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Anatomical and functional imaging correlates of chronic pain in cerebral palsy

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JHM IRB - eForm A – Protocol

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Anatomical and functional imaging correlates of chronic pain in cerebral palsy

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Chronic pain is reported in 2/3 of adults with cerebral palsy (CP) [1]. Physicians have historically attributed pain to orthopedic complications, tone abnormalities, and systemic complications [2], which would be expected to be nociceptive. However, over 40% of hemiplegic CP respondents with pain report neuropathic pain characteristics [3]. Alterations in brain somatosensory pathways have been found both structurally and functionally. Sensory thalamocortical white matter tracts appear to be affected in children with CP born preterm [4]. Cortical somatosensory representation also appears to be altered [5]. Decreased mechanical pain sensitivity [6] and higher-level cortical sensory deficits [7] have been described in CP. Contributions of sensory deficits and alterations in cortical processing to chronic pain symptoms frequently reported in CP are not well-understood. We hypothesize that neuropathic pain amplification in CP as well as motor and other sensory deficits are symptoms of the same widespread sensorimotor network disruption extending beyond periventricular white matter. This hypothesis predicts that individuals with more severe motor deficits have more features of neuropathic pain as well as more abnormal anatomic connectivity in somatosensory networks. We anticipate data that will increase understanding of chronic pain in CP by identifying presence of a component of neuropathic pain. Better understanding could affect management of pain in patients with CP.

2. Objectives (include all primary and secondary objectives)

Primary: Identify and characterize sensorimotor network disruption patterns associated with chronic pain and motor deficits in CP

Secondary:

- Improve understanding of anatomical brain network changes in CP associated with sensory deficits and pain
- Identify non-invasive imaging-based neurobiomarkers applicable to sensory loss and pain in CP

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

A diagnosis of CP implies an early, non-progressive brain injury [8]. Motor learning studies have shown that white matter networks can selectively change diffusion parameters in an experience-dependent fashion over as few as 6 weeks [9]. Careful examination of structural changes in the pain network thus allows better understanding not only of the initial injury but also of network-wide remodeling. We posit (based on

selective spinal volume loss seen in our animal models) that remodeling extends into ascending spinothalamic tracts in the spine.

PVWMI is the most common MRI finding in CP [10]. Though attention was initially largely paid to motor fibers, our lab has identified that sensory fibers in the posterior thalamic radiations appear to be particularly affected and that apparent decreased integrity of these fibers predicts motor functioning [4]. More recent studies suggest that posterior periventricular white matter represents a nexus with high densities of intertwined long-distance afferent, efferent, crossing, and associative fibers [11]. The conventional DTI MRI model is mathematically unable to map white matter tracts near fiber crossings [12] -- including components of interest in somatosensation and CP (e.g. posterior thalamic radiations, corticocortical association fibers). Next-generation diffusion MRI models such as high angular resolution diffusion imaging (HARDI) [12] able to overcome this limitation have been demonstrated but are not yet commonplace. Use of higher-order diffusion models allow visualization of corticocortical connections and has identified previously undiscovered white matter tracts [13]**.** Higher-order diffusion models have been used successfully in CP [14] but have not been used to evaluate somatosensory pain networks.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Recruitment: **Clinic Screening** -screen up to 500 individuals in total **ICTR Screening** -screen up to 5000 individuals in total	**Survey participation (under waiver of documentation of informed consent)**	**Remote consent**	**On-site visit 2** -up to 60 participants (50 individuals with CP, 10 control participants) meeting criteria Kirby Center **2020-onwards: Resuming**
- Use ICTR/Epic filters containing basic eligibility criteria (e.g. diagnosis, age) to distribute flyer/link -Interested individuals fill out a REDcap form containing remaining eligibility criteria	-Individuals meeting eligibility criteria sent survey	-Individuals who completed survey, if interest indicated, contacted regarding further participation (allowing review of medical records/imaging results, interest in later in-person visits) -Secure REDcap survey link to online consent document sent; consent reviewed synchronously via telephone or secure Enterprise Zoom	- MRI/fMRI scan (90m)

Paper documents indicating consent will be kept in a locked compartment in a locked room, and only investigators will have access. Following consent, subjects will be assigned a pseudorandom numeric identifier **(see separate identifier number table);** the table of research identifier/personally-identifying subject correspondences will be kept in a single file on the secure KKI server system.

ICTR-based screening: We will consult with ICTR CCDA to identify individuals 1) with a diagnosis of CP (ICD-9 343.* OR ICD-9 333.71 OR ICD-10 G80.*), 2) age 8 or older, and 3) had not previously completed this study, and 4) had not previously been contacted about this study and explicitly declined to participate.

Group 1: Individuals with active Epic MyChart access: Individuals meeting criteria 1-4 who have active Epic MyChart will be contacted via the JH ICTR MyChart recruitment service. They will receive an IRB-approved recruitment flyer providing interested individuals with a link to complete screening. Follow-up messages may be sent to individuals who do not respond.

Group 2: Individuals without active Epic MyChart access: A list of email addresses for individuals meeting criteria 1-4 who do not have active Epic MyChart will be provided by JH ICTR CCDA. The same IRB-approved recruitment flyer will be sent once via JH REDcap providing interested individuals with a link to complete screening.

Survey participation: Individuals who complete screening as above and qualify will receive email survey invitations. These invitations will contain the following text:
"Your completion of the survey or questionnaire will serve as your consent to be in this research study."

Survey (via JH REDcap) will also query willingness to 1) permit access to medical records and 2) to participate in in-person research. Indication of interest in either will prompt contact to obtain informed consent.

Example questionnaire protocol:

CFCS Level	Description	Self questionnaire	Caregiver questionnaire usage
I	A person independently and effectively alternates between being a sender and receiver of information with most people in most environments.	Long form (~100 items)	Validation only
II	A person independently alternates between being a sender and receiver with most people in most environments but the conversation may be slower.	Short form (~65 items)	Validation only
III	A person usually communicates effectively with familiar communication partners, but not unfamiliar partners, in most environments.	Short form (~65 items)	Validate pain report, supplement objective information
IV	The person is not always consistent at communicating with familiar communication partners.		Primary information source

V	A person is seldom able to communicate effectively even with familiar people.	[redacted]	Primary information source

Example adult vs. pediatric battery:

Current adult instruments (self-report and self/caregiver questionnaire)	**Pediatric Self-report**	**Pediatric Parent Questionnaire**
PROMIS Pain Intensity 3a	PROMIS Ped Pain Intensity SF 1a	PROMIS Ped Proxy Pain Intensity SF 1a
PROMIS Pain Interference 4a	PROMIS Ped Pain Interference SF 8a	PROMIS Ped Proxy Pain Interference SF 8a
PROMIS Pain Behavior 7a	PROMIS Ped Pain Behavior SF 8a	PROMIS Ped Proxy Pain Behavior SF 8a
PROMIS Pain Quality	PROMIS Ped Pain Quality SF 8a	-
CPUP Pain location	CPUP Pain location (Westbom 2017)	CPUP Pain location
PainDETECT	-	-
AQoL-4D	KIDSCREEN-10 (Dickenson 2007)	KIDSCREEN-10 Parent form
PHQ-4	PHQ-4	-
PCS	PCS-C	-
PSS	PSS-C (White 2014)	-
ISI	-	PISI (Byars 2016)
SOAPP-R	NIDA-modified ASSIST – Substance use	NIDA-modified ASSIST – all
CPCI Vineland-3 (caregiver report) BRIEF-A (self-report or caregiver report)	KCS BRIEF-2 Self-report	- Vineland-3 (caregiver report) BRIEF-2 Parent report

Review of medical records: Following consent, medical records will be reviewed and extracted by provider-level research associates (for subjects with CP only). Data extracted from the medical record, the structured interview, and the structured physical exam will be entered by provider-level research associates into a database indexed by the research identifier number via a secure data entry system (REDCap, Nashville, TN) recording data directly into secure JH servers. Extant brain and spine imaging will be stored as de-identified DICOM files on secure KKI servers. Items for the REDCap form **(see separate sample data sheet for information extracted from the medical record, from the structured interview, and from the structured physical examination)** are primarily based on the CP Research Network (CPRN) database entries but are expanded using validated instruments to NIH-NINDS recommended common data elements (CDE) for CP. Instruments include quality of life scales (AQoL-8D) and the NIH-developed PROMIS pain scales. The collected information is designed to be cross-compliant with both NIH and CPRN standards while adequately addressing the question at hand and minimizing burden to subjects.

Structured Interview and Physical Examination (discontinued post-COVID restrictions): Information not attainable from the medical record (e.g. subjective measures regarding pain, quality of life, and sociopsychological functioning) will be obtained via a structured interview between a provider-level research associate and the subject +/- caretaker. The subject +/- caretaker will communicate responses, which will be recorded into RedCAP in real-time by the research associate. The degree of reliance on individual interview responses vs. pre-filled questionnaire will be determined by degree of communicative ability (example breakdown in table below). A non-invasive physical examination will then document and quantify motor abnormalities (e.g. grading of spasticity and dystonia) as well as other contributing

abnormalities (e.g. balance abnormalities or orthopedic deformities), which will similarly be recorded into REDCap in real-time by the research associate. In the process of optimizing the structured interview, we may reformat items and add or remove interview instruments but will maintain overall interview/exam length less than 2 hours. If a subject desires, the study visit can be halted at any time and either continued at a later date or not.

Analysis of existing neuroimaging: Previously-acquired traditional MRI obtained for clinical purposes will be requested and reviewed to detect correlation between routine neuroimaging markers of perinatal brain injury and CP and pain. If of suitable quality, quantitative analysis methods (e.g. analysis of brain lobe and ventricular volumes for volumetric anatomical sequences, analysis of white matter volumes from DTI sequences) may be applied to prior images.

MR Scanning Methods: Research unsedated MRI scans (outside of usual care) will be performed using a 3T Philips scanner at the F.M. Kirby Research Center. An MRI scanning protocol will be at the F.M. Kirby Research Center; the protocol will not last more than 1.5 hours. Acquisitions will include a triplanar survey, functional and anatomical multi-slice imaging of the brain as well as MRI of selected spinal levels. Protocols will be used that do not involve use of contrast agents and limit power/tissue absorption as well as otherwise remain within FDA and Kirby Center safety regulations. When possible, MRI will be performed within 3 months of initial survey/interview administration. If MRI is scheduled >3 months after initial survey/interview administration, a brief survey will be re-administered to screen for changes in pain/clinical status.

b. Study duration and number of study visits required of research participants.

Our imaging protocol will require no more than 1.5 hours of scan time per participant; participants will be selected who can complete scanning in one session.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

N/A

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

A control group of typical subjects without CP with groupwise similar ages and genders will be included to demonstrate typical norms.

f. Definition of treatment failure or participant removal criteria.

N/A

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

N/A

5. Inclusion/Exclusion Criteria

Subjects with CP: Caregiver questionnaire only

Inclusion criteria (must be YES to all):

1) Individual 8+ years of age
2) Diagnosis of cerebral palsy

Subjects with CP: Core Study (Survey)
Inclusion criteria (must be YES to all):
1) Individual 8+ years of age
2) Adult subject able to indicate understanding and affirmative consent
OR
Adult/child subject unable to indicate understanding and affirmative consent AND subject assents AND LAR consents
3) Diagnosis of cerebral palsy
4) CFCS I-III and able to respond unambiguously to at least 65 multiple-choice items

Control subjects: Core Study (Survey)
Inclusion criteria (must be YES to all):
1) Individual 8+ years of age
2) Adult subject able to indicate understanding and affirmative consent
OR
Adult/child subject unable to indicate understanding and affirmative consent AND subject assents AND LAR consents

Exclusions (must be NO to all):
1) Clinically-significant neurologic or developmental diagnosis

Subjects with CP undergoing MRI
Inclusion criteria (must be YES to all):
1) Individual 8+ years of age
2) Adult subject able to indicate understanding and affirmative consent
OR
Adult subject unable to indicate understanding and affirmative consent AND subject assents AND LAR consents
3) Diagnosis of cerebral palsy
4) Clinical imaging demonstrating isolated periventricular white matter injury
5) Clinical judgment that all neurologic symptoms are attributable to non-progressive periventricular white matter injury
6) Able to lie still in scanner for 1.5 hours in at most 2 sessions and be able to have MRI

Control subjects undergoing MRI:
Inclusion criteria (must be YES to all):
1) Individual 8+ years of age
2) Adult subject able to indicate understanding and affirmative consent
3) Able to lie still in scanner for 1.5 hours and be able to have MRI

Exclusions (must be NO to all):
1) Clinically-significant neurologic or developmental diagnosis

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

N/A

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

Primary outcome variables include brain and spine volumes and diffusion scalars for tracts of interest including the posterior thalamic radiations as well as somatosensory association fibers and the spinal spinothalamic tract.

b. Secondary outcome variables.

None

c. Statistical plan including sample size justification and interim data analysis.

An ANOVA will be used to compare MRI-based parameters (e.g. volumes and diffusion MRI scalars) between the three groups. Tracts of interest and specific diffusion MRI scalars will be selected *a priori* to minimize multiple comparisons confounds. Based on effect size seen in the PLIC tract in our prior study using DTI including 24 subjects with CP[16], a power analysis suggests that a sample size of 7 per group allows a power of 0.8 while maintaining α of 0.05. As higher-order diffusion sequences gather strictly more information than DTI techniques, we expect them to be even more sensitive.

d. Early stopping rules.

Subjects may withdraw from the study at any time and for any reason.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The proposed research presents no more than minimal physical, psychological, legal, or financial risk to participants. Magnetic resonance imaging is a minimal risk procedure when able to be done without sedation, as planned based on the age range for this study. Subjects that are susceptible to injury from high-power magnetic fields (e.g. presence of metallic objects (such as pacemakers) implanted in his/her body) will be identified using the Johns Hopkins Radiographic Sciences Department screening form prior to imaging. Study team members who will be in the control room or scanning room of the MRI suite are required to undergo MRI safety training provided by the Radiographic Sciences Department. Risks during the scan may include anxiety from loud noises or the enclosed space of the scanner. Breach of confidentiality and incidental findings on MRI is also a potential risk. We do not anticipate any risks to study personnel, as only subjects who are trained in MRI safety will be allowed access to the MRI scanner.

b. Steps taken to minimize the risks.

The magnet in the scanner can cause electronic devices like pacemakers, beepers, and watches to malfunction, and some metal objects can be pulled into the magnet. If a subject has an electronic device (like a pacemaker) implanted in his/her body there is a risk that the metal may move or be dislodged. To minimize this risk, we will ask subjects/parents a series of questions before the scan to make sure the subject does not have any metal on or in his/her body, and we will ask him/her to take off any metal objects he/she

may be wearing (such as a watch or jewelry). No sedation is used. Scanning sessions will be terminated immediately upon the request of the participant, or if the participant becomes upset by the noise, claustrophobia, anxiety or poor performance during testing. Participants with implanted electrical devices or ferromagnetic foreign bodies in critical soft tissues will be excluded from this study.

Also, we may discover an abnormality on the MR exam that we are not expecting. Some findings may require additional tests to find out what they are. Any unexpected results will be shared with the participant. The participant will also be told any new facts that could affect whether s/he wants to stay in the study.

All assessment information will be considered confidential. No participant will be identified by name in any presentation of the results. Identification numbers will code data entered for computer analysis, and the data coordinator will keep all names and code numbers. Findings will be made available to legitimate agents of the participants (physicians) only with the express, written consent of the subject.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or study deviations will be reported to the Johns Hopkins IRB within 48 hours of occurrence.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Strict maintenance of confidentiality of subject data and identifying information will be utilized to minimize legal risks. Any physical data will be kept in a locked office in a locked cabinet to which only key study members have the key. Electronic data will be kept on a secure, password-protected server with access limited to key research team members; image processing will occur on a dedicated, password-protected computer in a locked office with access limited to key research team members. Study documents and files outside of the linking document will be deidentified and marked with a study identifier only.

e. Financial risks to the participants.

None.

9. Benefits

a. Description of the probable benefits for the participant and for society.

The participant is unlikely to receive any direct benefits from being in the study. This research will be used to better improve prognosis and management of pain in cerebral palsy patients in the future.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Individuals completing all survey components will receive an honorarium of $10 by mail.

We will additionally provide an honorarium of $20 per in-person visit to cover time and travel expenses. Parking at KKI is free for research subjects.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no costs to the subjects for any of the procedures in this study. Participants will be responsible for paying for food and transportation. Free valet parking will be offered at the Institute.

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