018

Two time recipient

Delta Gamma Beta Epsilon

American University; Washington DC

Gloria Brown Scholarship

2014 - 2018

Four time recipient

American University; Washington DC

PROFESSIONAL MEMBERSHIPS

American Psychological Association

April 2019- Present

Graduate Student Affiliate

Leading scientific and professional organization representing psychology in the United States

Society of Behavioral Medicine

April 2019- Present

Updated: July 2020

Multidisciplinary, professional society working to improve health by changing behavior

PSI CHI

Sept 2017- Present

International Honor Society in Psychology

CURRENT CERTIFICATIONS

**Quantitative Sensory Testing Training by the German Research
Network on Neuropathic Pain**

2019 – Present

Characterize the somatosensory phenotypes of patients with neuropathic pain

Human Research

2018-Present

Behavioral Researchers Who Interact with Research Subjects
CITI Program

Protecting Human Research Participants

2017-Present

National Institute of Health Office of Extramural Research

REFERENCES

Available upon request

PERSONAL INFORMATION

Family name, First name: **SZABÓ, Edina**



EDUCATION

- 11/21/2019 *PhD in psychology (summa cum laude)*
ELTE Eötvös Loránd University, Budapest, Hungary
Supervisor: Dr. Kökönyei, Gyöngyi
- 2012 *Master in psychology*
ELTE Eötvös Loránd University, Budapest, Hungary

CURRENT POSITION(S)

- 2020 – *Postdoctoral research fellow*
Department of Anesthesiology, Critical Care and Pain Medicine
Boston Children's Hospital | Harvard Medical School, Boston, MA, USA

PREVIOUS POSITIONS

- 2018 – 2019 *Assistant research fellow*
MTA-SE-NAP 2 Genetic Brain Imaging Migraine Research Group, Budapest, Hungary
- 2017 – 2019 *Assistant lecturer*
ELTE Eötvös Loránd University, Budapest, Hungary
- 2015 – 2017 *Assistant research fellow*
MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Budapest, Hungary
- 2014 – 2015 *Research psychologist*
MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Budapest, Hungary

SCHOLARSHIPS

- 2017 – 2018 New National Excellence Program, Predoctoral Scholarship (Ministry of Human Capacities)
- 2010 – 2011 Erasmus Scholarship, International Studies in Psychology (MA), Warsaw University, Poland

TEACHING EXPERIENCES

Research Paper in Personality Psychology. As a PhD student and later as an assistant lecturer, I have supervised thesis work in the Hungarian and English bachelor (BA) program. During this course, the students take part in an empirical study and learn how to collect and analyse

data, and how to follow the rules of scientific publications.

Psychopathic aspects and self-control functions in adolescents. This BA course is aimed at students who would like to obtain a general overview of the psychopathic disorder and the developmental precursor to adult psychopathy, which is one of my main research topics.

RESEARCH EXPERIENCES

- 2019 – 2020 Anger rumination and addiction (supported by the ELTE Institutional Excellence Program; supervisor: Dr. Kökönyei, Gyöngyi)
- 2018 – 2019 Mental and somatic health among young people in the context of perseverative cognition (supported by the Hungarian National Research, Development and Innovation Office; Personality, Health and Emotion Regulation Research Group)
- 2018 – 2019 Comparison of brain mechanisms in migraine and tension type headache (supported by the Hungarian Brain Research Program; SE-NAP 2 Genetic Brain Imaging Migraine Research Group, supervisor: Dr. Juhász, Gabriella)
- 2015 – 2017 Functional magnetic resonance imaging (MRI) and genetic biomarker investigations in migraine (supported by the the Hungarian Academy of Sciences and the Hungarian Brain Research Program; SE-NAP B Genetic Brain Imaging Migraine Research Group, supervisor: Dr. Juhász, Gabriella)
- 2014 – 2015 Environmental and heritable factors in human depression: genomic and imaging approaches (supported by the Hungarian Academy of Sciences, Semmelweis University; MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, supervisor: Prof. Dr. Bagdy, György)
- 2013 – 2019 Callous-unemotional (CU) traits and their association with emotional processing (Doctoral School of Psychology, ELTE Eötvös Loránd University, supervisor: Dr. Kökönyei, Gyöngyi)

INVOLVED IN CO-EDITING

Hungarian Journal of Applied Psychology, 2016/4, Special Issue: Criminal Psychology.

AWARDS

- 2018 Sapere Aude Junior Award, ELTE Eötvös Loránd University
- 2017 ÚNKP-17-3-III-ELTE-346, New National Excellence Program of The Ministry of Human Capacities

RELEVANT SKILLS/TRAININGS

- 2019 Comprehensive Meta-Analysis (CMA) Software Workshop, ELTE Eötvös Loránd University, Budapest, Hungary
- 2018 Functional MRI of the Brain Software Library (FSL) Course, Oxford University, United Kingdom
- 2017 Introduction to R Programming Course, ELTE Eötvös Loránd University, Budapest, Hungary
- 2016 Statistical Parametric Mapping (SPM) Course, University College London, United Kingdom
- 2015

PUBLICATIONS

- Szabó, E.**, Galambos, A., Kocsel, N., Édes, A. E., Pap, D., Zsombók, T., Kozák L. R., Bagdy, Gy., Kökönyei, Gy., & Juhász, G. (2019). Association between migraine frequency and neural response to emotional faces: An fMRI study. *NeuroImage: Clinical*, 22. doi:[10.1016/j.nicl.2019.101790](https://doi.org/10.1016/j.nicl.2019.101790)
- Édes, A. E., McKie, S., **Szabó, E.**, Kökönyei, G., Pap, D., Zsombók, T., Hullám, G., Gonda, X., Kozák, L. R., McFarquhar, M., Anderson, I. M., Deakin, J. F. W., Bagdy, G., & Juhász, G. (2019). Spatiotemporal brain activation pattern following acute citalopram challenge is dose dependent and associated with neuroticism: A human phMRI study. *Neuropharmacology*, 107807. <https://doi.org/10.1016/j.neuropharm.2019.107807>
- Édes, A. E., McKie, S., **Szabó, E.**, Kökönyei, G., Pap, D., Zsombók, T., Magyar, M., Csépany, E., Hullám, G., Szabó, A. G., Kozák, L. R., Bagdy, G., & Juhász, G. (2019). Increased activation of the pregenual anterior cingulate cortex to citalopram challenge in migraine: An fMRI study. *BMC Neurology*, 19. <https://doi.org/10.1186/s12883-019-1478-0>
- Galambos, A., **Szabó, E.**, Nagy, Z., Édes, A. E., Kocsel, N., Juhász, G., & Kökönyei, Gy. (2019). A systematic review of structural and functional MRI studies on pain catastrophizing. *Journal of Pain Research*, 12, 1155–1178. doi:[10.2147/JPR.S192246](https://doi.org/10.2147/JPR.S192246)
- Kocsel, N., Galambos, A., **Szabó, E.**, Édes, A. E., Magyar, M., Zsombók, T., Pap, D., Kozák, L. R., Bagdy, Gy., Kökönyei, Gy., Juhász, G. (2019). Altered neural activity to monetary reward/loss processing in episodic migraine. *Scientific Reports*, 9. doi:[10.1038/s41598-019-41867-x](https://doi.org/10.1038/s41598-019-41867-x)
- Kocsel, N., Köteles, F., Szemenyei, E., **Szabó, E.**, Galambos, A., & Kökönyei, Gy. (2019). The association between perseverative cognition and resting heart rate variability: A focus on state ruminative thoughts. *Biological Psychology*, 145, 124–133. doi:[10.1016/j.biopsycho.2019.04.004](https://doi.org/10.1016/j.biopsycho.2019.04.004)
- Szabó, E.**, Halász, J., Morgan, A., Demetrovics, Zs., & Kökönyei, Gy. (2019). Callous-unemotional traits and the attentional bias towards emotional stimuli: Testing the moderating role of emotional and behavioural problems among high-risk adolescents. *Clinical Child Psychology and Psychiatry*. doi:[10.1177/1359104518822690](https://doi.org/10.1177/1359104518822690)
- Szabó, E.**, & Kökönyei, Gy. (2019). [Psychometric properties of the Inventory of Callous-Unemotional Traits in a high-risk sample of adolescent boys]. *Psychiatria Hungarica*.
- Szabó, E.**, & Kökönyei, Gy. (2018). [Measuring emotional processing in youth with psychopathic traits: Research review]. *Hungarian Journal of Psychology*, 73(2), 237–267. doi:[10.1556/0016.2018.73.2.6](https://doi.org/10.1556/0016.2018.73.2.6)
- Kökönyei, Gy., Galambos, A., Édes, A. E., Kocsel, N., **Szabó, E.**, Pap, D., Kozák L. R., Bagdy, Gy., & Juhász, G. (2018). Anticipation and violated expectation of pain are influenced by trait rumination: An fMRI study. *Cognitive, Affective & Behavioral Neuroscience*. doi:[10.3758/s13415-018-0644-y](https://doi.org/10.3758/s13415-018-0644-y)
- Szemenyei, E., Reinhardt, M., **Szabó, E.**, Szabó, K. G., Urbán, R., Harvey, S. T., Morgan, A., Demetrovics, Zs., & Kökönyei, Gy. (2018). Measuring psychological inflexibility in

children and adolescents: Evaluating the Avoidance and Fusion Questionnaire for Youth. *Assessment*. doi:[10.1177/1073191118796558](https://doi.org/10.1177/1073191118796558)

- Szabó, E.**, Kocsel, N., Édes, A., Pap, D., Galambos, A., Zsombók, T., Szabó, Á., Kozák, L. R., Bagdy, Gy., Juhász, G., & Kökönyei, Gy. (2017). Callous-unemotional traits and neural responses to emotional faces in a community sample of young adults. *Personality and Individual Differences*, 111, 312–317. doi:[10.1016/j.paid.2017.02.026](https://doi.org/10.1016/j.paid.2017.02.026)
- Magyar, M., Gonda, X., Pap, D., Édes, A. E., Galambos, A., Baksa, D., Kocsel, N., **Szabó, E.**, Bagdy, Gy., Elliott, R., Kökönyei, Gy., & Juhász, G. (2017). Decreased openness to experience is associated with migraine-type headaches in subjects with lifetime depression. *Frontiers in Neurology*, 8, 270. doi:[10.3389/fneur.2017.00270](https://doi.org/10.3389/fneur.2017.00270)
- Kocsel, N., **Szabó, E.**, Galambos, A., Édes, A. E., Pap, D., Elliott, R., Kozák, L. R., Bagdy, Gy., Juhász, G., & Kökönyei, Gy. (2017). Trait rumination influences neural correlates of the anticipation but not the consumption phase of reward processing. *Frontiers in Behavioral Neuroscience*, 11, 85. doi:[10.3389/fnbeh.2017.00085](https://doi.org/10.3389/fnbeh.2017.00085)
- Kocsel, N., Mónok, K., **Szabó, E.**, Morgan, A., Reinhardt, M., Urbán, R., Demetrovics, Zs. & Kökönyei, Gy. (2017). Gender invariance and psychometric properties of the nonproductive thoughts questionnaire for children. *Assessment*. doi:[10.1177/1073191117706140](https://doi.org/10.1177/1073191117706140)
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- Eisinger, A., Magi, A., Gyurkovics, M., **Szabó, E.**, Demetrovics, Zs., & Kökönyei Gy. (2016). [Iowa Gambling Task: Illustration of a behavioral measurement.] *Neuropsychopharmacologia Hungarica*, 18 (1), 45-55.
- Szabó, E.**, Galambos, A., Szabó, J., & Kökönyei, Gy. (2016). [The subtypes of psychopathic disorder: Primary and secondary variants]. *Hungarian Journal of Applied Psychology*, 16(4), 49–70. doi:[10.17627/ALKPSZICH.2016.4.49](https://doi.org/10.17627/ALKPSZICH.2016.4.49)
- Szabó, E.** (2015). Book reviews: Handbook on psychopathy and law. *Journal of Behavioral Addictions*, 4 (4), 319-322. doi:[10.1556/2006.4.2015.046](https://doi.org/10.1556/2006.4.2015.046)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Scott Alexander Holmes

eRA COMMONS USER NAME (credential, e.g., agency login): SCOTTHOLMES1

POSITION TITLE: Research Associate / Instructor in Department of Anesthesia, Critical Care and Pain Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
McMaster University, Hamilton, Canada	BSc	2009	Kinesiology
The University of Western Ontario, London, Canada	MSc	2012	Kinesiology – Neuroscience
McGill University, Montreal, Canada	PhD	2017	Neuroscience
McGill University, Montreal, Canada	Postdoc	2018	Neuroscience
Harvard Medical School, Boston, United States of America	Postdoc	2019	Neuroscience - Anesthesiology

A. Personal Statement

My research interests pertain to evaluating the factors that impair, mediate, and improve the interaction between human motor and sensory systems. The physical connections that carry a sensory stimulus through to a motor response are highly complex and may involve brain regions implicated in diverse processes such as affection and cognition. To date, research attention has been focused on understanding how sensory stimuli are processed, perceived and acted on through motor performance. Little attention has been devoted towards how motor performance can influence sensory processing and perception. This reciprocal perspective offers significant potential in terms of further understanding sensorimotor integration, and how disorders of sensation (e.g., chronic pain) may be treated through techniques such as neuromodulation and movement therapies. My research interests are focused around three domains: (1) evaluating how motor performance and sensory perception are impacted in sensory disorders at the behavioral and physiological levels, (2) evaluating the cross-network integration and hierarchy of motor regions within the brain and their relevance to sensorimotor behavior in health and disease, and (3) the efficacy of neuromodulation protocols to modulate the integration of sensorimotor networks with other brain regions to produce adaptive behaviors. I apply advanced statistics, including multivariate analyses, neuroimaging, psychophysics and neuropsychological testing to evaluate brain and behavior.

B. Positions and Honors***Committee Involvement***

2019- Boston Post-Doctoral Association - Board Member, Boston, Massachusetts, USA
 2013-2017 Institutional Review Board - Faculty of Medicine, McGill University, Montreal, Canada
 2011-2012 Levy Fund Committee Member; University of Western Ontario, London, Canada

Honors

2017	Canadian Traumatic Brain Injury Research Consortium Travel Award; Source: Canadian Traumatic Brain Injury Research Consortium; Value: \$1000
2015	endMS Travel Award; Source: endMS: Multiple Sclerosis Society of Canada; Value: \$500
2014	F. S. B. Miller Fellowship; Source: McGill University; Value: \$12,000
2014	endMS Travel Award; Source: Quebec-Ottawa RRTC; Value: \$700
2013	David G. Guthrie Fellowship; Source: McGill University; Value: \$12,000
2011	Kinesiology Travel Award; Source: University of Western Ontario; Value: \$520.00
2011	Western Graduate Research Scholarship; Source: University of Western Ontario; Value: \$11,300
2011	Kinesiology Travel Award; Source: University of Western Ontario; Value: \$700
2010	Western Graduate Research Scholarship; Source: University of Western Ontario; Value: \$11,300
2009	The McMaster Athletic Council Award; Source: McMaster University
2009	Sister Christine Gaudet Scholarship Fund and Dr. S. Gordon Ross Memorial Fund Award; Source: St. Michael's Hospital; Value: \$500
2008	Sister Christine Gaudet Scholarship Fund and Dr. S. Gordon Ross Memorial Fund Award; Source: St. Michael's Hospital; Value: \$1000

C. Contributions to Science

Neurosurgery Research Internship (May – July 2010)

Research during this internship was focused on understanding how psychometric measures are applied in the context of patients diagnosed with a traumatic brain injury. An emerging problem in the field related to the paucity of available tools for assessing TBI related traits such as aggression despite extensive literature to support its prevalence. Our goal during this internship was to evaluate the available clinical tools used to assess aggression in the clinical setting for their validity in the context of TBI. Findings outlined clinical recommendations based on a systematic review of the literature.

- a. Cusimano M, **Holmes SA**, Sawicki C, Topolovec-Vranic J (2014). *Assessing aggression in the Traumatic Brain Injury population: a systematic review of validated aggression scales. Journal of Head Trauma Rehabilitation.* 29(2): 172-84

Master's degree – The University of Western Ontario – 2010-2012

Research during my master's degree focused on understanding how visual systems contribute towards motor control under different environmental contexts. The two systems are predicated on the computation of relative (perception based – susceptible to illusions) versus absolute (used typically to support motor control as they compute the fine detailed dimensions of a target object) visual cues are inherently distinct and have significant differences in terms of their computational requirements and association with memory processes. Findings from my master's work have demonstrated that the use of visual cues during motor control is more dynamic than previously thought and reflects an integration of both systems during online motor control. Moreover, I was able to demonstrate that dimensionality (i.e., 2D and 3D targets) of an object will determine how we use different visual pathways in the brain. Results have garnered attention from researchers in Germany and the Netherlands to pursue similar work which has since become a major area of research in the sensorimotor neurosciences. This work has application towards virtual environments, human machine interfaces and understanding clinical disorders.

- a) Heath M, Jazi SD, **Holmes SA**. (2015). An inverse grip starting posture gives rise to time-dependent adherence to Weber's law. A reply to Ganel et al. *Journal of Vision.* 15(6): 1
- b) **Holmes SA**, Lohmus J, McKinnon S, Mulla A, Heath M. (2013). Distinct visual cues mediate aperture shaping for grasping and pantomime-grasping tasks. *Journal of Motor Behavior.* 45(5): 431-9.
- c) **Holmes SA**, Heath M (2013). Goal-Directed Grasping: The Dimensional Properties of an Object Influence the Nature of the Visual Information Mediating Aperture Shaping. *Brain and Cognition* 82(1):18-24
- d) Heath M, **Holmes SA**, Mulla A, Binsted G. (2012). Grasping time does not influence the early adherence of aperture shaping to Weber's law. *Frontiers in Neuroscience.* 6 (332)
- e) **Holmes SA**, Mulla A, Binsted G, Heath M. (2011). Visually and memory-guided grasping: aperture shaping exhibits a time-dependent scaling to Weber's law. *Vision Research.* 51(17): 1941-8

- f) Weiler J, **Holmes SA**, Mulla A, Heath M. (2011). Journal of Motor Behavior. Pro- and antisaccades: dissociating stimulus and response influences the online control of saccade trajectories. 43(5): 375-81.
- g) Heath M, Mulla A, **Holmes SA**, Smuskowitz L. (2011). The visual coding of grip aperture shows an early but not late adherence to Weber's law. Neuroscience Letters. 490 (3): 200-4

Doctoral degree – McGill University – 2012-2017

Research during my doctoral studies was concentrated on understanding the meaning of atypical brain activity observed in clinical populations. Debate existed in regard to understanding if this activity should be interpreted as adaptive or maladaptive. Researchers have called for a better understanding of brain mechanisms regulating functional adaptation. My research focused on a pathway in the brain responsible for performance monitoring and evaluating how this pathway was related to behavioral performance in the context of pathology to the brain in persons with multiple sclerosis (MS). I was able to demonstrate the significance of this pathway in maintaining general cognitive performance in the context of MS pathology. Findings from this research can be directly applied towards tracing pathways of adaptation in persons with MS and understanding the adaptive versus maladaptive nature of atypical brain activity. This work also calls for a paradigm shift in terms of how brain activity is evaluated in clinical populations. Currently whole brain analyses are performed; however, this research advocates for a hierarchical approach towards evaluating atypical brain activity based on considerations for mechanisms of adaptation. Findings highlight why some individuals are able to better adapt to their disease than others.

- a) Nantes J, Proulx S, Zhong J, **Holmes SA**, Narayanan S, Brown R, Hoge RD, Koski L. (2017). GABA and glutamate levels correlate with MTR and clinical disability: insights from multiple sclerosis. Neuroimage; doi: 10.1016
- b) Zhong J, Chen DQ, Nantes JC, **Holmes SA**, Hodaie M, Koski L. (2017). Combined structural and functional patterns discriminating motor disability in multiple sclerosis using multivariate approaches. Brain Imaging and Behavior 11(3): 754-768
- c) Zhong J, Nantes JC, **Holmes SA**, Koski L. (2016) Abnormal functional connectivity and cortical integrity influence dominant hand motor disability in multiple sclerosis: A multi-modal analysis. Human Brain Mapping. 37(12): 4262-4275
- d) Nantes JC, Zhong J, **Holmes SA**, Narayanan S, LaPierre Y, Koski L. (2016) Cortical damage and disability in multiple sclerosis: relation to intracortical inhibition and facilitation. Brain Stimulation. 9(4): 566-73
- e) Nantes JC, Zhong J, **Holmes SA**, Whatley B, Narayanan S, Arnold D, Koski L. (2015) Intracortical inhibition abnormality during the remission phase of multiple sclerosis is related to upper limb dexterity and lesions. Clinical Neurophysiology - doi:10.1016

Post-doctoral fellowship: Pediatric neurotrauma – McGill University – 2017-2018

Research during this fellowship was targeted at developing a diagnostic test for concussion in pediatric subjects. Because brain damage resulting from a mild traumatic brain injury is believed to be subtle, current clinical focus relies heavily on subjective symptom reporting for diagnosis. My efforts were targeted at understanding if a task could be developed to reliably identify individuals with a concussion by using functional magnetic resonance imaging (fMRI). Findings from our research showed that we were able to recreate trends in brain activity that were symptom level dependent in several cohorts of pediatric mTBI subjects. Application of this data will contribute towards validating a concussion test using fMRI and can be used to understand specific neuropsychological deficits in this population to improve return to play or school paradigms.

- a) Gagnon I, **Holmes SA**, Ptito A (2017) Introduction. Sports concussion: A complete guide to recovery and management. ISBN # 9781498701624. Publisher: CRC: A Taylor Francis Group
- b) Saluja RS, ***Holmes SA**, Chen J-K, Guberman G * **Shared first authorship**. Emerging diagnosis technology: What is coming up in terms of the use of imaging technology in concussion care? Sports concussion: A complete guide to recovery and management. ISBN # 9781498701624. Publisher: CRC: A Taylor Francis Group
- c) **Holmes, SA**, Saluja, RS, Chen, J-K, Gagnon, I, Ptito, A. (2018) Evaluating task-based brain network activity in pediatric subjects with an mTBI: mechanisms of functional compensation are symptom-level dependent. Brain Injury. DOI: 10.1080/02699052.2018.1552023.

Post-doctoral fellowship / Instructor: Pediatric pain disorders – Harvard Medical School – 2018 - Current

Research during this position is targeted at understanding pain mechanisms in the context of sensorimotor integration. My efforts are aimed at integrating neuropsychological, neurophysiological, and neuroimaging data using advanced statistical analyses to classify and understand abnormal brain structure and function in efforts to improve patient care. I divide my research time between two central projects: evaluating the factors that mediate the transition from acute to chronic pain in a neuropathic pain cohort; and classifying and understanding the progression of post-traumatic headache in pediatric concussion subjects. I have also completed projects relating to the use of neuroimaging to differentiate pain conditions using advanced imaging techniques. An improved understanding of the brain mechanisms that govern the remission and progression of pain symptoms will inform future patient care through biomarkers of chronic pain disorders and biomarkers for neuromodulation and pharmacotherapy.

- a) **Holmes SA**, Upadhyay J, Borsook D. (2019) *Delineating conditions and subtypes in chronic pain using neuroimaging*. PAIN Reports 4(4); e768
- b) **Holmes SA**, Barakat N, Bhasin M, Lopez N, Youssef A, Zurokowski D, Simons L, Burstein R, Borsook D. (2020) Acute painful nerve injury: Biological and Behavioral Markers of Pain following Nerve Injury in Humans. *Neurobiology of Pain* doi: 10.1016/j.ynpain.2019.100038
- c) McEvoy H, Borsook D, **Holmes SA**. (2019). Clinical Features and Sex Differences in Pediatric Post-Traumatic Headache: A Retrospective Chart Review at a Boston Area Concussion Clinic. *Cephalagia* doi:10.1177/0333102419896754
- d) Lemme J, **Holmes SA (*co-first author)**, Sibai D, Lebel A, Simons L, Burstein R, Upadhyay J, Borsook D. (2019). Altered Brain Network Connectivity between Pain Regions of the Brain Underlies Persistent Post-Traumatic Headache and Pain Symptoms in a Pediatric mTBI Cohort. Under Review at *Journal of Neurotrauma*.
- e) **Holmes SA**, Kim A, Borsook D. (2020). The Brain and Behavioral Correlates of Motor-Related Analgesia (MRA). Under Review: *Neurobiology and Behavioral Reviews*.
- f) **Holmes SA**, Staffa S, Karapanagou A, Lopez N, Karian V, Borra R, Zurakowski D, Lebel A, Borsook D. (2020) Biological Laterality and Peripheral Nerve DTI Metrics. Under Review: *Journal of Peripheral Nervous System*.

D. Additional Information: Research Support and/or Scholastic Performance

Recently Awarded Research Support

The David Borsook Project Fund Award.
2021

(PI: Holmes) 03/01/2020 –

Beyond pain: Evaluating how movement in the context of pain may promote analgesia.

The aim of this award is to evaluate how motor and sensory regions interact to determine pain levels in persons with a hyperkinetic movement disorder.

Role: Principle Investigator. Funds awarded: \$51,520

The Anesthesia Research Distinguished Trailblazer Award

(PI: Holmes) 03/01/2020 – 2021

Enhancing analgesia in chronic pain through exercise: Responsively of sensory-motor networks and factors that moderate the analgesic response.

The aim of this award is to evaluate how a physical activity paradigm modulates brain structure in motor and sensory regions in pediatric subjects with fibromyalgia.

Role: Principle Investigator. Funds awarded: \$25,000

Current Research Support

R01 NS095655

(PI: Borsook) 7/10/2015 – 5/13/2021

Post-Traumatic Headache in Children: Alterations of Brain Function, Blood Flow and Inflammatory Processes

The aim of this research program is to evaluate how headaches in persons with a mild traumatic brain injury are related to changes in blood flow and autonomic dysregulation.

Role: Co-Investigator

R01HD083133-01A1

(PI: Borsook) 4/17/2015 – 4/17/2021

Central and Peripheral Measures of Pain: Recovery and Resistance

The aim of this research program is to evaluate the extent to evaluate factors that influence the divergence of how neuropathic pain evolves and devolves in pediatric subjects with an ankle sprain injury.

Role: Co-Investigator

Department of Defense

(PI: Sieberg) 08/15/2019-08/14/2022

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

The aims are to define changes in brain structure and function as a correlate of subjective measures of pain and psychophysical functioning in adolescent, young adult and adult women with endometriosis and to longitudinally compare brain metrics pre and post-surgery.

Role: Co-Investigator

Invited talks

- 2019 *Understanding posttraumatic headache in youth with concussion: tracing the path of recovery.* The Translational Research Center for TBI and Stress Disorders (TRACTS), Veterans Affairs, Boston, MA, USA
- 2019 *How and acute painful stimulus may drive chronic brain changes: Understanding a brain in pain using multi-modal approaches.* Pain Division – Boston Children’s Hospital, Boston, MA, USA.
- 2018 *The use of machine learning in neuroimaging to identify migraine patients.* PAIN and the Brain Research Group; Harvard Medical School, Boston, USA.
- 2017 *The use of functional magnetic resonance imaging to evaluate adult and pediatric subjects with concussion.* Cognition and Circuits Lecture Series; McGill University, Montreal, Canada

Undergraduate Mentorship

- J. Kim Evaluating functional brain abnormalities in pediatric subjects with neuropathic pain. Boston University - 2019
- M. Dobra Evaluating the neuropsychological correlates of abnormal functional brain activity in pediatric subjects with post-traumatic headache. Northeastern University - 2019
- E. Rothman Evaluating the thermal sensitivity changes in an ankle sprain cohort with chronic neuropathic pain. University of Connecticut - 2019
- K. Carr Evaluating the impact of mild traumatic brain injury on thermal sensation in the trigeminal nerve – University of Rhode Island - 2019
- D. Phillips Evaluating the use of k-means clustering as a tool for data mining in the context of pediatric patients with an mTBI. Simons University – 2019
- C. White Evaluating the extent to which fear of pain is elevated in a pediatric cohort with neuropathic pain. Boston University - 2019
- C. Kennedy Evaluating working memory in pediatric mild traumatic brain injury. McGill University - 2018

Graduate Mentorship

- J. Lemme Evaluating task-related brain activity during a working memory task in patients with post-traumatic headache patients. The University of New England - 2018
- G. Guberman Evaluating white matter pathology in pediatric subjects using advanced diffusion weighted imaging. McGill University - 2018

Reviewer and Teaching Experience

Grant Reviewer

Netherlands Organization for Scientific Research

Journals reviewed for

Pain

Journal of Military, Veteran and Family Health

Scientific Reports

Teaching Assistant (2010 - 2012); University of Western Ontario; London, Canada

Class: Introduction to Psychomotor Behavior (Class size: Apr. 500); Professor: Dr. Matthew Heath, PhD

Class: Movement Neuroscience (Class size: Apr. 60); Professor: Dr. Matthew Heath, PhD

Class: Sport Psychology (Class size: Apr. 400); Professor: Dr. Bob Larose, PhD

Class: Introduction to Psychomotor Behavior (Class size: Apr. 400); Professor: Dr. Matthew Heath, PhD

RUNNING HEAD: Novel use of OA to assess EAP

Title: Commentary: Novel use of Offset Analgesia to assess adolescents and adults with treatment resistant endometriosis-associated pain

Authors: Claire E. Lunde,^{1,2,5} Edina Szabo,^{1,4} Scott A. Holmes,^{1,4} David Borsook,^{1,4} & Christine B. Sieberg¹⁻³

Ms. Lunde and Dr. Szabo both equally contributed to first authorship of this manuscript

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2. Biobehavioral Pediatric Pain Lab, Department of Psychiatry, Boston Children's Hospital, USA
3. Department of Psychiatry, Harvard Medical School, USA
4. Department of Anesthesiology, Harvard Medical School, USA
5. Nuffield Department of Women's and Reproductive Health, Medical Sciences Division, University of Oxford, UK

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David Borsook: David.borsook@childrens.harvard.edu

Abstract

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 to better elucidate the neural mechanisms that may contribute to and maintain EAP – offset analgesia (OA). This commentary will provide justification and rationale for the use of OA in the study of EAP.

Conclusions: 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.

1. **Endometriosis and Pain**

Endometriosis, a debilitating condition in which uterine tissue grows outside the uterus, affects approximately 176 million adults and adolescents worldwide (Simoens et al., 2012) and costs the US economy approximately \$78 billion annually in pain-related disability (Soliman, Surrey, Bonafede, Nelson, & Castelli-Haley, 2018). 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) (Bourdel et al., 2019). 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 (Abbott et al., 2004). Despite 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 (Lamvu et al., 2019). Endometriosis in adolescents is an even more challenging clinical 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 the disease, and direct effective therapies at an early age (Sieberg, Lunde, & Borsook, 2020). Small pilot studies (As-Sanie et al., 2012, 2016) 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. As the onset of this condition may begin before menarche

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(Brosens et al., 2016; Dowlut-McElroy & Strickland, 2017) and adult women report their symptoms beginning during adolescence (Ballweg, 2003), 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 that is considered one of the central mechanisms facilitating (or preventing) pain and contributing to pain chronification.

2. 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 (*i.e.* 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 (Sieberg et al., 2020). Studies reflecting changes in the CNS have found increased sensitivity to pain within and outside of the areas of CPP 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 (As-Sanie et al., 2012, 2016). 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

RUNNING HEAD: Novel use of OA to assess EAP

the endogenous pain modulation system (As-Sanie et al., 2012). Such findings support the notion that the alterations in the central processing of pain likely contribute to CPP in endometriosis.

3. Offset Analgesia in Experimental Settings

OA was first defined by Grill and Coghill (2002) 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. 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 (*i.e.* 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 (Nahman-Averbuch et al., 2014). In addition, OA seems to be largely related to activation in brain regions involved in pain modulation (*i.e.* PAG, dorsolateral prefrontal cortex, anterior insula, brainstem) whereas CPM reduces pain mainly through a spinally mediated mechanism (Nahman-Averbuch et al., 2014). OA is increasingly used to measure endogenous pain inhibition because, 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 (Hermans et al., 2016). Current adolescent studies utilize Quantitative Sensory Testing (Rolke et al., 2006), set of psychophysical methods to assess pain sensitivity and sensory nerves, to produce measures of ongoing CNS and Peripheral Nervous System sensitization, which has been the main focus in the field. General chronic pain (Tham et al., 2016), complex regional pain syndrome (Sethna, Meier, Zurakowski, & Berde, 2007), migraines (Zohsel, Hohmeister, Oelkers-Ax, Flor, & Hermann, 2006), abdominal pain (Duarte, Goulart, & Penna,

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2000), sickle cell disease (Brandow, Stucky, Hillery, Hoffmann, & Panepinto, 2013; O’Leary, Crawford, Odame, Shorten, & McGrath, 2014), fibromyalgia (King et al., 2017), juvenile idiopathic arthritis (Cornelissen et al., 2014) and cerebral palsy (Blankenburg et al., 2018), 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 (Brawn, Morotti, Zondervan, Becker, & Vincent, 2014) have suggested that the central effects should be further explored, the use of OA could provide insight to the underlying neural mechanisms and persistence of CPP.

OA has also been examined in MRI setting (Derbyshire & Osborn, 2009; Yelle, Oshiro, Kraft, & Coghill, 2009; Yelle, Rogers, & Coghill, 2008; Zhang et al., 2018), typically using the 3-temperature paradigm (**Figure 1**) (Grill & Coghill, 2002) defined by a rating of 5 out of 10 on a visual analog scale (VAS). Using a thermal stimulator which is placed in contact with the skin, a preset computer-controlled temperature paradigm delivers the specific temperature pattern. A response to this dynamic test stimulus 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. Notably, this standard 3-temperature paradigm has not been tested on children or adolescents who may require a substantially lower temperature to achieve 50% of maximal heat pain perceived by individual patients. Subjects then rate heat pain intensity continuously in real time in proportion to their pain intensity during fMRI testing. The magnitude of OA is quantified by the difference (or by the percentage of difference) between the highest VAS scores during the dynamic stimulus and the lowest VAS scores during the controlled stimulus.

4. Offset Analgesia as a Clinical Tool

Recent studies reported decreased or absent OA responses in patients with chronic pain disorders. More specifically, significant difference have been observed between control subjects and patients with fibromyalgia (Oudejans, Smit, Van Velzen, Dahan, & Niesters, 2015), neuropathic pain (Niesters, Hoitsma, Sarton, Aarts, & Dahan, 2011), migraine (Szikszay, Adamczyk, Carvalho, May, & Luedtke, 2020), and chronic pain of various etiologies (Kobinata et al., 2017; Zhang et al., 2018). In addition, three studies focusing only on chronic patients indicated decreased OA responses in patients with diabetic polyneuropathy, knee osteoarthritis (Niesters et al., 2014) and chronic radicular pain (although there was a large interindividual variation (Niesters et al., 2011; Petersen, Simonsen, Olesen, Mørch, & Arendt-Nielsen, 2019; Suzan, Treister, Pud, Haddad, & Eisenberg, 2015)). 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**). Notably, some of these studies also reported that OA responses could not be modified in patients with chronic pain by analgesics such as ketamine, morphine (and placebo (Niesters et al., 2011)), NSAIDs and acetaminophen (Petersen et al., 2019), tapentadol (Niesters et al., 2014), and hydromorphone (Suzan et al., 2015). In the study by Zhang et al. (2018), functional magnetic resonance imaging (fMRI) was used to investigate brain activations to the attenuated OA effects in patients with various chronic pain disorders. Compared to healthy controls, reduced brain

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activation was found in regions associated with the descending pain modulatory (anterior cingulate cortex, dorsolateral prefrontal cortex) and reward systems (medial prefrontal cortex, putamen, nucleus accumbens). Based on these studies, the attenuated OA responses found in patients with chronic pain indicate the 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.

5. Offset Analgesia in Endometriosis

Although OA response has been found to be attenuated in patients with various chronic pain conditions, it is unknown in CPP and endometriosis. With ongoing pain (intermittent or constant) alterations in the sensitivity/responsivity of neural networks encompass those beyond the classic sensory pathways (*i.e.* 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 (Simons, Elman, & Borsook, 2014). 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 multi-faceted 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 robustness of measured OA would thus be a reflection of an altered brain system in

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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 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.

6. 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 effected by different analgesics, the reported clinical pain intensity decreased after treatment (Niesters et al., 2011; Petersen et al., 2019; Suzan et al., 2015), 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 (CBT) 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

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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.

7. 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 CPP. The 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 EAP within adolescents and adults with endometriosis is of great

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importance and the proposed utilization of OA as a new approach for pain treatment will move the field of female reproductive health forward.

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Massachusetts Department of Public Health State of Emergency: Updates, Emergency Order & Guidance

On March 10, Governor Charlie Baker declared a state of emergency.

Boston Children's Hospital Research Reopening Procedures and Phases

Clinical Research- The following has been taken from the BCH Clinical Research Restart Plan

Clinical research is a complex enterprise that occurs in many locations in and around the BCH campus. With that in mind, the following considerations were incorporated into the policies:

- Location of research: Clinical research participants are evaluated in typical clinical settings, a small number of ambulatory clinical research units (i.e., Experimental Therapeutics Unit) as well as a small number of non-clinical environments (Autumn St., Boylston Ave.)
- Type of research: Interventional studies that offer a possibility of direct benefit (therapeutic trials) and non-interventional research, including surveys and biorepositories.
- COVID-19 related research: Research related specifically to COVID-19 is overseen by the Coronavirus Research Oversight Committee (CROC) and subcommittees, including the COVID-19 Scientific Review Committee.
- Impact on clinical operations: Early phases of this plan have been developed to minimize the impact clinical research has on clinical operations (particularly in the ambulatory settings).
- Study Team considerations:
 - o The health and safety of the BCH community—our patients as well as our study teams—is our highest priority and is a primary driver of this phased approach. Every effort should be taken to minimize the number of on-site study team members; particularly limiting time spent in clinical settings.
 - o Study teams will be expected to follow hospital policy as it relates to the proper use of PPE, both in the clinical settings and in non-clinical environments. A required training is being developed to assist in this process.
- Institutional Review Board (IRB):
 - o The IRB is continuing to accept and process all submissions, even if they're not related to coronavirus research. Approval by the IRB is not endorsement that the clinical research activity may begin. All clinical research activities must follow the Hospital's policies for reopening clinical research.
 - o Investigators conducting research under a reliance agreement of an external IRB must still follow the Hospital's policies for reopening clinical research activities. In addition, investigators need to be certain that reopening of any research is also in accordance with any restrictions of the reviewing IRB.
 - o The restriction to not allow research subjects who may be on a placebo to return for hospital visits remains in place until further notice. Research protocols that include placebos that cannot be replaced by all remote interactions/assessments for drug administration, assessments and safety evaluations must continue to be discussed with the IRB on an individual basis. Please contact Susan Kornetsky to discuss your individual situation. The IRB will continue to evaluate when this restriction may be lifted.

In developing these phases, the following concepts were prioritized:

Phase I	• Expansion of interventional trial enrollments • Limited restart of non-interventional studies if required evaluations do not impact clinical operations or increase COVID-19 exposure risk.
Phase II	• Reopening of non-clinical settings to study subjects (1 & 21 Autumn St. and 1295 Boylston St.) • Expansion of non-interventional enrollments and patient-facing personnel • Expansion of allowable evaluations in all studies • Relaxed restrictions on study subject movement around hospital
Phase III	• Further expansion of non-interventional enrollments • Further expansion of allowable evaluations in all studies
Phase IV	• Full operations (New normal) • No restrictions on study personnel (except in setting of COVID-19 + subjects)

Clinical Research Restart (non-COVID-19 Research) Ambulatory Settings		
Phase	Allowable Visits & Evaluations[#]	Study team personnel who can physically interact with subject[†]
Interventional Therapeutic Studies (including compassionate use access studies)[§]		
I	• Subjects with COVID-19 may not enroll onto interventional studies unless one of the following conditions is met: ◦ Subject has cleared COVID-19 precautions ◦ Study is for treatment of a life-threatening condition or malignancy ◦ Study is related to COVID-19 research^{††} • In-person visits <i>must</i> include one of the following ◦ Drug/device administration ◦ Required safety or efficacy evaluations ◦ Other required evaluation related to primary study aims • Additional evaluations related to secondary study aims may be obtained during visit as long as they do not: ◦ Significantly prolong visit ◦ Require subject moving to another clinical location for the <i>sole</i> purpose of these evaluations • Evaluations related to exploratory aims and optional study evaluations are not permitted during Phase 1 unless: ◦ the evaluation is a patient sample or test that can be added on to a previously scheduled venipuncture or procedure.	• Licensed personnel • Limited non-licensed personnel*
II	• Subjects with COVID-19 may not enroll onto interventional studies unless one of the following conditions is met: ◦ Subject has cleared COVID-19 precautions ◦ Study is for treatment of a life-threatening condition or malignancy ◦ Study is related to COVID-19 research^{††} • In-person visits <i>must</i> include one of the following ◦ Drug/device administration ◦ Required safety or efficacy evaluations ◦ Other required evaluations related to primary or secondary study aims • Evaluations related to exploratory aims and optional study evaluations may be obtained as long as they do not: ◦ Significantly prolong visit ◦ Require subject moving to another clinical location for the <i>sole</i> purpose of these evaluations	• Licensed personnel • Limited non-licensed personnel*
III	• As in Phase II with the following additional allowances ◦ All required and optional evaluations are allowed	• Licensed personnel • Limited non-licensed personnel*
IV	• No restrictions	• No restrictions*

Clinical Research in Non-Clinical settings (non-COVID-19 research) Clinical research taking place in non-clinical settings pose unique challenges with complying with COVID19 restrictions. These settings include 1 Autumn St., 21 Autumn St. and 1295 Boylston St. and in some rare instances, basic/translational laboratories. Bringing study subjects back into these locations will require additional infrastructure to ensure best practices are taking place in the setting of the pandemic. We are actively exploring these needs and the policies below are tentative and require further development. During Phase I, no on-site study subject visits or evaluations may occur in non-clinical settings.

Clinical Research Restart (non-COVID-19 Research) Non-Clinical Environments (Autumn St, Boylston St., Longwood Center)			
Phase	Allowable Visits & Evaluations	New Enrollments?#	Study team personnel who can physically interact with subject†
Non-interventional Studies (no direct benefit to subjects through therapeutic intervention), including Biorepositories			
I	- No on-site visits allowed - Remote and virtual visits allowed	Yes; remote or e-consent only	No face-to-face encounters
II	- In-person visits are allowed if all of the following are met: - Virtual visit is not feasible - Required evaluations are related to primary study aims - Patient does not have COVID-19 or has cleared precautions if previously positive.†† - Evaluations related to other study aims may be obtained as long as they do not: - Require subjects to move to another clinical location - Optional studies should not be performed on-site during Phase II	Yes; remote consent is encouraged	- Licensed personnel - Limited non-licensed personnel*
III	- As in Phase II with the following additional allowances - All required and optional evaluations are permitted. - Patient does not have COVID-19 or has cleared precautions if previously positive. ††	Yes; remote consent is encouraged	- Licensed personnel - Limited non-licensed personnel*
IV	No restrictions	Yes	No restrictions
* Non-licensed personnel may not physically interact with any subject with a history of COVID-19 until the subject has cleared COVID-19 precautions. # Refer to “Consenting Practices” section below. † Refer to Appendix A. †† COVID-19 related research is covered below			

Guide to Developing an Ambulatory Clinical Research reopening plan in NonClinical Buildings

Planning will be vitally important to the success of your clinical research unit operations reopening. You will need to ensure social distancing and the safety of your staff and study subjects when developing your plan. Please refer to the internal BCH website for the Overarching Guidance for Reentry as well as detailed information regarding PPE, Symptom Attestation Options, visitor policy, and other useful tools and checklists. Below is a set of recommendations to help you create a robust plan for resuming your clinical research operations.

- Open incrementally: Consider a step-wise approach to reopening so that the clinical research unit may quickly identify and address any challenges presented. Identify what visits can be done or should continue to be performed remotely. Begin with a few in-person visits a day, working on a modified schedule. Communicate your weekly schedule clearly to your staff.
- Institute safety measures for study subjects: To ensure that subjects are not coming into close contact with one another, utilize a modified schedule to avoid high volume or density. Consider a flexible schedule, with perhaps a longer span of the day, with more time in-between visits to avoid backups.
- Ensure workplace safety for all employees: Contact BCH facilities to implement social distancing and safety protocols in your clinical research unit, such as rearranging common areas to increase the distance between subjects, install plexiglass, etc.
- Environmental Services: Establish open communication with Environmental Services regarding cleaning schedules and protocols regarding shared spaces. 857-218-5118 (x85118)
- Pre-screen subjects before in-person visits: Clinical research staff should screen all subjects and parents for symptoms prior to each visit per BCH policy and at the time of arrival. During the screening call, direct all subjects to an attestation location to be screened for symptoms and to pick up a BCH mask. If subjects and parents are symptomatic, please reschedule their in-person visit 14 days out.
- Room Log: Implement a paper log system to track all people entering an exam/test room, including study personnel, study subject, and parent. Limit entries to rooms to essential members only.

All Plans should address the following:

1. Adherence to Boston Children's Hospital infection control practices: Social distancing using physical barriers and cues are in place, as well as reminders regarding wearing masks and staying 6-feet apart whenever possible.
2. Training of staff must include the following 4 elements (a-d), as well as others specific to the particular clinical program:
 - a) Pre-screening all patients 24-48 hours prior to coming to the hospital and a plan of how they will manage patients who screen positive prior to the visit (i.e. convert to virtual, reschedule or see in the appropriate PPE)
 - b) Cleaning of high-touch surfaces between patients
 - c) Staff must wear an ear-loop mask except when eating, drinking or alone in a private office
 - d) Patients, families and visitors are strongly encouraged to wear an ear-loop mask except when eating, drinking or alone in a room
3. Staff have been trained on how to access the COVID-19 internal web page, AOD advisories, and other sources of current information on infection control practices Subject tracking: All clinical research visits will need to be tracked and reported to the main hospital. Study teams are expected to report study subject visits at least a day in advance using this link. Data reported should be aggregated by floor so that no PHI data will be collected. Submitting your Plan Each Department/Division should develop reentry plans for each ambulatory location. Individual PI's or study teams should not individually submit plans but should work within their Dept/Div to develop the plan. Prior to submission, these plans should be reviewed and vetted by the appropriate Departmental/Divisional leadership (Chair/Chief, Research Director or other designee) prior to the plan being submitted for review by Hospital Leadership.

Mask Distribution Stations

There is a new Mask Distribution Station in the lobby of 1 Autumn. Staff coming into this location will have to use the Mobile Symptom Attestation App to attest to their symptoms prior to receiving a mask. Staff should have their phone ready to show the screener that they are cleared to come to work. This location will be open from 6:30am-10:30am Monday-Friday. Staff can receive a mask from the other mask distribution stations outside of that timeframe. These locations include:

- Main Hospital (shuttle bay, front door, patient family garage bridge)
- Waltham lobby
- Karp Lobby
- 333 Longwood Ave

Research Scanning:

1. The Boston campus would be restarted in two stages:
 - o Stage I would allow 2 evenings, totaling 5 hours a week, at Binney 7. This area is remote and social distancing guidelines could be easily followed due to the large workspace.
 - o Once Stage I is successful Stage II would include expanding to 5 evening a week, 12.5 hours with access to the Binney 2 Prisma. The Binney 2 Prisma will only allow one researcher due to social distancing guidelines and the amount of workspace.
2. Waltham would allow the previous MRI research imaging schedule of Monday through Saturday to be activated. Due to the restricted work space, a technologist would have to vacate Zone III to allow the occupancy of 1 researcher from the study. Only 1 researcher will allowed at the exam for the appointment duration.
3. In the Waltham, Peabody, and Weymouth sites for all other modalities (CT, ultrasound, x-ray) only 1 researcher would be allowed in the waiting area with the participant.
4. In order to safely image research participants during COVID-19 recovery, researchers will be required to adhere to the institution's PPE and social distancing policies along with the screening of participants. Prior to any participant entering the institution the principal investigator is responsible for contacting the participant within 72 hours of their scheduled imaging appointment to perform the MRI safety screening form and the COVID-19 screening form.
5. Any research participant who is screened and communicates positive symptoms will not be allowed at the institution and their appointment should be immediately cancelled. Any appointment cancelled due to COVID-19 related symptoms or illness will not be charged.
6. All pre-imaging assessments are no longer allowed to be performed in pre-procedure rooms. In Waltham these assessments will take place in the Mock MRI area and testing rooms. In Boston these assessments will need to be coordinated with modality leadership.

7. On the day of the imaging event, one researcher is permitted to accompany the participant and only one parent/guardian. The researcher is required to provide both screening forms to the imaging technologist.
8. In Waltham due to social distancing guidelines if the exam requires the researcher to occupy Zone III or Zone IV one clinical technologist will vacate the control room. Whomever the researcher who accompanies the patient to the appointment must be the same person occupying Zone III or Zone IV. *Researchers cannot substitute out during the imaging appointment. To limit exposure, it must be the same researcher at the exam for the duration of the appointment.* Two Level IV (super users) trained personnel may scan a human subject.
9. All PPE, social distancing, and sanitizing policies put forth by the clinical department will be followed by all researchers. Any researcher in violation of this policy or any of the clinical policies will have their badge access revoked.

Perceived Stress (Ages 13-17) – Item Bank/Fixed Form

Please respond to each question or statement by marking one box per row.

In the past month...		Never	Almost Never	Sometimes	Fairly Often	Very Often
SC011	How often have you been angered because of things that happened that were outside of your control?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC014	How often have you felt difficulties were piling up so high that you could not overcome them?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC007	How often have you felt that things were going your way?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC001	How often have you been upset because of something that happened unexpectedly? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC009	How often have you been able to control irritations in your life?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC002	How often have you felt that you were unable to control the important things in your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC003	How often have you felt nervous and “stressed”?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC010	How often have you felt that you were on top of things?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC008m	How often have you found that you could not handle (OR manage) all the things that you had to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC006	How often have you felt confident about your ability to handle your personal problems?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Perceived Stress (Ages 18+) – Item Bank/Fixed Form

Please respond to each question or statement by marking one box per row.

In the past month...		Never	Almost Never	Sometimes	Fairly Often	Very Often
SC001	How often have you been upset because of something that happened unexpectedly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC002	How often have you felt that you were unable to control the important things in your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC003	How often have you felt nervous and “stressed”?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC006_R	How often have you felt confident about your ability to handle your personal problems?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC007_R	How often have you felt that things were going your way?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC008	How often have you found that you could not cope with all the things that you had to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC009_R	How often have you been able to control irritations in your life?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC010_R	How often have you felt that you were on top of things?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC011	How often have you been angered because of things that happened that were outside of your control?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC014	How often have you felt difficulties were piling up so high that you could not overcome them?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5



36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- ☐ 1 - Excellent
 - ☐ 2 - Very good
 - ☐ 3 - Good
 - ☐ 4 - Fair
 - ☐ 5 - Poor
-

2. **Compared to one year ago**, how would you rate your health in general **now**?

- ☐ 1 - Much better now than one year ago
 - ☐ 2 - Somewhat better now than one year ago
 - ☐ 3 - About the same
 - ☐ 4 - Somewhat worse now than one year ago
 - ☐ 5 - Much worse now than one year ago
-

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
4. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
5. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
6. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
7. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
8. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
9. Walking more than a mile	☐ 1	☐ 2	☐ 3
10. Walking several blocks	☐ 1	☐ 2	☐ 3
11. Walking one block	☐ 1	☐ 2	☐ 3
12. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

- | | Yes | No |
|---|-----------------------|-----------------------|
| 13. Cut down the amount of time you spent on work or other activities | ☐ | ☐ |
| | 1 | 2 |
| 14. Accomplished less than you would like | ☐ | ☐ |
| | 1 | 2 |
| 15. Were limited in the kind of work or other activities | ☐ | ☐ |
| | 1 | 2 |
| 16. Had difficulty performing the work or other activities (for example, it took extra effort) | ☐ | ☐ |
| | 1 | 2 |
-

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

- | | Yes | No |
|--|-------------------------|-------------------------|
| 17. Cut down the amount of time you spent on work or other activities | ☐ 1 | ☐ 2 |
| 18. Accomplished less than you would like | ☐ 1 | ☐ 2 |
| 19. Didn't do work or other activities as carefully as usual | ☐ 1 | ☐ 2 |
-

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ☐ 1 - Not at all
 - ☐ 2 - Slightly
 - ☐ 3 - Moderately
 - ☐ 4 - Quite a bit
 - ☐ 5 - Extremely
-

21. How much **bodily** pain have you had during the **past 4 weeks**?

- ☐ 1 - None
 - ☐ 2 - Very mild
 - ☐ 3 - Mild
 - ☐ 4 - Moderate
 - ☐ 5 - Severe
 - ☐ 6 - Very severe
-

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ☐ 1 - Not at all
 - ☐ 2 - A little bit
 - ☐ 3 - Moderately
 - ☐ 4 - Quite a bit
 - ☐ 5 - Extremely
-

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ 1 - All of the time
 - ☐ 2 - Most of the time
 - ☐ 3 - Some of the time
 - ☐ 4 - A little of the time
 - ☐ 5 - None of the time
-

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.



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Pain Sensitivity Questionnaire

This questionnaire contains a series of questions in which you should imagine yourself in certain situations. You should then decide if these situations would be painful for you and if yes, how painful they would be. **Let 0 stand for no pain; 1 is an only just noticeable pain and 10 the most severe pain that you can imagine or consider possible.** Please mark the scale with a cross on the number that is most true for you. Keep in mind that there are no "right" or "wrong" answers; only your personal assessment of the situation counts. Please try as much as possible not to allow your fear or aversion of the imagined situations affect your assessment of painfulness.

1. Imagine you bump your shin badly on a hard edge, for example, on the edge of a glass coffee table. How painful would that be for you?

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

2. Imagine you burn your tongue on a very hot drink.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

3. Imagine your muscles are slightly sore as the result of physical activity.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

4. Imagine you trap your finger in a drawer.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

5. Imagine you take a shower with lukewarm water.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

6. Imagine you have mild sunburn on your shoulders.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

7. Imagine you grazed your knee falling off your bicycle.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

8. Imagine you accidentally bite your tongue or cheek badly while eating.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

9. Imagine walking across a cool tiled floor with bare feet.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

10. Imagine you have a minor cut on your finger and inadvertently get lemon juice in the wound.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

11. Imagine you prick your fingertip on the thorn of a rose.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

12. Imagine you stick your bare hands in the snow for a couple of minutes or bring your hands in contact with snow for some time, for example, while making snowballs.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

13. Imagine you shake hands with someone who has a normal grip.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

14. Imagine you shake hands with someone who has a very strong grip.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

15. Imagine you pick up a hot pot by inadvertently grabbing its equally hot handles.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

16. Imagine you are wearing sandals and someone with heavy boots steps on your foot.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

17. Imagine you bump your elbow on the edge of a table ("funny bone").

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

Pediatric Depressive Symptoms – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...		Never	Almost Never	Sometimes	Often	Almost Always
488R1r	I could not stop feeling sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
461R1r	I felt alone.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5041R1r	I felt everything in my life went wrong.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5035R1r	I felt like I couldn't do anything right.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
711R1r	I felt lonely	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
228R1r	I felt sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
712R1r	I felt unhappy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3952aR2r	It was hard for me to have fun.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pediatric Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...		Never	Almost Never	Sometimes	Often	Almost Always
2220R2r	I felt like something awful might happen..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
713R1r	I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
227bR1r	I felt scared	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5044R1r	I felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3459bR1r	I worried when I was at home	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2230R1r	I got scared really easy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
231R1r	I worried about what could happen to me ..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3150bR2r	I worried when I went to bed at night	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ12	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ36	How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ3	How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ13	How much did pain interfere with your family life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pediatric Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...		Never	Almost Never	Sometimes	Often	Almost Always
1698bR1r	I felt angry when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2035R1r	I had trouble doing schoolwork when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3793R1r	I had trouble sleeping when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9004r	It was hard for me to pay attention when I had pain.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2045R1r	It was hard for me to run when I had pain .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2049R1r	It was hard for me to walk one block when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
1703R1r	It was hard to have fun when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2180R1r	It was hard to stay standing when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Emotional Distress - Depression – Short Form 8b

Please respond to each item by marking one box per row.

In the past 7 days....

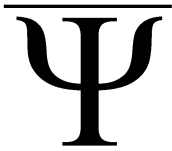
		Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05	I felt that I had nothing to look forward to.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP17	I felt sad.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	I felt like a failure.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PCS-C

Thoughts and feelings during pain

We are interested in what you think and how strong the feelings are when you are in pain. Below are 13 sentences of different thoughts and feelings you can have when you are in pain. Try to show us as clearly as possible what you think and feel by putting a circle around the word under each sentence that best reflects how strongly you have each thought..

- | | | | | | |
|-----|--|--------|------------|----------|-----------|
| 1. | When I am in pain, I worry all the time about whether the pain will end. | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 2. | When I am in pain, I feel I can't go on like this much longer. | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 3. | When I am in pain, it's terrible and I think it's never going to get better. | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 4. | When I am in pain, it's awful and I feel that it takes over me | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 5. | When I am in pain, I can't stand it anymore | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 6. | When I am in pain, I become afraid that the pain will get worse | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 7. | When I am in pain, I keep thinking of other painful events | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 8. | When I am in pain, I want the pain to go away | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 9. | When I am in pain, I can't keep it out of my mind | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 10. | When I am in pain, I keep thinking about how much it hurts | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 11. | When I am in pain, I keep thinking about how much I want the pain to stop | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 12. | When I am in pain, there is nothing I can do to stop the pain. | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |
| 13. | When I am in pain, I wonder whether something serious may happen | | | | |
| | NOT AT ALL | MILDLY | MODERATELY | SEVERELY | EXTREMELY |



PCS-EN

Client No.: _____ Age: _____ Sex: M() F() Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain ...

- ☐ I worry all the time about whether the pain will end.
- ☐ I feel I can't go on.
- ☐ It's terrible and I think it's never going to get any better.
- ☐ It's awful and I feel that it overwhelms me.
- ☐ I feel I can't stand it anymore.
- ☐ I become afraid that the pain will get worse.
- ☐ I keep thinking of other painful events.
- ☐ I anxiously want the pain to go away.
- ☐ I can't seem to keep it out of my mind.
- ☐ I keep thinking about how much it hurts.
- ☐ I keep thinking about how badly I want the pain to stop.
- ☐ There's nothing I can do to reduce the intensity of the pain.
- ☐ I wonder whether something serious may happen.

...Total

Updated 11/11

PASS

Individuals who experience pain develop different ways to respond to that pain. We would like to know what you do and what you think about when in pain. Please use the rating scale below to indicate how often you engage in each of the following thoughts or activities. Circle any number from 0 (NEVER) to 5 (ALWAYS) for each item.

		<u>NEVER</u>				<u>ALWAYS</u>
1.	I think that if my pain gets too severe, it will never decrease	0	1	2	3	4 5
2.	When I feel pain I am afraid that something terrible will happen	0	1	2	3	4 5
3.	I go immediately to bed when I feel severe pain	0	1	2	3	4 5
4.	I begin trembling when engaged in activity that increases pain	0	1	2	3	4 5
5.	I can't think straight when I am in pain	0	1	2	3	4 5
6.	I will stop any activity as soon as I sense pain coming on	0	1	2	3	4 5
7.	Pain seems to cause my heart to pound or race	0	1	2	3	4 5
8.	As soon as pain comes on I take medication to reduce it	0	1	2	3	4 5
9.	When I feel pain I think that I may be seriously ill	0	1	2	3	4 5
10.	During painful episodes it is difficult for me to think of anything else besides the pain	0	1	2	3	4 5
11.	I avoid important activities when I hurt	0	1	2	3	4 5
12.	When I sense pain I feel dizzy or faint	0	1	2	3	4 5
13.	Pain sensations are terrifying	0	1	2	3	4 5
14.	When I hurt I think about the pain constantly	0	1	2	3	4 5
15.	Pain makes me nauseous (feel sick)	0	1	2	3	4 5
16.	When pain comes on strong I think I might become paralyzed or more disabled	0	1	2	3	4 5

17.	I find it hard to concentrate when I hurt	0	1	2	3	4	5
18.	I find it difficult to calm my body down after periods of pain	0	1	2	3	4	5
19.	I worry when I am in pain	0	1	2	3	4	5
20.	I try to avoid activities that cause pain	0	1	2	3	4	5

Emotional Distress – Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

FOPQ-Child Report

These questions ask about how you look at pain ***when you hurt or are in pain for a few hours or days***. Please read each statement carefully. Circle the number that shows how much you agree or disagree with each statement.

	Strongly Disagree	Disagree	Unsure	Agree	Strongly Agree
1. My pain controls my life.	0	1	2	3	4
2. I begin shaking/trembling when doing an activity that increases pain.	0	1	2	3	4
3. I can't do all the things normal people do because it's so easy to hurt my body.	0	1	2	3	4
4. When I feel pain, I am afraid that something terrible will happen.	0	1	2	3	4
5. Pain causes my heart to beat fast or race.	0	1	2	3	4
6. I cancel plans when I am in pain.	0	1	2	3	4
7. Feelings of pain are scary for me.	0	1	2	3	4
8. When I hurt I can't stop thinking about the pain.	0	1	2	3	4
9. I worry when I am in pain.	0	1	2	3	4
10. I cannot go back to school until my pain is treated.	0	1	2	3	4
11. I think that if my pain gets too bad, it will never get better.	0	1	2	3	4
12. I find it difficult to calm my body down when having pain.	0	1	2	3	4
13. I avoid making plans because of my pain.	0	1	2	3	4
14. I'm afraid that when the pain starts it's going to be really bad.	0	1	2	3	4
15. I walk around in constant fear of hurting.	0	1	2	3	4
16. I put things off because of my pain.	0	1	2	3	4
17. I go immediately to lie down or rest when I feel really bad pain.	0	1	2	3	4

	Strongly Disagree	Disagree	Unsure	Agree	Strongly Agree
18. I stop any activity if I start to hurt or my pain becomes worse.	0	1	2	3	4
19. I can't think straight when I feel pain.	0	1	2	3	4
20. I choose to miss things that are important to me so that I won't feel my pain.	0	1	2	3	4
21. I do not go to school because it makes my pain worse.	0	1	2	3	4
22. When I am in pain, I stay away from other people.	0	1	2	3	4
23. When I sense pain, I feel dizzy or lightheaded.	0	1	2	3	4
24. I do not think that I will ever be able to go back to a normal school schedule.	0	1	2	3	4

Contact Information

Contact Name (if under 18, please use Parent/Guardian name): _____

Primary Contact Number: _____ Secondary Contact Number: _____

Email: _____ Preferred Method of Contact: _____

Participant Information

Name: _____

Date: _____

Date of Birth: _____

Age: _____ Gender: _____ Race/Ethnicity: _____

Height: _____ Weight: _____

Year in school (if applicable): _____

School Name (if applicable): _____

Medical Screening

Current OR history of mental health conditions (i.e. Depression, Anxiety, etc.)?

Circle: yes/no

If yes, please describe:

Currently taking any medications, supplements, birth control?

Circle: yes/no

If yes, please describe:

Surgery?

Circle: yes/no

If yes, please describe (include year, reason, etc.):

Head trauma?

Circle: yes/no

If yes, please describe (include year, reason, etc.):

Headaches or migraines?

Circle: yes/no

If yes, please describe (include year, reason, etc.):

Irritable Bowel Syndrome?

Circle: yes/no

If yes, please describe (include year, reason, etc.):

Fibromyalgia?

Circle: yes/no

If yes, please describe (include year, reason, etc.):

Chronic Pelvic Pain?

Circle: yes/no

If yes, please describe (include year, reason, etc.):

Other significant medical problems not listed (please specify): _____

Pregnant?

Circle: yes/no

What is your pain level today?

Circle: 1 2 3 4 5 6 7 8 9 10
(no pain) (worst pain)

Have you experienced pain in the past 3 months?

Circle: yes/no

If yes, please describe:

Average pain level of period?

Circle: n/a 1 2 3 4 5 6 7 8 9 10
(no pain) (worst pain)

When was your last menstrual period? _____

Are you currently taking any hormonal form of birth control?

Circle: yes/no

If yes, please describe the type:

If yes, when did you start the birth control? _____

Social History

Do you use recreational drugs?

Circle: yes/no

If yes, please describe:

Do you drink alcohol?

Circle: yes/no

If yes, how many servings do you consume per week? _____

REPORT OF ACTION

Principal Investigator Christine Sieberg, PhD, EdM, MA

Protocol Title Examining Pain, Psychosocial, and Sensory Factors in Adolescents and Young Women with Endometriosis

Protocol Number IRB-P00021783

Amendment Approval Date: 4/8/2019

IRB Expiration Date: 3/11/2020

IRB ACTION: AMENDMENT – APPROVAL

COMMENTS:

The Institutional Review Board has approved the amendment submitted 3/20/2019. This amendment proposes the following changes:

- Additional questionnaires were given to participants.
- Conducted an assessment of descending brainstem control using conditioned pain modulation (CPM).
- Participants in The Women's Health Study: From Adolescence to Adulthood (A2A) (IRB-P00004267) were sent a flyer regarding a new study and an option to opt-out of being contacted via their preferred method given to A2A.
- Conducted an assessment of autonomic nervous system function by measuring blood pressure and electrocardiography (ECG).
- Participants underwent an initial screening procedure (in-person or over the phone). Second screening included an in person visit conducted by Dr. David Borsook which included review of medical records.
- Participants within the Control cohort who had completed the study had the option to refer other people to the study and were given an additional \$5 via their Clincard per referral.
- Increased the age range of participants in all cohorts to 50 years old.
- Participant reimbursement will be increase by \$20.
- Under the previously approved neuroimaging component: 1) QST protocol during fMRI scan.
- Additional exclusionary criteria were added for participants undergoing the neuroimaging component.
- Added consent forms for neuroimaging component.
- Removed Devon Huntly, Hannah Olsen, Sehar Resad, Samantha Rizzo, Whitney Sanford, and Jacqueline Smith from BCH staff
- Added David Zurakowski and Amy Shafir to BCH staff

The approved consent form is available on-line through the BCH Informed Consent Library. To obtain the consent form, please go to <http://chbcfapps/research/consents>. The ICLibrary should be accessed each time you need a consent form to ensure that the current version of the consent is always used. Do not store the consent forms on your computer or make copies for future use. Note that the activation/expiration date on the consent form can only be changed or modified by the staff of the IRB Office. Children and adolescents are required to sign the consent form in addition to the parent(s)/guardian(s). If you determine a particular child is not capable, you will need to provide the rationale on the informed consent after the parental signatures. Please also note that subjects cannot be enrolled in a study if the consent

form has expired. A copy of the consent should be kept in your files. The subject/family must also be given a signed copy.

The occurrence of unanticipated problems should promptly be reported to this office. Any revisions, amendments, or changes to the protocol require prior IRB approval.

The IRB has asked me to notify all investigators that files are subject to audit at any time.

Sincerely,

A handwritten signature in cursive script, appearing to read "Lauren Sever".

Lauren Sever, IRB Coordinator
For the Institutional Review Board

Tell us how we are doing! <https://www.surveymonkey.com/s/irbsatisfactionsurvey>

Project Narrative

Background:

○ FY18PRMRP Topic Area:

The proposed grant, *Defining the role for descending pain modulation and reward-aversion processes towards the development of chronic pain in endometriosis*, brings together experts in the field of Pain Medicine, Behavioral Science, Neuroscience, Gynecology/Surgery, and Epidemiology to address a critical gap in knowledge pertaining to **endometriosis**; specifically, **neural mechanisms contributing to chronic pelvic pain (CPP)** in this population. One of the FY18 PRMRP Topic Areas is Endometriosis while a second is Chronic Pain Management. It is estimated that endometriosis affects 10-20% of women during the reproductive years¹. As of 2014, 200,692 women were in the Active component of the U.S. Armed Forces and 156,180 women were in the Reserve and National Guard², and as of 2015, 9.4 percent of the Veteran population was female³, thus elucidating the mechanisms contributing to pain and disability in endometriosis is timely and relevant. Given that chronic pain 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.

○ Reasoning of Proposed Work:

Factors such as the presence of extrauterine endometrial glands and stroma, and the subsequent inflammation and fibrosis associated with endometriosis, can lead to persistent inflammatory pain, infertility, and significant disruption of quality of life⁴. There are a number of reasons for the proposed work: (1) Costs. The public health and economic impact is staggering, costing the U.S. an estimated 78 billion dollars annually⁵. (2) Diagnosis. Adolescents and young women are uniquely impacted by endometriosis as it often presents as cyclic and non-cyclic persistent pelvic pain resulting in high rates of misdiagnosis and delayed treatment⁶; of note, two-thirds of surveyed women diagnosed with endometriosis in adulthood presented with symptoms of the disease before the age of 20⁷. These diagnostic delays can contribute to pain persistence, disability, impaired emotional functioning, and decreased quality of life. Specifically, high rates of anxiety and depression have been found in patients with endometriosis⁸. (3) Difficulty with current treatment. 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. Approximately 30% of women report no improvement in their pelvic pain after surgery and the degree of short-term pain improvement among the remaining patients varies and pain frequently relapses without evidence of recurrent disease⁹. Interestingly, the presence and severity of pelvic pathology does not correlate with symptom burden and pain frequently recurs even without visible disease at repeat laparoscopy¹⁰. (4) Brain Changes. Little research on how CPP confers changes to the brain that result in increased resistance to treatment or chronification has been conducted across adolescent and adult populations with endometriosis (*i.e.*, from early onset to major manifestations during development). *We suggest that 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 the latter, profound changes in neural networks that involve anxiety, cognition, memory, and normal function of the brains pain inhibitory (descending modulation) systems are thought to take place.* Through these changes one easily measurable process is a change in descending pain inhibition, which is diminished in chronic pain conditions¹¹. Such attenuation can be evaluated using a paradigm that measures offset analgesia (OA) via the suppression of descending pain modulatory and reward systems (**Figure 1**). Specifically, OA is a form of endogenous pain inhibition characterized by a disproportionately large reduction in pain perception after a small decrease in temperature during noxious thermal stimulation¹²; however, OA is attenuated in patients with chronic pain (*e.g.*, fibromyalgia¹³ and neuropathic pain¹⁴) as shown in **Figure 2**. Diminished robustness of OA measures 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.

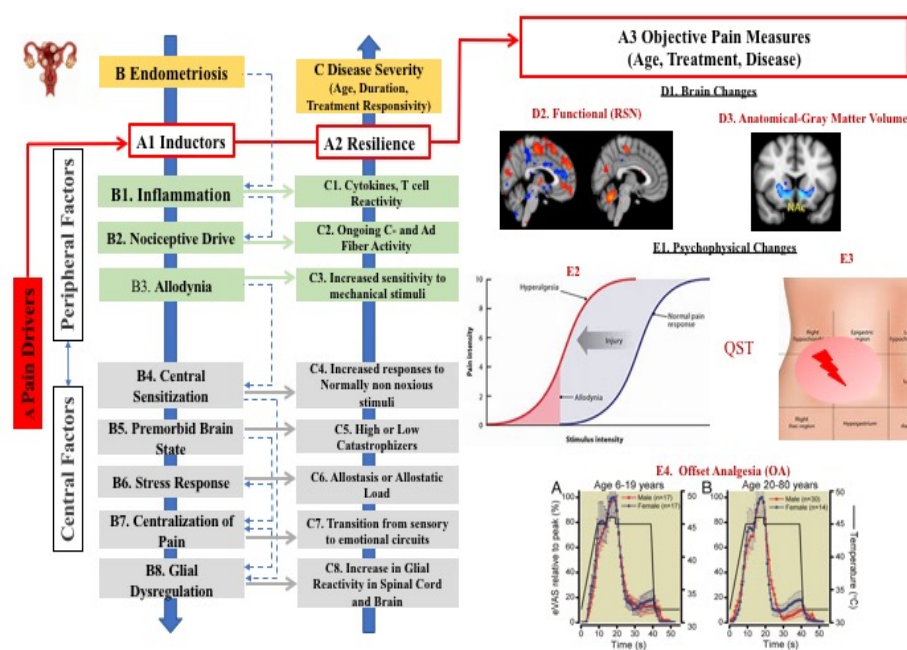
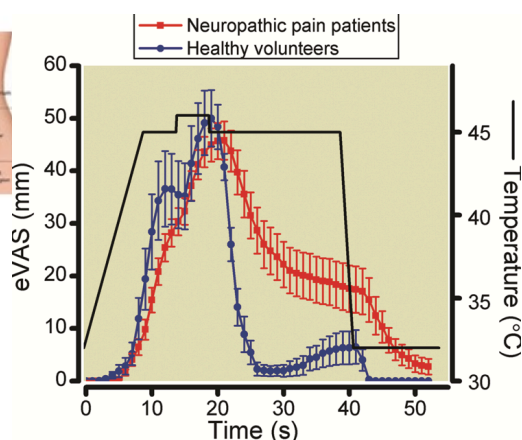


Figure 2¹³: OA is attenuated in patients with chronic neuropathic pain. eVAS responses to the three-temperature paradigm (black line) in neuropathic pain patients (n = 10, red squares) and age-matched healthy controls (n=10, blue circles). Values are mean $\pm$ SEM. eVAS = electronic visual analog score.



Previous Experience:

Experience in Chronic Pain Research:

The **Biobehavioral Pediatric Pain Lab (BPP)** at *Boston Children's Hospital (BCH)* was co-founded and is directed by **Dr. Sieberg (PI)**. Dr. Sieberg has built a research foundation in the bio-behavioral aspects of pediatric chronic pain specifically in the psychophysics of pain in both preclinical and clinical models. A major focus of the BPP lab's funded research is to identify young people who demonstrate amplified Central Nervous System (CNS) processing of pain-related information, and who are

at elevated risk for adverse pain-related outcomes and reduced benefits of pain-reducing treatments. Dr. Sieberg has extensive expertise in chronic pain research in children, adolescents, and young adults, specifically in pain psychosocial measure development, pain treatment outcome research, and the role of psychosocial factors in the maintenance and exacerbation of chronic pain, as well as in pain psychophysics and the assessment of pain-modulatory processes in both animals and humans. **Dr. Borsook** (Partnering PI) is a Professor in Anesthesiology at *Harvard Medical School (HMS)*. With over 250 publications in brain systems relating to pain conditions and brain effects of analgesics, Dr. Borsook is a leading clinician and researcher in the field of pain. He is the former Director of the *Pain Clinic* at *Massachusetts General Hospital (MGH)*, has served on the NIH Council, and was one of the first to publish on functional Magnetic Resonance Imaging (fMRI) in pain. Dr. Borsook is the founding Director of the *Center for Pain and the Brain (CPB)* at BCH, MGH, and McLean Hospitals at HMS (see below for details on the CPB).

Experience in Phenotyping Endometriosis:

The **Boston Center for Endometriosis (BCE)** was founded in 2012 by **Drs. Laufer and Missmer (Co-Investigators)** and includes a partnership between BCH and *Brigham & Women's Hospital (BWH)*, both affiliated

with HMS. The BCE brings together internationally recognized leaders in the field of endometriosis to offer both young and adult women cutting edge treatment with the focus on short-term intervention and long-term management across their life span. The BCE has created a multidisciplinary team for endometriosis care with their specialists conducting clinical trials, research studies and publishing numerous papers in medical journals. In addition to diagnosing and managing teen and adult women's endometriosis, the BCE is a hub for unprecedented research advancement, including a biorepository for both intervention and observational studies. For example, the BCE just completed recruitment for the *Women's Health Study: from Adolescence to Adulthood (A2A)*, a hospital- and community-based endometriosis-focused longitudinal cohort that was launched in 2012 and which enrolled over 1200 females; the largest adolescent endometriosis cohort in the world. Additionally, in 2014 as a member of the *World Endometriosis Research Foundation Board of Directors*, Dr. Missmer, helped conceive of and became Co-Principal Investigator of the *Endometriosis Phenome and Biobanking Harmonization Project (EPHect)*. EPHect has recently published four papers¹⁵⁻¹⁸ aimed at the standardization of reporting and pathological processing of endometriosis. This consensus was reached after two workshops in 2013 covering four topics: (1) surgical phenotypes¹⁸ (2) clinical & covariate phenotype¹⁷ (3) fluid biospecimen collection, processing and storage¹⁶; (4) tissue collection, processing & storage¹⁵ with 54 leaders in endometriosis research, sampling, and management worldwide. Dr. Sieberg (PI) is a consulting faculty member and pain expert at the BCE. Drs. Sieberg, Missmer, and Shafrir (Post-doctoral Fellow) have two papers being prepared for publication exploring pain sensitivity and stress in women with endometriosis and pelvic pain and work together on several grant funded projects exploring deep phenotyping of endometriosis associated pain, including the following: (1) Marriott Foundation Investigator Award (Sieberg, PI; Missmer & Shafrir, Co-Is)- *Elucidating the Psychophysical Factors Contributing to Chronic Pelvic Pain in Adolescent and Young Adult Women with Endometriosis*; (2) Innovative Medicines Initiative (IMI-2)/ European Commission (Sieberg, Site PI; Missmer & Shafrir, Co-Is)- *Translational Research in Pelvic Pain*; (3) NIH R01 (Missmer, PI; Sieberg, Co-I)- *What is Endometriosis? Deep Phenotyping to Advance Diagnosis and Treatment*; (4) BCE Trainee Grant (Shafrir, PI; Sieberg, Mentor) - *Advancing Our Ability to Identify Endometriosis Patients with Central Pain Sensitization Using Biologic Markers and Endometriosis Lesion Characteristics*

- Experience in Pain Neuroimaging Across the Lifespan:

The **CPB** directed by Dr. David Borsook is a multidisciplinary group that has research facilities at both pediatric (BCH) and adult (MGH & Mclean) hospitals. The CPB was amongst the first to conduct fMRI of pain in both adults and in children, with more than 200 papers in the field, and two books, one on brain imaging in drug development, and one on migraine. Although we have published extensively and have been involved in work with children (amongst the first) with chronic pain¹⁹⁻²⁵ perhaps migraine provides a good example of our track record in working with healthy subjects and patients across the age span of 12-44yrs of age that has included multiple publications (*Pediatric*²⁶⁻³²; *Adult*: over 50 publications, but relevant ones to this submission include^{26,33-41}) and prior NIH grants in pediatric (R01NS075018: *Multimodal Brain Measures of Migraine with Age: Pre-puberty to Adult*) and adult (R01NS073997: *Brain Markers of Low and High Frequency Episodic Migraine*; K24: *Imaging Pain and Analgesia: Mentoring in Basic and Applied Research*) migraine populations. Migraine may parallel disease phenotypes to endometriosis in that it is a visceral pain that is intermittent in nature in its episodic form, involves inflammation, and it can chronify; visceral and intermittent pain and inflammation can be modified by vagal stimulation (visceral – brain connectivity). In addition to the work produced by the study, all the migraine data in children and adults will be made available for comparative analysis of a disease entity that spans the same age range. The PI's, Drs. Sieberg and Borsook have worked together for over 5 years clinically, and more recently in the research setting when Dr. Sieberg joined the CPB as an independent investigator. Joint publications have included^{42,43} and Dr. Sieberg is involved with a number of new co-authored papers as well as current and submitted NIH grants on related topics of chronic pain. Specifically, one recent R01re-submission (Borsook MPI; Sieberg Co-I) that scored a 16th percentile on the first submission and which is currently under review (R01AR073893) mirrors the process here – evaluating chronic pain and the neural underpinnings of pain-related catastrophizing in children and adults with fibromyalgia. As an OA expert, Dr. Borsook is currently a Co-PI on a project entitled *Endogenous Modulation and Central Sensitization in New Daily Persistent Headache (NDPH) in Children*” being conducted at BCH and funded by

the *Migraine Research Foundation*. The first primary aim of this grant is to define differences in altered modulatory systems using OA as well as detailed clinical descriptors as part of a clinical evaluation in NDPH pediatric patients. The second primary aim is to define the effects of naltrexone on patients with NDPH using OA.

○ Preliminary Data:

○ Relationship between Endometriosis and CPP:

Results of data we analyzed and that is being prepared for manuscript submission from a cohort of adult women with: (1) surgically confirmed endometriosis and no pain, (2) surgically confirmed endometriosis with CPP, (3) surgically confirmed CPP and no endometriosis, and (4) healthy controls, who completed pressure-pain QST, an external systemic tender points exam, and a pelvic exam to determine internal tenderness, indicate that the CPP and no endometriosis and the endometriosis with CPP groups experienced more systemic tenderness and more comorbid chronic pain syndromes compared to the endometriosis and no CPP and healthy control groups. When controlling for age and number of comorbid pain syndromes, Generalized Linear Models (GLM) revealed that the women with endometriosis and no pain had significantly higher low pressure-pain thresholds compared to women with endometriosis with CPP, while the CPP and no endometriosis group had significantly lower high pressure-pain threshold scores compared to healthy controls, a difference also found between the endometriosis with CPP group and healthy controls. When examining the number of pelvic tender-points, the CPP and no endometriosis group had significantly more pelvic tender-points on physical exam compared to the endometriosis and no CPP group and the endometriosis with CPP group had significantly more pelvic exam tender-points compared to the endometriosis and no pain group. These QST and pelvic exam results suggest that perhaps the endometrial lesions are not driving the CPP and that CPP separate from endometriosis may be responsible for the development of centralized pain amplification.

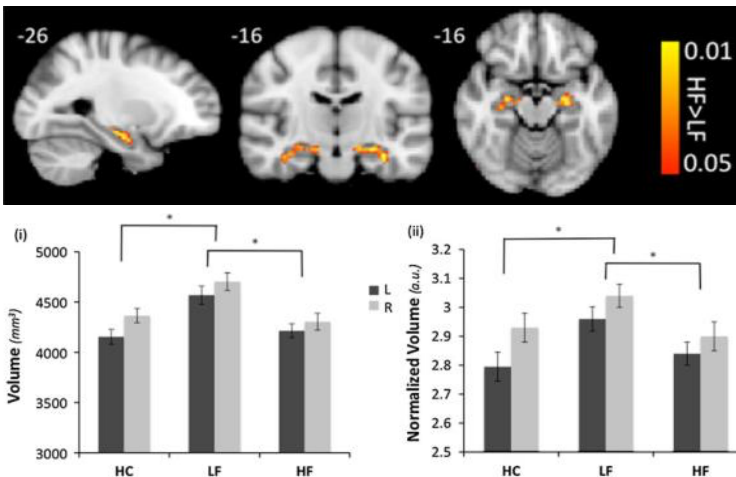


Figure 3. Evaluation of Hippocampal volume changes and response to noxious heat in Migraine vs. Healthy controls from our prior work⁴¹ Top: Response to pain. Contrast analysis of the High Frequency (HF) versus Low Frequency (LF) migraine group in response to the “pain threshold +1 °C” stimuli revealed significantly higher deactivation in bilateral hippocampus in the LF patients Bottom: Differences in hippocampal volume. The bar plots show the hippocampal volume comparisons for LF, HF, and healthy controls. LF migraineurs had a significantly larger hippocampal volume. (i) Raw volume comparisons—for the statistical analysis the left and right hippocampal volumes of the cohorts were compared while using the total intracranial volume and age as covariates. (ii) The same comparison for normalized volumes (normalized to the total intracranial volume) volumes. Bar heights represent the mean value for each volumetric measurement. Error bars represent the 95 % confidence interval of the mean. Asterisk denotes a significance level of the corresponding P value reported. The data shows that pain frequency (i.e., attacks) drives brain gray matter changes an approach we will use in this grant proposal.

○ Endometriosis and Quantitative Sensory Testing (QST):

In keeping with the thesis of increased pain sensitivity in patients with CPP and endometriosis, we have produced preliminary QST data, used to assess responses to standardized noxious stimuli and the only method to assess central sensitization, in a sample of 51 young women ages 12-22 years with surgically confirmed endometriosis and 35 healthy age-matched controls (data collection ongoing). This data suggests that women with endometriosis not only have significantly lower pain thresholds in the four abdominal quadrants compared to healthy

controls but also in the deltoid, an unaffected body part. The latter finding is akin to patients with migraine that have decreased pain thresholds and increased pain to brush and heat in body parts usually involving the head, but which may extend to other regions⁴⁴, suggesting a profound process occurring in the CNS. In our sample, 56% of the women also meet criteria for

temporal summation, an increased perception of pain to repetitive painful stimuli and a surrogate of central sensitization.

○ Brain Imaging:

As noted above our group has extensive experience in imaging both in adults and children. We provide a few examples in **Figures 3 and 4.**

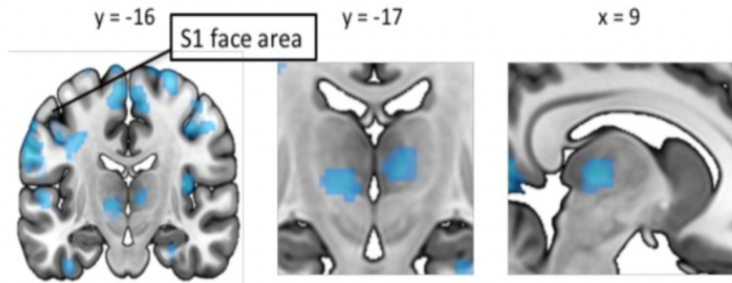


Figure 4: Increased periaqueductal gray (PAG)-based functional connectivity in Migraine vs. Controls. A between-groups comparison of pain-induced PAG connectivity showed that in comparison to healthy controls, migraineurs had increased connectivity with the bilateral thalamus, supplementary motor area and the primary somatosensory cortex face area. Montreal Neurological Institute coordinates are marked in the respective dimensions. Blue areas show statistical significance ($p < 0.05$) between the two groups. The data suggest that migraineurs have increased sensitivity to pain as a result of diminished descending modulation. Other work supports alteration in descending modulation in such circuits in chronic pain^{13,14}.

○ Endometriosis and Brain Imaging:

Brain correlates using fMRI of these and other changes known to occur in chronic pain have not previously been examined in adolescent or young adult women with endometriosis; however some pilot studies conducted in adult women with endometriosis and/or CPP suggest that adult women with CPP have decreases in regional gray matter volume in brain regions associated with pain processing including the thalamus, cingulate gyrus, putamen, and insula⁴⁵, suggestive of pain amplification related to CNS changes found in other chronic pain conditions such as fibromyalgia⁴⁶ and vulvodynia⁴⁷. Additionally, another study by the same group⁴⁸ found that women with endometriosis-associated CPP demonstrated increased concentrations of excitatory neurotransmitters in the anterior insula and had greater intrinsic connectivity of the same anterior insula region to the medial prefrontal cortex both known to be regions important in pain processing and reward neurocircuitry. Additionally, increased connectivity between these two regions was positively correlated with anterior insula combined glutamate and glutamine concentrations, as well as with pain intensity, anxiety and depression symptom severity. These studies suggest that pelvic pain is likely not sufficiently explained by the presence of endometriosis and may be due to dysfunction in the CNS pain regulatory system; however, these studies included small samples with only adult participants. How endometriosis and CPP impact the adolescent brain is not well understood and therefore we have generated preliminary resting state data (Figure 5) on 10 adolescent girls with endometriosis and CPP (mean age=17 years, SD=1.9) compared to 17 healthy female controls (mean age=17 years, SD=2.5). Data is shown for connectivity with an important brain region – the anterior insula as an example.

Functional Connectivity Patterns with Anterior Insula (Left & Right) as a Seed Region

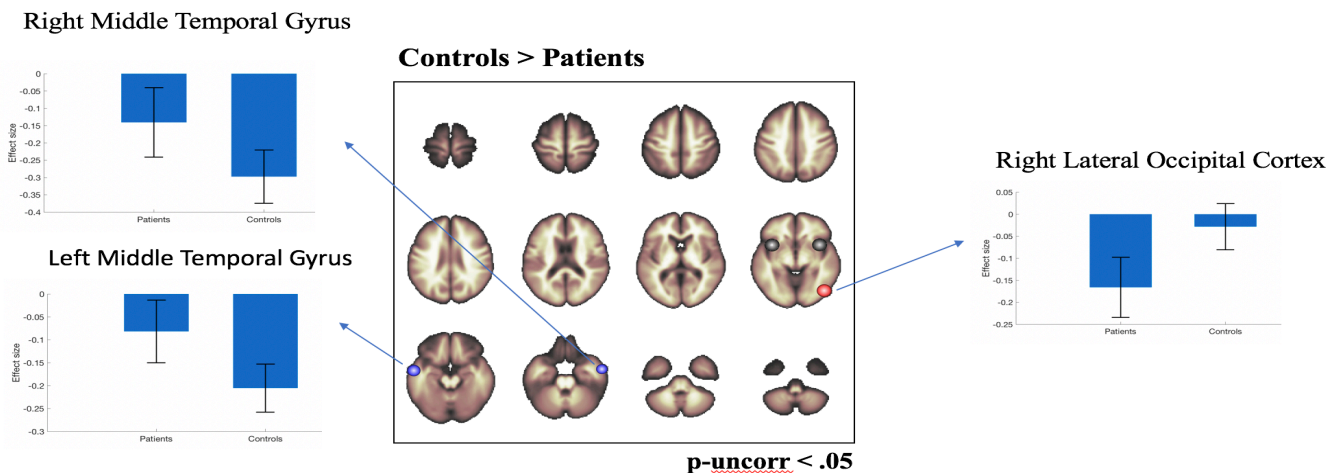


Figure 5. Comparing Functional Connectivity Patterns in the Anterior Insula (AI) as a Seed Region in Adolescents with Endometriosis Compared to Age-Matched Healthy Controls. Controls > Patients (reverse of Patients > Controls); p-uncorr < .05: Lateral Right Occipital Cortex; Left Middle Temporal Gyrus (TG); Right Middle TG. The data suggest that differences are present in pediatric patients with endometriosis as shown by functional connectivity with the anterior insula. The region is involved in autonomic function and interoception. The connection between the AI and TG may relate to memory and interpretation of emotional awareness, particularly as it relates to integration of interoceptive signals including sensorimotor integration⁴⁹⁻⁵¹.

Our Question: How adolescents with a developing brain and nervous system compare to adult women with endometriosis is not known and is necessary in order to discover patient characteristic and disease subtype-specific algorithms that will establish personalized, precision medicine for endometriosis diagnosis and subsequent treatment selection. Failure to meet these needs has resulted in diagnostic delays and inadequate symptom remediation for hundreds of girls and women, causing significant personal and economic health costs⁵².

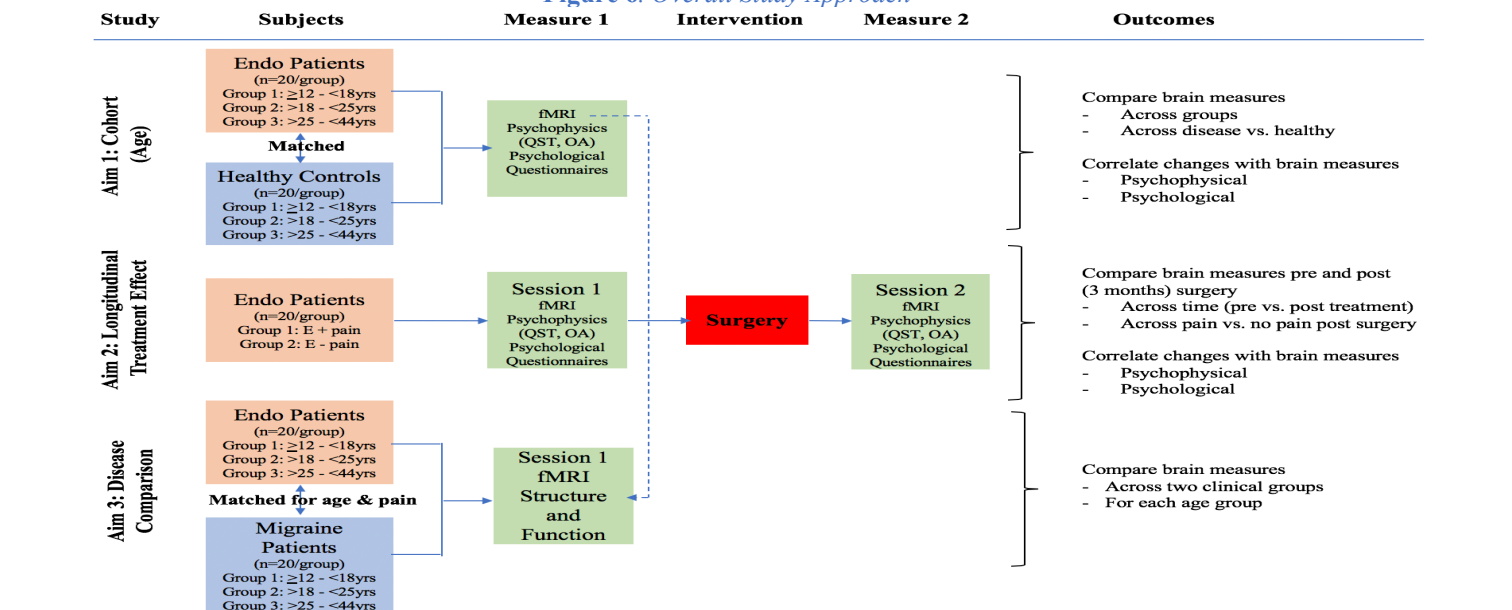
Our Team: We have assembled an interdisciplinary team comprised of Psychology (Sieberg), Gynecology (Laufer & Missmer), Pain Medicine (Sieberg & Borsook), Neuroscience (Borsook & Burstein), Imaging (Borsook, Upadhyay), Epidemiology and Statistics (Missmer, Shafir, & Zurakowski) experts to further understand the process that enhances brain sensitivity and propose to use OA as a measure that defines abnormalities in brain modulation of pain that may contribute to the development and persistence of CPP in women with endometriosis.

The Problem: There is a critical need to identify mechanisms contributing to treatment resistance in this population in order to identify those at greatest risk for pain and to identify brain and psychological factors that may predict the potential to undergo pain chronification. *This is especially important in the current opioid epidemic with new research highlighting that 24% of Obstetrician/Gynecologists prescribe opioids for endometriosis-related pain*⁵³.

Importance of the Study: The expected outcomes from this study will: (1) enhance our understanding of the neurobiology of CPP in patients with endometriosis; (2) provide a metric to follow such patients in the clinic; (3) potentially provide a metric for those who will chronify; (4) understand the age-related changes that may occur with the disease; and (5) define an initial paradigm that may enhance our capability for developing individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

Overall Hypothesis: We hypothesize that (1) intermittent or ongoing pain in patients with endometriosis produces a sensitized peripheral and central nervous system (peripheral and central sensitization) that becomes maladaptive (centralization of pain) in patients who chronify vs. those that do not, and (2) that there will be differences in brain circuit responsivity with age. **Figure 6 shows the overall approach.**

Figure 6. Overall Study Approach



Specific Aims and Hypotheses:

AIM 1a: To define changes in brain structure and function as a correlate of subjective measures of pain and psychophysical functioning in adolescent, young adult and adult women with surgically confirmed endometriosis vs. healthy controls. **AIM 1b:** To correlate psychophysical measures (QST responses & psychological questionnaires) and brain changes with levels of OA. For Aim 1a and 1b, we will measure brain changes using fMRI, evaluate psychological functioning using a battery of questionnaires, and assess pain sensitivity through the use of QST (mechanical pain thresholds, wind-up temporal summation, & pressure pain) in three cohorts of women, all post-pubertal (ages 12-17;18-25; 26-44) with surgically confirmed endometriosis and healthy age-matched controls.

Hypotheses: (1) There will be a difference in the effects of endometriosis on brain structure and function that will depend on age/development; (2) Alterations in brain metrics will be observed in patients with greater adverse psychological functioning (e.g., decreased quality of life, high pain catastrophizing) and greater pain sensitivity, as measured by QST, compared to those patients with more normative psychophysical functioning and healthy controls; and (3) The increased pain observed in patients will negatively correlate with OA, a measure of descending modulatory pain control.

AIM 2a: To longitudinally compare brain metrics pre and post-surgery (structure and function) using fMRI with the same subjective measures noted in Aim 1 (QST responses & psychological questionnaires) in young women (ages 12-25) presenting for surgery for endometriosis. **AIM 2b:** To correlate psychophysical measures with levels of OA. Post-hoc analyses will differentiate women based on pain sub-group: (1) Endometriosis, no Pain; (2) Endometriosis with CPP.

Hypotheses: (1) Significant differences in brain measures will be found between patients with and without pain at post-surgery. Brain differences will be observed in the regions known to impact pain processing such as the medial prefrontal cortex and the anterior insula; (2) Women with CPP post-surgery will have central neurobiological abnormalities prior to surgery within systems mediating somatosensory and affective processing, as well as a diminished OA response, and greater psychosocial risk factors. Moreover, we hypothesize that in treatment-responsive endometriosis patients, baseline pain in conjunction with aberrant central neurobiology will normalize at a 3-month post-surgery assessment.

AIM 3: To compare brain metrics of adolescents, young adults, and adult women with endometriosis in Aim 1 with female patients ages 12-44 with migraines in the CPB's existing databases who have undergone structural and functional MRIs. This aim will provide preliminary data for future planned research exploring the use of medications for the treatment of migraines (e.g., triptans) for the treatment of endometriosis.

Hypothesis: Migraine may parallel disease phenotypes to endometriosis in that it is a visceral pain that is intermittent in nature in its episodic form, involves inflammation, and it can chronify.

Research Strategy:

○ Overview:

The aims of our study will be completed using a series of cross-sectional (**Aim 1**) and longitudinal (**Aim 2**) evaluations and comparisons in several samples of patients with endometriosis and/or CPP defined by age (**Aim 1**) and pain status (**Aim 2**). The groups in Aim 1 will also be demographically matched to samples of healthy controls. All groups will undergo comprehensive fMRI including resting state as well as evoked stimuli, including noxious physical stimuli. Endometriosis vs. Migraine (*i.e.*, Disease State) will be compared in **Aim 3**.

○ Study Participants:

We plan to have 20 participants in each age group for Aim 1 and 50 participants in Aim 2 (not including 10% attrition rate). Given that 30% of patients report no post-operative pain improvement, having 50 pre-surgical patients in Aim 2 will expect to have 35 treatment responders and 15 non-responders at the post-surgical scan.

Dr. Sieberg (PI) is a consultant and collaborator at the BCE as well as an attending psychologist at BCH where the majority of patient participants will be recruited. For Aim 1, participants with surgically confirmed endometriosis will be recruited from the BCE, specifically at Dr. Laufer's (Co-I) two clinics; the BCH *Center for Young Women's Health* and the BWH *Center for Reproductive Medicine*, where he specializes in the treatment

of adolescent and adult women with endometriosis. For Aim 2, patients presenting for surgery for suspected endometriosis at BCH will be recruited by the Research Assistant at the time of their clinic appointment at BCH. Aim 2 includes adolescent and young women in order to best understand a population who is at-risk for not having pain under control in time to enlist in the military, as well as to focus on an age cohort who is active in the military. Healthy controls for Aim 1 will be recruited from Partners Healthcare recruitment database, of which BWH is a part, the BCH database, and community-based advertisements. This patient recruitment and sampling strategy will enable enrollment of a broad, representative population and facilitate meeting our patient enrollment objectives. Specifically, the BCE has a rich history of recruiting subjects for research studies; the A2A study (see details above) recruited over 1200 women in 6 years. Clinically, Dr. Laufer (Co-I) performs an average of 20-24 surgeries/month at BCH on patients with suspected endometriosis and follows patients with endometriosis at both BCH and BWH. He sees approximately 380 new patients with endometriosis at BCH and approximately 190 new endometriosis cases at BWH every year.

○ *Inclusion and Exclusion Criteria for Patients:*

Female subjects will need to meet the following inclusion criteria: (1) Aim 1- 12-44 years; Aim 2- 12-25 years; (2) Surgically confirmed endometriosis for Aim 1; presenting for surgery for endometriosis for Aim 2; (3) Right handed; (3) Ability to read, understand, and provide written informed assent/consent. Exclusion criteria include: (1) Comorbid acute pain condition (pain < 3 months); (2) Comorbid chronic pain condition with pain intensity greater than that attributed to endometriosis or a history of chronic pain (> 3 months); (3) Current use of opioid analgesics; (3) Pregnant; (4) Significant medical history aside from endometriosis (*e.g.*, asthma, TBI, neurological, psychiatric - any involving a history of psychosis such as, schizophrenia, bipolar disorder, severe personality disorders); (4) Contraindication to MRI (*e.g.*, implanted ferrous metal; > 240 pounds because of gantry limits); and (5) Current or recent use of recreational drugs.

○ *Inclusion and Exclusion Criteria for Controls:*

Healthy age-matched female control subjects will be demographically matched to their endometriosis counterparts in Aim 1 and will meet the same exclusion criteria, and be free from acute or chronic pain conditions, as well as from any medical condition with putative CNS influence.

In order to minimize the influence of hormonal variability for all participants the following exclusionary criteria will be implemented: (1) No history of hysterectomy or oophorectomy; (2) No participants who are already in menopause, defined as the cessation of menses for 12 consecutive menses, unrelated to exogenous hormonal influences; (3) All testing will occur between days 2 and 10 of the menstrual cycle, in an effort to decrease the effects of hormone fluctuation. Participants taking hormonal contraceptives will be able to complete study visits at any point in their menstrual cycle.

○ *General Procedures:*

Eligible patients for both aims will be identified during clinic appointments with Dr. Laufer and recruited by the BCE Research Assistant. This method has been effective for each study the BCE has conducted, including enrolling 1200 patients in a 6-year period for the A2A study. Each patient interested will be referred to the CPB's RA to undergo an initial screening procedure (in-person or over the phone), where a general overview of the study will be given, contraindication for MRI be reviewed, and follow-up screening visit scheduled for interested and eligible patients. During the mandatory in-person screening visit, participants will undergo a brief physical exam by a physician (Dr. Borsook), review of medical records, and have their eligibility confirmed. Informed consent/assent procedures will be followed. This set of screening procedures has been extensively utilized by our team for 20+ years and for a wide range of neuroimaging studies. A detailed check list will accompany all screening and scan session visits to ensure standard operating procedures are followed^{54,55}. Once enrolled, at each study visit (one visit for Aim 1, two visits for Aim 2), participants will complete pain and psychological questionnaires selected from the *U.S. Department of Health and Human Services Patient-Reported Outcomes Measurement Information System* (PROMIS) measures as well as other validated questionnaires. Participants will also undergo a QST protocol including light touch detection, pressure pain, mechanical pain and temporal summation (a surrogate of central sensitization), as well as an OA protocol in parallel to that of Martucci and colleagues⁵⁶, the latter which will occur in the scanner during the imaging protocol. Healthy control subjects will

be recruited from our own databases at BCH, BWH, BCE, & CPB as well as advertisements posted on social media and at local colleges and universities.

- Psychophysical Measures (Table 1):

- Questionnaires:

Several pain and disease-related, as well as psychological questionnaires will be administered prior to each scan (**Table 1**). As the mechanistic and neurobiological constructs of CPP are poorly understood, it is important to assess how psychological variables such as anxiety, depression, pain-related fear, pain catastrophizing (*i.e.*, excessive worry about pain), and stress, which all have known neurobiological underpinnings⁵⁷⁻⁶⁵, impact brain metrics, such as the OA response, to maintain a chronic pain state in women with endometriosis. For example, greater pain perception relates to poorer mental health, particularly symptoms of anxiety and depression⁶⁶⁻⁶⁸. We therefore propose to assess these constructs with standardized self-report questionnaires that have been validated in children and adults to determine how they may be associated with the altered brain networks that characterize the pain state in adolescents, young adult, and adult women with endometriosis. While prior work has suggested that pain catastrophizing often supersedes the influence of more general measures of negative affect⁶⁹⁻⁷² by statistically mediating the effects of depression and anxiety on pain outcomes, we will examine the shared and non-shared variance, across age groups, in measures of catastrophizing, fear, anxiety, and depression, evaluating each as a mechanism contributing to alterations in the functional brain circuitry that is the target of this study. Additionally, stress is important to consider when examining the maintenance of chronic pain as they are two distinguished yet overlapping processes⁷³ with imaging studies of responses to stress or pain demonstrating noticeable spatial overlap in the amygdala, hippocampus, striatum, insula, and anterior cingulate cortex^{74,75}.

Table 1. Clinical & Psychological Questionnaires and QST for Aims 1 & 2

Measure	Construct Assessed	Role in Study
<i>Demographic Form</i>	Age, race, ethnicity, SES	Covariates
<i>Medical Record Chart Review</i>	Medications, Medical conditions Surgery related variables (<i>e.g.</i> time since surgery, Endometriosis stage at time of surgery, etc)	Covariates
<i>Medication Quantification Scale</i> ⁷⁶	Quantifying medication regimen use in chronic pain populations	Covariate
<i>Numerical Rating Scale (NRS)</i>	Pain intensity (current, worst, & typical)	Predictor; Covariate
<i>Health Status Questionnaire (SF-36)</i> ^{77,78}	Health related quality of life; emotional & physical functioning	Predictor; Covariates
<i>Pain Sensitivity Questionnaire (PSQ)</i> ⁷⁹	Pain perception based on painful daily life situations	Predictor; Covariate
<i>Pain Catastrophizing Scale (Adult & Child Versions) (PCS & PCS-C)</i> ^{80,81}	Negative thinking related to pain with magnification, rumination, and helplessness as subscales.	Predictor; Covariate
<i>Pain Anxiety Symptoms Scale (PASS)</i> ⁶⁵ (<i>Adult</i>) & <i>Fear of Pain-Child (FOPQ-C)</i> ⁸³	Pain-related fear and anxiety	Predictor; Covariate
<i>Patient Reported Outcomes Measurement Information System (PROMIS) Subscales</i> ⁸⁰ (<i>Pediatric & Adult Versions Accordingly</i>)	Anxiety Depression Stress Pain Impact	Predictors; Covariates
<i>Light Touch Detection and Pain Thresholds</i>	Diagnoses mechanical sensation abnormalities ⁸⁴	Predictors; Covariates
<i>Dynamic Mechanical Touch Sensation</i>	Stimulus-evoked touch and allodynia (<i>e.g.</i> , a non-painful stimulus causing pain) ^{84,85}	Predictors; Covariates
<i>Sensation of Pressure and Pressure-pain Sensation</i>	Static mechanical pressure sensation in the skin and in deep tissues ⁸⁶	Predictors; Covariates
<i>Temporal summation</i>	Wind-up pain perception to repeated punctate stimuli, a surrogate of central sensitization ⁸⁵	Predictors; Covariates

○ QST Protocol:

One unknown question is whether CPP patients (compared with controls) have altered localized or generalized skin sensitivity (allodynia^{87,88}) to stimuli as has been reported in migraine patients⁸⁹ and is a measure of disease chronification and treatment resistance/responsivity⁹⁰⁻⁹¹. All participants will undergo a QST protocol (**Table 1**) prior to each scan to assess pain sensitivity. QST is used to assess responses to standardized noxious stimuli in a controlled laboratory setting and is the only method to assess central sensitization. Research using QST has highlighted variability in pain sensitivity and pain modulation as a putative phenotypic contributor to the risk for development of chronic pain. Central sensitization likely assumes a significant role in the development of CPP. While the heightened sensitivity of peripheral pain receptors following a local trauma or infection, such as that caused by endometriosis, usually resolves with time, in CPP this hypersensitivity is sustained and amplified by an extensive central neural network that results in neuropathic pain⁹². Most pelvic organs, as well as somatic pelvic tissues to which the pain is referred, share at least part of their central sensory projection. This may trigger the phenomena of cross-sensitization and central sensitization. Animal models support the theory that central sensitization likely results in CPP in this population via a viscera-visceral referred hyperalgesia, a process in which increased input to the nervous system from one visceral domain can sensitize neurons that receive convergent input from another visceral domain⁹³. Because almost all spinal neurons that receive visceral input also receive somatosensory input from the muscle and skin through viscerosomatic convergence, precise localization and discrimination of sensory information is hindered⁹⁴. While these animal models provide insight into the potential role of central sensitization in CPP associated with endometriosis, there has been virtually no research conducted among humans. One study found that peripheral pressure-pain thresholds were lower in women with endometriosis and CPP and in women with CPP without endometriosis when compared to both women with endometriosis and no CPP and pain-free women⁹⁵. *The interplay between brain metrics, psychosocial variables and QST-assessed pain responses to predict pain outcomes in women with endometriosis has not been examined and is the focus of the current proposal. Allodynia may be an easy clinical metric to evaluate potential disease chronification or persistence as noted above for migraine.* All of the procedures are non-invasive, low-risk, and have extensive use in adult⁹⁶⁻⁹⁹ and pediatric¹⁰⁰⁻¹⁰¹ populations. The QST protocol will be conducted on the 4 abdominal quadrants as well as a non-region of interest (e.g., thumbnail for pressure, deltoid for mechanical).

○ Statistical Approach for Psychophysical Measures:

For Aims 1 and 2, patients with endometriosis (and healthy controls for Aim 1) will be compared on all study parameters (pain, hypersensitivity, emotional well-being). They will be dichotomized between those with ongoing high pain (7-10/10) vs. those with low-moderate pain (3-6/10). For all pain, emotional functioning, and QST analyses, we will first quantify distributions among the participants. We will then evaluate confounding by patient demographics, such as current age, race, anthropometry, lifestyle factors (e.g., physical activity, diet), and complementary and alternative medicine strategies. We will also evaluate confounding by clinical variables such as time since surgery (for Aim 1), endometriosis phenotypic presentation at surgery, and time from symptom onset. Our primary hypotheses and confounding will be analyzed by multivariable logistic, Poisson, or linear regression as the outcome dictates, with odds ratios, relative risks, or average effects and 95% confidence intervals calculated. Age will be considered an *a priori* covariate, while other variables will be controlled for by multivariable analysis to minimize any possible confounding. Model performance will be assessed by R-squared and deviance statistics.

○ Imaging Protocol (Table 2):

Table 2. *Structural and Functional MRI Aims 1 & 2*

Measure	Construct Assessed	Role in Study
Anatomical MRI of gray matter structures	Cortical thickness	Covariates- how these structures vary as a function of age (Aim 1), from pre-post-surgery (Aim 2), & diagnosis (endometriosis vs. migraine) (Aim 3)
	Subcortical volume	
	Total gray matter volume	

	Total white matter volume	
	Gray matter volume density	
<i>Diffusion Tensor Imaging of white matter pathways</i>	White matter pathway integrity as determined by probabilistic mapping Voxel and white matter pathway-specific anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity	Covariates- how these pathways vary as a function of age (Aim 1), from pre-post-surgery (Aim 2), & diagnosis (endometriosis vs. migraine) (Aim 3)
<i>Resting-state functional magnetic resonance imaging</i>	Strength of functional connectivity at the level of CNS networks	Predictor; Co-variates
<i>Evoked functional magnetic resonance imaging</i>	Evoked CNS responses to innocuous, mildly noxious & noxious heat stimuli CNS signature of offset analgesia	Outcome

○ Imaging Techniques:

We will implement an imaging protocol, which enables an evaluation of structural (white and gray matter structures) and functional properties (during resting- and evoked states) of the CNS properties. We have developed and implemented a neuroimaging framework that has the sensitivity and specificity to differentiate chronic pain patient populations from healthy controls. Moreover, using regression of interest analyses we are able to determine whether and how neuroimaging-based measures correlate with behavioral and clinical outcomes^{38,102,103}. Our scan sessions will include (1) anatomical MRI, (2) resting state fMRI, and (3) an fMRI assessment of OA; a psychophysical test of endogenous pain inhibition^{104,105}. Imaging will be performed on one of the Center's 3-Tesla MRI scanners (Trio or Skyra, Siemens, Erlangen, Germany) equipped with multi-array head coils. Anatomical MRI will be used to assess cortical and subcortical volumetrics and gray matter densities, but also utilized to guide spatial normalization of fMRI data. Anatomical MRI data will be collected using a standard multi-echo T1-weighted MPRAGE sequence. Functional MRI will be performed using a new gradient echo T2*-weighted pulse sequence with Simultaneous Multi-Slice (SMS) acquisition for significantly improved spatiotemporal resolution (Multiband factor=5, TR/TE = 1250/33ms, flip angle = 60°, in-plane resolution = 2x2 mm, 75 AC-PC aligned slices, slice thickness = 2.0 mm). Total scan time is estimated at 1.5 to 2 hours per neuroimaging session, a scan duration we have used in prior work^{28,34,106}.

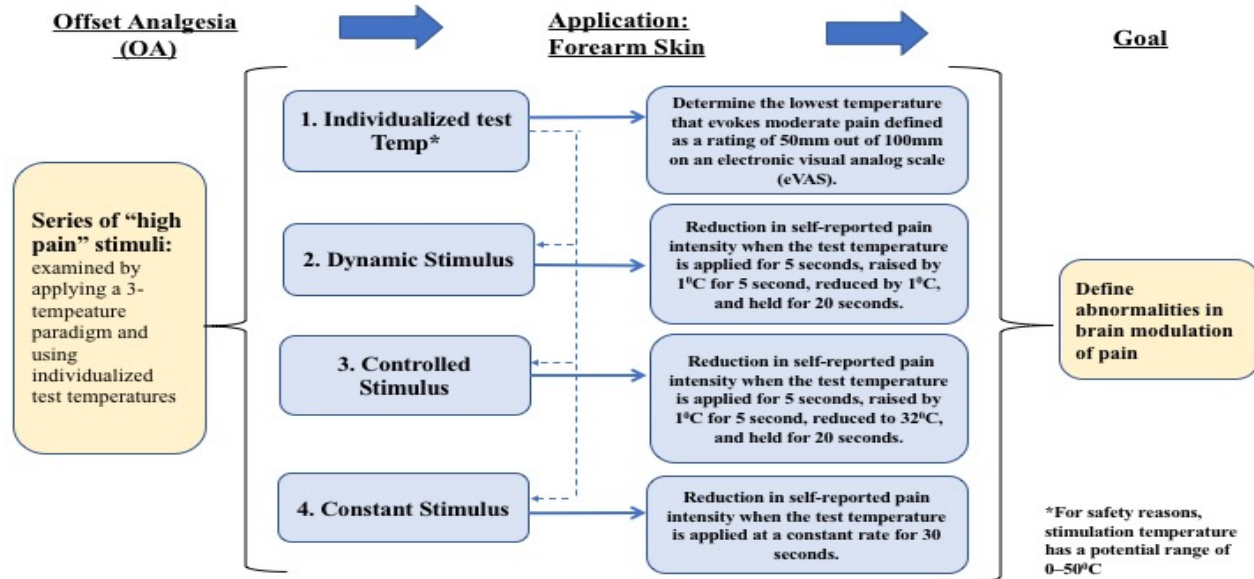
○ Resting State BOLD fMRI (rs-fMRI):

For the rs-fMRI scan, 6 minutes of rs- fMRI data will be collected with subjects resting comfortably, eyes open, in the scanner. These scans will be completed at the beginning of the scan session to avoid residual effects of evoked pain testing.

○ Evoked Pain fMRI OA:

OA will be examined using a method based off of Martucci and colleagues¹⁰⁷ (**Figure 7**). During the whole-brain fMRI data collection, we will apply a 3-temperature paradigm defined as a rating of 50mm out of 100mm on an eVAS. Testing will be completed using the MEDOC Pathway Pain and Sensory Evaluation System- ATS fMRI Model. The entire thermode- stimulating surface is placed in contact with the skin on the volar surface of the non-dominant forearm and secured by a Velcro band without stretch. The thermode baseline temperature is kept at 32°C (room temperature) and stimulation temperature has a potential range of 0–50°C for safety reasons. A preset computer-controlled temperature paradigm is programmed to deliver a specific temperature pattern. During all tests, patients will rate heat pain intensity continuously in real time using the linear, electronic visual analogue scale (eVAS). Patients will use their dominant hand to operate sliding knob of the eVAS with the following two anchors on 0 to 100 mm line. The left endpoint designated as “no pain sensation” (0 mm) and the right endpoint as “most intense pain sensation imaginable” (100 mm). Patients will be instructed to move the slider in proportion to their pain intensity in real time during testing.

Figure 7. OA Procedure



○ Statistical Approach for fMRI Analyses:

Individual and group-level analyses will be performed on structural and functional MRI data using a combination of tools available from validated neuroimaging data analysis packages including FSL, AFN, and Freesurfer¹⁰⁸⁻¹¹⁰

○ Anatomical MRI Analysis:

Using FreeSurfer tools, cortical and sub-cortical volumetric analysis will be performed¹¹¹⁻¹¹³. The initial processing steps will include: (1) motion correction, (2) averaging of two volumetric T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) datasets, (3) removal of non-brain tissue, (4) automated Talairach transformation, (5.) segmentation of the subcortical white matter and deep grey matter volumetric structures, (5) intensity normalization, (6) tessellation of the grey matter/white matter boundary, (7) automated topology correction, (8) surface deformation and (9) registration of the subjects' brains to a common spherical atlas. Once the cortical thickness and sub-cortical volumes are calculated and normalized to the whole brain volumes, statistically significant differences between the study groups (*age for Aim 1, treatment responder vs. non-responder for Aim 2, & diagnosis- endometriosis or migraine for Aim 3*) will be assessed using an unpaired t-test (corrected for multiple comparisons). High test-retest reliability of the implemented analysis method has been previously shown¹¹⁴.

○ Resting-state fMRI Analyses:

For each subject's resting-state and evoked fMRI dataset, the following preprocessing steps will be taken; (1) motion correction, (2) skull-stripped, (3) brain extracted and (4) co-registration and transformed to the Montreal Neurological Institute template brain. Resting-state fMRI data will be de-noised for spatially specific temporal artefacts (subject movement, cardiac pulsation, and scanner artefacts) using the independent component analysis + Xnoiseifier (ICA+FIX) approach¹¹⁵, which includes de-trending the data and regressing out movement parameters. Processing of resting fMRI data analysis will be performed using ICA through Multivariate Exploratory Linear Optimized Decomposition into Independent Components and a validated dual regression approach¹¹⁶. Here, a voxel-wise comparisons of resting state functional connectivity is first temporally concatenated across all subjects, followed by calculation of group networks for individual subjects, which are then used for within- and between-subject group and difference maps (*across age group & endometriosis vs. control for Aim 1 & ongoing pain vs none-low pain for Aim 2*). This process will be completed for networks of interest such as reward-aversion, salience, default-mode, frontal-control, and somatosensory networks. Specifically, although prior studies have further separated endometriosis patients with pain into two pain subgroups (endometriosis with CPP and endometriosis with dysmenorrhea), no significant differences have been

found utilizing these distinctions¹¹⁷. As previously defined, CPP is moderate to severe pelvic pain that is rated ≥ 4 (on a 0-10 pain rating scale where 10 is the most painful), lasting at least 6 months, and occurring at least 14 days monthly. Dysmenorrhea is defined as moderate to severe pelvic pain that is rated ≥ 4 (on a 0-10 pain rating score), lasting at least 6 months, but only occurring 5-13 days each month. Dysmenorrhea pain occurs around the time of menstrual bleeding, whereas CPP is typically unrelated to menses. Participants categorized in the treatment responded group will report fewer than 4 days of moderate or severe pelvic pain per month. Group analyses will be performed to evaluate how resting-state functional connectivity is divergent amongst study cohorts; age for **Aim 1**, treatment responders vs non-responders for **Aim 2**, and endometriosis vs migraine patients for **Aim 3**. All functional connectivity intra- and inter-cohort difference maps will be set at a $p < 0.05$ (corrected for multiple comparisons) threshold. Similar to our past functional connectivity investigations, seed region analyses will also be performed, where the time series from Regions of Interest (e.g., amygdala, nucleus accumbens, anterior cingulate cortex) will be extracted and used as regressors of interest in whole-brain GLM analyses¹¹⁸.

- Evoked fMRI Analyses:

Preprocessing steps for evoked fMRI datasets (OA protocol) will mimic those utilized for resting-state fMRI analyses. Group-level analyses for evoked fMRI datasets will follow procedures outlines for resting-state fMRI.

- Covariate Analyses:

A number of non-imaging covariates and predictors of interest will emanate from this study (e.g., pain ratings, PROMIS measures, pain catastrophizing, health-related quality of life, pain sensitivity, temporal summation from QST, etc). Non-imaging endpoints (e.g. pain catastrophizing, PROMIS measures, health-related quality of life, pressure pain threshold, wind-up temporal summation) will be used as covariates of interest in group-level multivariable regression modeling analyses; thus, integrating imaging and non-imaging datasets.

- Additional Analyses:

Functional and structural imaging measures showing significant differences between study cohorts; age for Aim 1 and pre- and post-surgical periods for Aim 2, will be assessed for sensitivity, specificity and predictive accuracy (c-index) using receiver-operating characteristic (ROC) curve analysis. We will also calculate positive and negative predictive value with use of Bayes's theorem in order to properly incorporate prevalence into the calculations. It is of particular interest to determine the performance of brain imaging metrics (e.g., Δ nucleus accumbens, blood oxygen level dependent response) in differentiating responders (no CPP) from non-responders (CPP). Exploratory analyses using a multimodal correlational approach will also be performed, where pairwise correlations of psychophysical measures, chronic pain measures, and neuroimaging metrics for all patients will be calculated the nonparametric by Spearman's rank correlation coefficient. Variables will be ordered by increasing magnitudes of element-wise arctangent of the first 2 eigenvectors of the correlation matrix such that variables with comparable correlations are clustered together with groups compared with use of Fisher's Z transformation.

- General Statistical Considerations:

- Subject Number:

We will enroll 20 participants in each age group (12-17; 18-25; 26-44) for Aim 1 with corresponding healthy controls. 50 adolescent and young adult women will be enrolled in Aim 2. A ~10% attrition rate is assumed based on our prior experience, thus we anticipate enrolling 22 women per age group for Aim 1 and 55 women for Aim 2.

- Data Management:

Data will be double-entered into computerized data entry forms using REDCap and verified by two people. Ongoing review will ensure reliable data flow and identify inconsistencies or deviations. Extreme values will be investigated for accuracy of data collection and entry. Subject IDs will be used. No unique identifying patient data will be transcribed for analysis. Imaging data will be stored in a secure server with restricted access to subject information, anonymized datasets will be generated and used in all subsequent analysis. Statistical analysis will be performed using the institutions' licensed SAS system (version 9.4, SAS Institute, Cary, NC) and SPSS (version 23, IBM, Armonk, NY).

- Assumptions Violations:

To address our Specific Aims, our statistical plan will evaluate the effect of age and psychophysical functioning on brain metrics in CPP. We will assess the distribution of each outcome before performing any statistical tests. For data that is not normally distributed, we will either use (1) log transformation of scale to meet the normality assumptions of the statistical method or (2) non-parametric tests such as Wilcoxon signed rank test. We will perform standard tests to assess “carry over” effects¹¹⁹.

- Missing Data:

To minimize potential missing data we will use the following strategies: (1) exclude participants (and not consider them part of our target N) if we are unsuccessful in obtaining interpretable primary outcome data (e.g. lack of fMRI data due to excessive motion; not completing the post-surgical scan for Aim 2) and (2) monitor for reliability of data during all study phases to ensure timely corrective actions. We anticipate minimal missing data. However, if data are missing we assume it will be missing completely at random. Specifically, we make the reasonable assumption that missing an experimental procedure (i.e., scan or physiological test) is due to logistical problems and not related to experimental procedures or procedure results. Due to the nature of this study, we will not be able to impute data.

- Power Analyses:

To our knowledge, no prior work has elucidated brain metrics in patients with endometriosis across ages or from pre to post-surgery. As previously indicated as part of Aim 3, migraine may parallel disease phenotypes to endometriosis. We have demonstrated in multiple studies involving imaging and psychophysics in migraine patients highly significant differences between migraine patients and healthy controls in pain-induced periaqueductal gray connectivity, altered descending modulatory pathways, and hypersensitization of pain pathways with group sizes ranging from 9-40 participants per group^{28,34,35,120}. For Aims 1a and 1b, assuming a two-sided alpha level of 0.05, a sample size of n=20 per each of three age cohorts (ages 12-17; 18-25; 26-44) with age- and demographic-matched controls provides 80% power to detect a standardized difference of 1.0 in brain changes via fMRI and psychological functioning using one-way analysis of the variance (ANOVA) and post-hoc Student’s t-tests with Bonferroni-adjustment for multiple comparisons. Given that research has shown that 30% of patients report no post-operative pain improvement, we propose n=50 for Aim 2 in order to have n=35 treatment responders compared to n=15 non-responders at post-surgery. Assuming a two-sided alpha level of 0.05, these sample sizes provide 80% power to detect a standardized difference of 0.90 in continuous brain measures between patients with and without pain post-surgery using Student’s t-test. For Aim 3, using the sample size of n=20 per each of three age cohort with endometriosis specified in Aim 1, a sample size of n=20 patients in the same three age cohort ranges with migraines in the CPB’s existing databases provided 80% power to detect a standardized difference of 1.0 in brain metrics using one-way analysis of variance (ANOVA) and post-hoc Student’s t-tests with Bonferroni-adjustment for multiple comparisons with a two-sided alpha level of 0.05. All power analyses were performed using nQuery Advisor version 8.2¹²¹

- Potential Problems and Alternatives:

The following are potential problem and alternatives:

- Clinical:

Patient Loss: Attrition is always a concern in clinical research; however, in our past experience, we expect a 10% attrition rate and have accounted for that in the budget. Both the CPB and the BCE have a long history of successful patient recruitment and low attrition due to factors such as ongoing communication with participants enrolled in longitudinal studies and the use of remuneration. As mentioned above, to minimize potential missing data we will use the following strategies: (1) exclude participants (and not consider them part of our target N) if we are unsuccessful in obtaining interpretable primary outcome and (2) monitor for reliability of data during all study phases to ensure timely corrective actions.

Medications: Most pain studies involving fMRI faces the issue of potential confounds of long-term use of medication on brain activity. We will be studying groups of patients who will potentially be on a variety of *medications* (other than opioids, which are an exclusion). We will match the pediatric and adult endometriosis samples for medication use based on classes of medications rather than on dose or on specific medications (e.g., we will attempt to ensure that whatever percentage of adult patients are taking antidepressant medications is also reflected in a similar percentage of the adolescents using that class of medications). Inter-subject differences in

medication use will be operationalized using the *Medication Quantification Scale*⁷⁶, a validated measure of global analgesics where an individual patient's score on this scale can be used as a covariate of interest in the relevant analyses. Of note, participants taking *hormonal contraceptives* will be able to complete study visits at any point in their menstrual cycle. In the case of migraine patients, we have recruited individuals with episodic migraine using non-steroidal and triptans. We will control for these medications in our comparison studies by using the healthy volunteer comparators in each group.

- Technical:

Imaging Quality: Our standard procedures (Refer to Statistical Analyses above) will be used to minimize the likelihood of motion artifact during imaging.

- Brain Changes with Development:

In this study we will need to evaluate brain changes across development during which time there are changes including stronger functional-inter regional connectivity^{122,123}. Thus, while our within group comparisons (matched for age) or longitudinal group where each patients will be their own control (adults only; Aim 3), we should not have any problems with data analysis and comparisons. However, controlling for age with respect to potential effects of plasticity, responsively and connectivity when comparing across groups will be more difficult. Similar approaches for a region defined measure (*e.g.*, Amygdala) for RSNs have been reported elsewhere¹²⁴, while others have used resting state comparisons across adolescent and young adults¹²⁵ and have taken the approach of evaluating differences utilizing techniques that we can apply here (*e.g.*, regression analysis at a group level and RSN temporal frequencies and evaluation of specific RSN's that may be salient to the condition at hand (*e.g.*, for pain, we would focus on sensory-motor, default, salience networks). Another approach we will consider if significant differences are observed across age groups is to evaluate specific functional connectivity of specific regions of interest (*e.g.*, PAG as we have recently reported for an adult migraine group) or control for age as we have reported in our preliminary data for hippocampal regions (Wilcox et al., In submission).

- Grant Timeline: The study timeline is in **Table 3**.

Table 3. Grant Timeline

Aim 1 and 2 Calendar	1: Oct 1 st . 2019-Sept. 30 th 2020				2: Oct. 1 st 2020-Sept. 30 th 2021				3: Oct. 1 st -Sept. 30 th 2022			
Quarter	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
IRB approval; DoD HRPO submission												
Purchase equipment for OA paradigm												
Recruitment and training of all personnel												
Co-author review paper												
Co-author commentary on use of OA												
Recruitment for patients: Aim 1												
Recruitment for surgical patients: Aim 2												
Conduct experiments: brain imaging; QST and OA												
Quality improvement												
Data analyses												
Presentations and manuscript prep												

The results from this study will enhance our understanding of the neurobiology of endometriosis and CPP, including age-related changes resulting from the disease, define an initial paradigm that may enhance the evaluation of patients in the clinic, predict treatment outcomes and provide a step towards the use of objective measures for individually tailored patient-oriented interventions at both a behavioral and pharmacological level.

A Short Summary defining and comparing fMRI and fNIRS

Various functional neuroimaging advancements throughout the years has enabled the discovery and investigation of underlying cognitive processes, allowing researchers and physicians to better understand the brain and it's functionality. Since 1990, functional magnetic resonance imaging (fMRI) has been widely practiced in clinical research pertaining to cognitive functioning for clinical applications such as surgical planning, monitoring treatment, and as a biomarker in pharmacologic programs. A fMRI scan measures change in blood flow that occurs with brain activity, specifically measuring the indirect consequences of neural activity. It's important to note that fMRI scans do not directly measure brain activity but instead disruptions or changes in neural networks and communication. To better understand how fMRIs work and what they measure it's important to consider the following: neural activity is systematically associated with changes in relative concentration of oxygen in local blood supply; Oxygenated blood has different magnetic susceptibility relative to deoxygenated blood; and lastly, changes in the ratio of oxygenated/de-oxygenated blood can be inferred with fMRI by measuring the Blood-Oxygen level dependent response (BOLD). The source of the BOLD contrast is derived from the difference in magnetic susceptibility of deoxygenated blood, which is paramagnetic (attracted to an external magnetic field) and oxygenated blood, which is diamagnetic (repelled from an applied magnetic field); (Kim and Bandettini, [2012](#)). BOLD fMRI is a method used in functional magnetic resonance imaging that depicts the change in deoxyhemoglobin concentration in task-induced or spontaneous modulations to observe different areas of the brain. The relationship between the BOLD contrast and neural activity is quite complex as the signal increases in a fMRI it may be potentially linked to a variety of physiological variables, including hemodynamic response and unique properties of the neuro circuit (e.g., cell type, inhibitory/excitatory synaptic activity) (Logothetis and Wandell, [2004](#)). These factors can potentially limit the interpretation and "visibility" of neural activity. fMRIs are considered to be the method of choice due to it being noninvasive, repeatable, widely available and it's superior spatial resolution. This high-resolution activation maps produced by fMRI allow for visually communicable results which ultimately makes the method more accessible.

While fMRIs have been used in countless studies, an alternative imaging technique has emerged in addition to the fMRI. The fNIR (Functional near-infrared spectroscopy) is a near infrared imaging tool that is used for testing cognitive functionality and neural communication. (Borsook, 2015) This specific technique measures NIR light absorbance in blood of hemoglobin with and without oxygen and detects ongoing neural activity and connectivity. Similar to the fMRI the fNIR measures hemodynamic response to neural activity, but rather than relying on the paramagnetic properties of Hb, it relies on different absorption properties of biological chromophores (Hoshi, [2005](#); Ferrari and Quaresima, [2012](#)). A biological chromophore is a group of atoms within a molecule that generates its color through the absorption of light at different wavelengths. fNIRS research is expanding across a wide range of active areas of research such as neurodevelopment in infants (Boas et al., [2014](#)), verbal fluency (Schecklmann et al., [2008](#)), pain (Peng, K., Borsook, D. (2018), and working memory (Kwee and Nakada, [2003](#)). fNIRS have been used to measure hemodynamic response during activities that cannot be measured with a

fMRI scanner, such as walking, exercising and everyday tasks. One of the most characteristic feature of fNIRS systems is its portability being both wireless and battery operated- this allows for the study of neurocognitive processes in a unconstrained environments, such as the outdoors. Despite its convenient portability functional NIRS are limited in the detecting cortical activity, unlike the fMRI which is capable of whole brain measurement. fMRI scanners are also superior in measuring brain depth, while fMRI is able to detect activity in deep cortical and subcortical regions, fNIRS are only able to detect NIR light that penetrates the first few centimeters of cortical tissue.

David Borsook, co-investigator on the project has done extensive research involving fNIRS and testing their efficacy on measuring neural activity while stimulating pain in the various areas of the brain. Countless studies have been published throughout the years supporting the success of the fNIRS method in effectively measuring pain stimulation (Borsook, 2016) Along with testing how effective the fNIRS method is, Borsook has also investigated ways in which fNIRS may be unreliable, which is discussed in *Mayer waves reduce the accuracy of estimated hemodynamic response functions in functional near-infrared spectroscopy* (Meryem A Yücel, David Borsook, 2016) Dr. Borsook's knowledge and expertise on the fNIRS method is quite reputable and well published.

Below is a table which compares the strengths and limitations in both fMRI and fNIRS

Table 1

An overview of strengths and limitations associated with fMRI and fNIRS.

	fMRI	fNIRS
Strengths	• Non-invasive • Repeatable • Widely available • Superior spatial resolution • Whole brain measurement (lateral surface and depth)	• Non-invasive • Repeatable • Comparable temporal resolution to fMRI • Inexpensive • Portable • Less restriction on motion
Limitations	• Expensive • Strict restrictions of motion • Need for supine position • Noisy scanner • Physiological noise • Restrictions based on metal in the body • Restrictions based on claustrophobia	• Limited to frontal regions and surface analysis • Physiological noise (including superficial scalp signals) • Lacks anatomical information • Interpretation challenges related to multiple sources of vascular signal

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