Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Investigating the Pathogenesis of Paroxysmal Sympathetic Hyperactivity Using Lesion Analysis

Student Investigator's Name

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Date of Submission *(mm/dd/yyyy)*

03/11/2022

Graduation Year

2022

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

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Concentration Lead's Name

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Project/Research Question

What neurological networks are disrupted in patients with PSH?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Retrospective research study

Key words *(4-10 words describing key aspects of your project)*

Lesion network mapping, connectome analysis

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

N/A

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

N/A

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

None

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Next Steps

What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

The final steps of the connectome analysis are still ongoing. After that, next steps would be to reproduce these results with additional samples, and determine potential therapeutic targets within the identified functional connections.

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X _____

Student's full name

Mentor's Approval *(Signature/date)*

X _____

Mentor Name

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Report: *Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome that occurs in a subset of patients with severe acquired brain injury, most commonly traumatic brain injury (TBI).[1] Though the condition has been described since at least 1929, it has been underrecognized and was only recently formally named and defined with diagnostic criteria.[2,3] The syndrome consists of episodes of sympathetic activity such as tachycardia, hyperthermia, diaphoresis, and arterial hypertension, and decerebrate posturing.[3–5] Estimates of incidence range from 8% to 33%, regardless of the type of acquired brain injury, for both adult and pediatric patients.[1] PSH remains poorly understood and difficult to treat, with therapeutic options limited to supportive care with pharmacologic interventions.[5] The syndrome has been associated with longer rehabilitation periods, longer hospital stays, higher healthcare costs, and worse outcomes. [4,6–10]

Though originally proposed to be epileptic in etiology, the most recent hypotheses suggest that PSH occurs when brain injuries cause disconnection of cortical inhibitory centers from excitatory centers in the diencephalon, brain stem, and spinal cord.[5,11] There is also evidence for the role of peripheral catecholamine response in PSH, implicating central neurotransmitter systems.[1] PSH has been associated with parenchymal lesion burden and white matter tract injury, including diffuse axonal injury (DAI).[7,8,12–14] A recent diffusion tensor magnetic resonance imaging (MRI) study found PSH was associated with lesions in the corpus callosum and posterior limb of the internal capsule.[15] The variety of lesion locations in PSH patients makes it unlikely that any single brain lesion drives the disease. It is more plausible that a common network may be disrupted, rather than any single or group of structures.

Lesion network mapping is a novel approach that has been applied to study a variety of lesion-induced disorders.[16–19] Briefly, the technique involves applying lesions traced from diseased patients onto the human connectome, a normative map of functional connectivity in the brain, to determine what networks are disrupted in a disease.[16] Lesion network mapping is applicable to PSH, as the lesion burden in PSH patients varies considerably in location and distribution and the pathophysiology is unknown but suspected to involve network disconnection. We hypothesized that diffusion weighted imaging (DWI) could be used to detect diffusion restricting lesions with injuries such as DAI in PSH patients. We further proposed that lesion network mapping could be used to determine which of these lesion locations are associated with PSH, and what brain networks are disrupted in the disease.

Methods *(≥250 words)*

Patient recruitment

A total of 59 patients were selected, of whom 15 met criteria for PSH, as described in Figure 1. Patients were selected from two existing cohorts (QPSH and FAINT) prospectively obtained for prior studies. IRB approval was obtained prior to patient enrollment. Informed consent was obtained from patient or, if they were unable to provide informed consent, from the patient's legally authorized representative. If and when patients regained the ability to provide consent during the hospitalization, they were approached to reaffirm consent. Patients who refused consent or were unable to be consented were not included.

For the QPSH cohort, consecutive adult patients with head trauma presenting to a Trauma Bay of the emergency department (ED) with a Glasgow Coma Scale (GCS) score of 12 or less and requiring admission to the Trauma intensive care unit (ICU) were included. Patients were excluded if their GCS score was low and attributable to a cause other than brain injury, such as sedation, intoxication, or hemorrhagic shock. Patients were also excluded if they were discharged from the ED or admitted to a non-ICU ward. For the

FAINT cohort, trauma patients requiring admission to the trauma ICU were identified. Patient clinical data was obtained from the electronic medical record. Additional inclusion criteria for this study included availability of diffusion weighted magnetic resonance imaging (MRI) of the brain, and the presence of diffusion restricting intracranial lesions.

PSH was defined as at least 2 serial events of paroxysms of 3 or more of the following simultaneous characteristics: (1) tachycardia, (2) tachypnea, (3) hypertension, (4) fever, (5) dystonia (rigidity or decerebrate posturing), and (6) diaphoresis, with no other obvious causation (ie, alcohol withdrawal, sepsis). Patients were monitored for the entirety of their hospitalization. The Diagnosis Likelihood Tool (DLT) was calculated for each case using retrospective chart review. MRIs were obtained at the discretion of the treating team, without any specific protocol.

Lesion tracing and segmentation

We defined lesions as regions with abnormal restricted diffusion, in order to detect possible diffuse axonal injury and use a more objective, easily reproducible criteria. Each patient's diffusion weighted imaging (DWI) was used in conjunction with apparent diffusion coefficient (ADC) maps to identify regions in the brain with abnormally restricted diffusion, as shown in Figure 2. High signal on DWI images were confirmed by abnormally low ADC values, to avoid T2 shine-through. These lesions were manually segmented in Slicer-3D (slicer.org), a free opensource medial image computing software, using the paint function of the Segment Editor module (SparKit project, funded by Cancer Care Ontario (CCO)'s ACRU program and Ontario Consortium for Adaptive Interventions in Radiation Oncology (OCAIRO), Contributors: Csaba Pinter and Andras Lasso, Queen's University).[20]

Hemorrhagic contusions, hemorrhage, and hemorrhagic tracts associated with ventriculostomy tracts were identified using T1 weighted imaging and excluded from segmentation. For all cases, lesion tracing and segmentation was validated by two blinded readers. Segmentations were converted to binarized maps in Slicer-3D.

Lesion network mapping

Binarized lesion maps from Slicer-3D were registered onto a common brain template using FLS to be overlapped and assess for peak lesion overlap, separately for PSH and control patients.[21] Areas of peak lesion overlap were analyzed voxelwise for association with PSH, controlling for lesion volume.[22] Each individual lesion map and a publicly available connectome dataset based on 1000 normative subjects were coregistered to identify networks functionally connected with lesions, as previously described.[16,17,18,23] Resting state functional connectivity between lesion locations and other networks in the brain were determined in this manner.

Results *(≥500 words)*

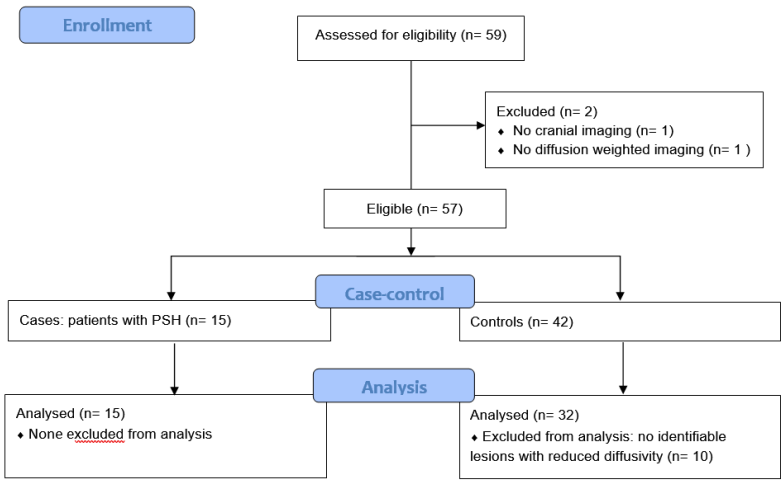

Figure 1. Modified CONSORT flow chart identifying patients with and without PSH.[24] Patients were identified from two previously collected prospective cohorts of trauma patients. Inclusion criteria included major trauma, ICU admission, and availability of magnetic resonance imaging of the brain (obtained at the discretion of the treating team), including diffusion weighted imaging. 57 patients were eligible, of which 15 had PSH.

Patient demographics

We identified a total of 59 patients who were assessed for eligibility. Two were excluded due to a lack of appropriate neuroimaging, and ten were excluded as they had no identifiable lesions demonstrating reduced diffusivity. 15 patients met criteria for PSH, while 32 patients were in the control group. PSH patients were younger, with an average age of 27 (+/- 12 years) compared to 51 (+/- 22 years) in the control group ($p < 0.001$). The PSH cohort had a median GCS score of 3 (3-4), lower than the median GCS score of 4 (3-8) in patients without PSH ($p = 0.04$). There were no significant differences in race or sex between groups.

Locating lesions in PSH patients

Lesions were identified by reduced diffusivity on neuroimaging, and varied in number and distribution across all patients (Figure 2). On visual inspection, lesions in PSH patients were often located in the deep white matter, particularly at the corpus callosum and in the centrum semiovale and corona radiata. Maximal overlap from lesions in all patients was identified in the left posterior corpus callosum, and to a lesser degree in the corona radiata (Figure 3a). When lesions in PSH patients were isolated and thresholded, maximal lesion overlap was seen in the left posterior corpus callosum (Figure 3b).

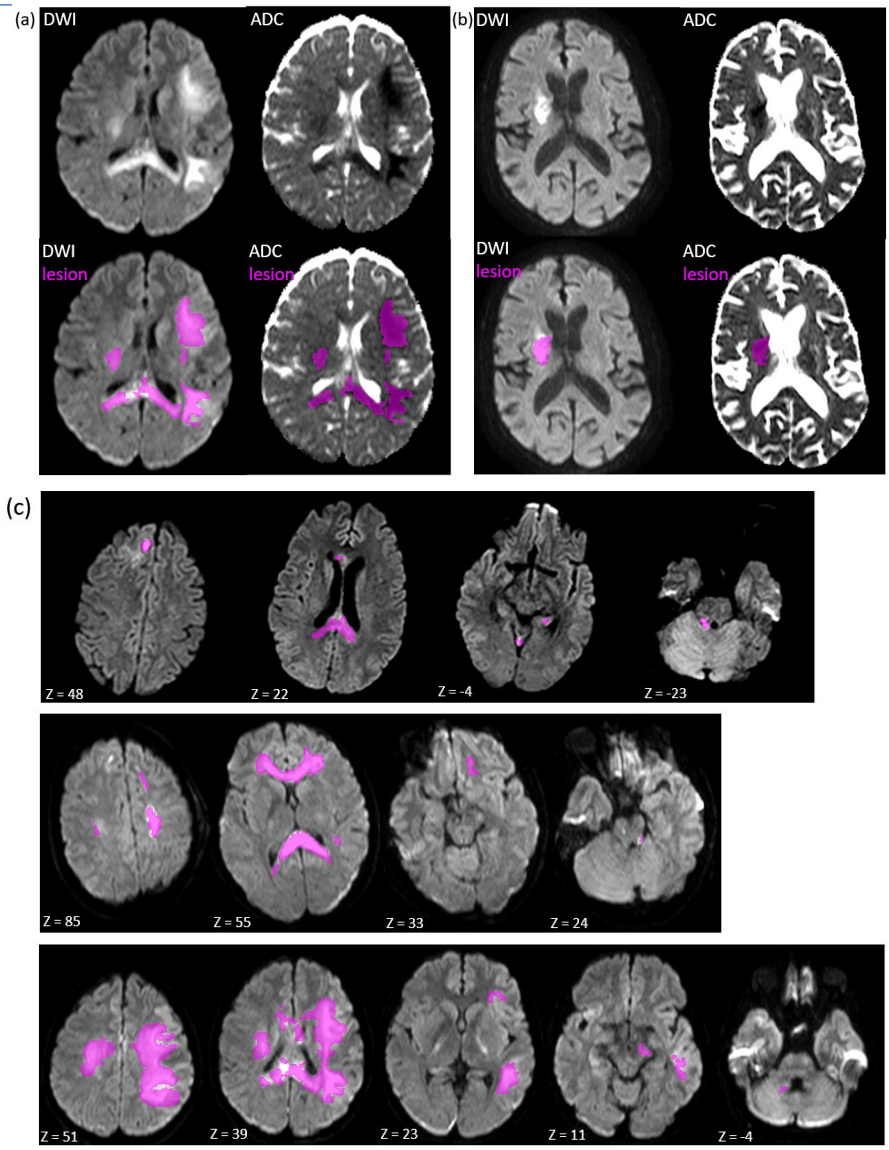

Figure 2. Examples of lesion tracing and distribution. Two examples of lesion tracing in Slicer-3D, in a PSH patient (a) and a control patient (b). Lesions were identified as diffusion restricting by using diffusion weighted imaging in conjunction with ADC maps, and tracings are shown in pink. Two examples of lesions associated with PSH are shown in (c).

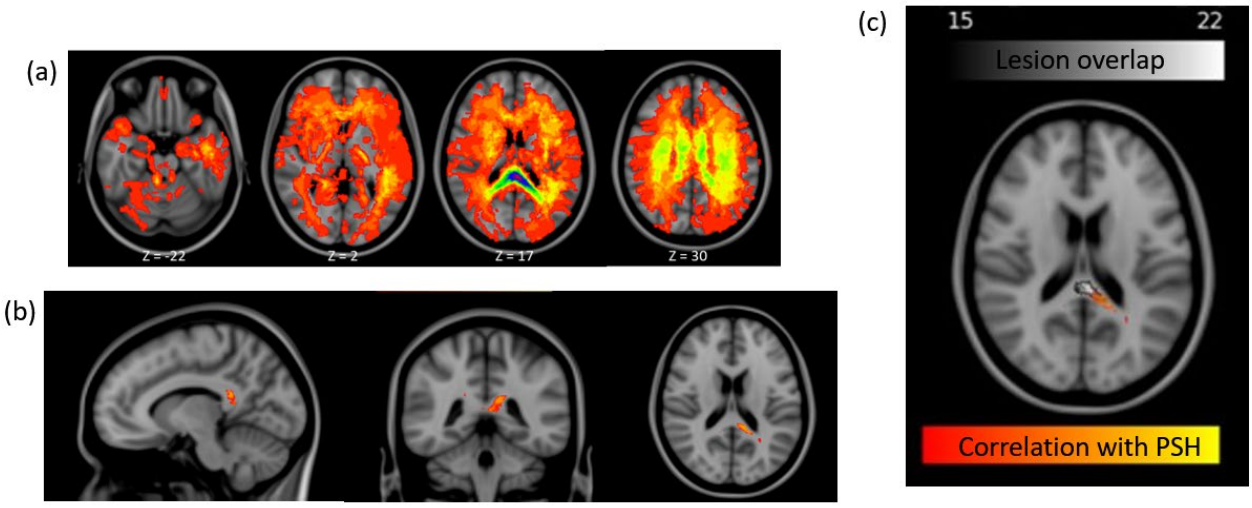

Figure 3. Lesion overlap and association with PSH. Lesions from all patients were overlapped on a common brain template using FSL (a). More significant overlap is shown in cooler colors, including in the corpus callosum and the corona radiata, while regions with less overlap are shown in warmer colors. Lesions from PSH patients only were similarly overlapped and thresholded, showing maximal overlap in the left posterior corpus callosum (b). Voxels were assessed for association with PSH, controlling for lesion volume as a covariate (c).

Lesion locations and networks associated with PSH

The region of the left posterior corpus callosum was analyzed voxelwise for association with PSH, controlling for lesion volume. A significant peak was identified adjacent to but not overlapping the site of maximal lesion overlap, indicating that lesions located in the left posterior corpus callosum were associated with PSH (Figure 3c). These voxels with significant association with PSH were further analyzed in conjunction with the normative connectome dataset to assess resting state functional connectivity between this location and the rest of the brain. In an exploratory analysis, the location of this cluster was functionally connected to the mesial temporal lobe, fornix, lateral hypothalamus, parietal lobe, ventral midbrain, inferior cerebellum, and dorsal pons (T value > 7, corrected $p < 0.05$; Figure 4).

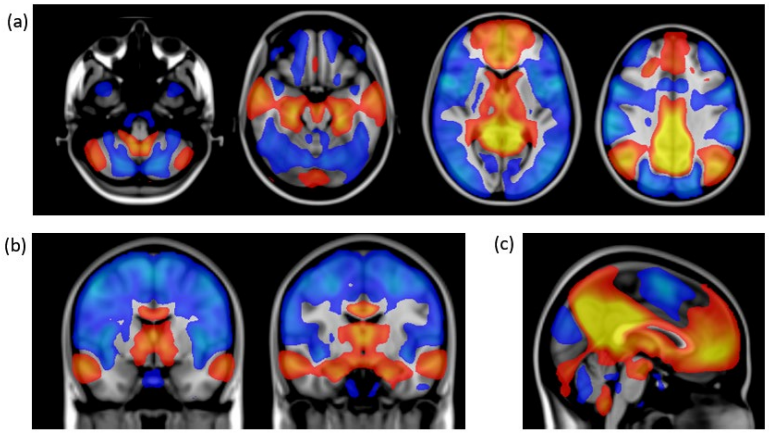

Figure 4. Resting state functional connectivity between the lesion location at the left posterior corpus callosum and brain networks. Individual lesion maps from PSH patients and a publicly available connectome dataset based on 1000 normative subjects were used in conjunction to identify regions functionally connected with the lesion location associated with PSH shown in Figure 3c. These regions included the mesial temporal lobe, fornix, lateral hypothalamus, parietal lobe, ventral midbrain, inferior cerebellum, and dorsal pons. Significant connectivity is shown in warmer colors, while less significant connectivity is

represented in cooler colors, seen in axial (a), coronal (b), and sagittal (c) representations.

Discussion *(≥500 words)*

In this prospectively acquired cohort of TBI patients, we identified lesion locations associated with PSH and the networks that are implicated. The results suggest the left posterior corpus callosum and associated connectivity to the mesial temporal lobe, fornix, lateral hypothalamus, parietal lobe, ventral midbrain, inferior cerebellum, and dorsal pons may be disrupted in PSH.

These findings further elucidate the pathogenesis of PSH, building on prior work. The most current hypotheses in the literature propose that disconnection underlies the pathophysiology of PSH.[5,25] Most recently, Baguley proposed the Excitatory: Inhibitor Ratio (EIR) model has been suggested, in which two related networks are disrupted. The disconnection of a descending inhibitory pathway sets the stage for maladaptive excitatory spinal circuits to form, which cause non-noxious stimuli to be perceived as noxious, resulting in the sympathetic storming of PSH.[11,25,26]

Previous work has determined that PSH is associated with younger patient age, injuries to the deep white matter, and diffuse axonal injury, which can be detected on diffusion weighted imaging radiographically.[13,27,28] Additionally, in trauma patients diffuse axonal injury (DAI) has been detected using DWI in fiber tracts such as the corpus callosum.[29] Lv et al. found an association between PSH and injury to the periventricular white matter, corpus callosum, basal ganglia, and brainstem.[9] Furthermore, Hinson et al. found that PSH was linked to lesions in the right-sided posterior limb of the internal capsule and in the splenium of the corpus callosum, implicating a disruption of fibers of the right insula. As such, to our knowledge this is the first investigation specifically using DWI to assess PSH lesions and is well-suited to detect DAI. Furthermore, this is the first investigation to use lesion network mapping and connectome analysis to study PSH, an innovative approach to determine pathophysiology of lesion-based disease.

Our results further elucidate the mechanism behind PSH. Significant association of lesions located in the left posterior corpus callosum with PSH implicates the white matter tracts of the brain. The fibers within the splenium connect occipital, parietal, and temporal regions, as well as the posterior cingulate, which has been shown to play a role in autonomic nervous system activity.[30] Our findings of the left posterior corpus callosum location's functional connections to the mesial temporal lobe, fornix, lateral hypothalamus, parietal lobe, ventral midbrain, inferior cerebellum, and dorsal pons extend the previous disconnection hypothesis, and suggest that a common brain network between these regions is what is specifically disrupted in PSH. Further analyses are needed to determine the significance and consistency of these functional connections, and will need to be reproduced in larger samples. Ultimately, these findings can guide future investigations into novel therapeutic interventions for PSH.

Our study has several limitations. First, hemorrhagic contusions were excluded from our analysis because blood products have a complex and unpredictable appearance on DWI.[29] However, these contusions could certainly cause abnormal diffusion restriction that we were not able to capture in our analysis, resulting in missed significant findings. The use of a manual approach for lesion tracing also created potential for errors and subjectivity, though the findings of a statistically significant lesion location and functional connections argue against such an effect. Additionally, MRIs were obtained at different times following trauma, and we did not consider the associated time-sensitive changes that may have been present in imaging. Considering that DAI and injuries in general can evolve over time, this is a limitation.

There are also limitations around our sample. This is a secondary analysis on cohorts designed for other studies, and these patients were not directly clinically observed by the authors. Our sample size was small, as patients with PSH were in the minority in our cohort. Characteristics of younger patient age and decreased GCS scores are in line with prior work, however.[7,8] The normative connectome dataset is from subjects aged 18-35 years, which is not ideally age-matched for our control group.[23]

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Conclusions *(2-3 summary sentences)*

Lesions located in the left posterior corpus callosum were associated with PSH. Functional connections to the mesial temporal lobe, fornix, lateral hypothalamus, parietal lobe, ventral midbrain, inferior cerebellum, and dorsal pons may also be associated with PSH.

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