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ABSTRACTS

Multi-Departmental Trainees' Research Day

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DEPARTMENT OF NEUROLOGICAL SURGERY

DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION

DEPARTMENT OF ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE

Oral Abstract O1

TOWARD A SMART CUFF MULTI-PARAMETER HEMODYNAMIC MONITORING VIA A SINGLE CONVENIENT DEVICE

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Introduction: Monitoring cardiac output (CO), venous pressure (VP) and blood pressure (BP) is essential for guiding clinical therapy. However, it requires multiple devices that are highly invasive, operator dependent, or expensive. Automatic arm cuff devices are universally employed for non-invasive BP monitoring in hospital patients. These devices measure the cuff pressure oscillations which indicate blood volume pulsations and may therefore be useful for CO monitoring. Furthermore, these devices show a peak at cuff pressure near mean arterial pressure (MAP) due to the sigmoidal volume-pressure relationship of blood vessels; therefore, an oscillation peak may also be present when VP is high and can be non-invasively detected.

Hypothesis: We hypothesized that an automated arm cuff device can non-invasively estimate CO and MAP and detect elevated VP from cuff-derived pulsatile signals.

Methods: *Device:* to test this hypothesis, we employed a custom cuff device that measures cuff pressure during servo-controlled linear deflation. For VP the device operated at low cuff pressure. We also incorporated a unique air flow sensor to also measure volume of air pumped into and out of the cuff. *Data Collection:* Under IRB approval, we obtained measurements with the custom device, the invasive BP waveform via radial artery catheter, the reference central VP (CVP) via central venous catheter, and reference CO via pulmonary artery thermodilution during major interventions in liver transplant and cardiac surgeries. *Data Analysis:* We applied a basic analysis to estimate CO in L/min as the product of heart rate, maximum amplitude of the "volume oscillogram" (i.e., product of cuff pressure oscillations amplitude and the compliance of the arm-cuff system derived from the measured arm-cuff volume-pressure relationship, as a function of cuff pressure), and the body to arm surface area ratio. We also proposed a new MAP estimate as the peak position of the "volume oscillogram." For comparison we estimated the conventional MAP as the peak position of the cuff pressure oscillogram. Moreover, we observed that a cuff pressure peak showed at low cuff pressures when the reference CVP was high, while no such peak was observed at low CVP. We then developed a basic algorithm to detect the presence or absence of low-pressure oscillations peak. We then evaluated whether this marker was able to classify CVP≥12 mmHg vs CVP<12 mmHg.

Results: We found that cuff estimated CO and reference CO have a correlation of r=0.60 for N=34 patients. For comparison, we applied basic pulse contour method for CO estimation from the invasive BP waveform, which has a correlation of r=0.62 with reference CO. For the same cohort we found that the proposed MAP was more accurate than the conventional MAP when compared with invasive reference, the correlation improved from 0.79 to 0.86, and the bias and precision errors were reduced from 6.1 to -0.83 mmHg and 8.1 to 6.5 mmHg, respectively. In a smaller cohort of N=8, we found that low-pressure oscillations peak method achieved a sensitivity of 68% and a specificity of 89% for the CVP classification.

Conclusions: These initial findings suggest that CO, MAP, and VP may be detectable non-invasively using an automated arm cuff device.

Significance: Automatic arm cuff devices may provide feasible multi-parameter hemodynamic monitoring, potentially improving patient management.

Research/Grant Support: This work was supported by the NIH Grant HL163691.

Abstract 1

MEDIAL ELBOW SENSORY EFFECTS OF INTER-TRUNCAL SUPRACLAVICULAR BLOCK

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Introduction: Supraclavicular Brachial Plexus Block (SCB) is the preferred method for UE nerve blockade, and is commonly used for elbow surgery. One potential limitation is coverage of the medial elbow region, due to overlapping cutaneous dermatomes [1,2]. We conducted an observational study to evaluate the adequacy of anesthesia at the medial elbow after SCB with inter-truncal injection of local anesthetic solution, as ulnar sparing can occur even though most areas appear blocked, even when the other areas of the upper extremity are well blocked [3].

Hypothesis: Inter-truncal supraclavicular block does not reliably provide adequate sensory anesthesia of the medial elbow

Methods: After IRB approval (Study 24070135) adult patients undergoing SCB for upper extremity surgery were approached for participation. The patients underwent SCB with 20-22 ml of bupivacaine 0.5% using ultrasound guidance, deposited between trunks and deep to the inferior trunk. At 20-25 minutes after block, the patient was evaluated for sensitivity to cold and sharp stimulus, as well as motor effects in the blocked extremity. The primary outcome was sensory score at medial elbow (successful block equated to score of 0 or 1 out of 4). Secondary outcomes included the overall block score, proportion with sensory score of greater than 4, requirement for local anesthetic supplement by surgeon and/or conversion to general anesthesia, and pain score in PACU.

Results: 30 patients were included in this convenience sample, including a variety of different surgeries (Table 1). Seven patients (23.3 %) had abnormal sensory exam before surgery, four of these due to ulnar compression. Medial elbow sensation was successfully blocked in 20 (67.7%) patients; the mean sensory score at this site was 1.0 (1.2) out of possible four (Table 2). 2 of 6 patients undergoing elbow surgery and 8 of 24 undergoing other surgeries had preserved sensation at the medial elbow.

Conclusions: Two-thirds of patients exhibited successful sensory block of the medial elbow with two cases requiring surgeon local supplementation and one requiring general anesthesia.

Significance: These results may assist anesthesiologists in planning regional techniques for incisions medial to the elbow, such as including a subcutaneous injection in the proximal arm for the cutaneous nerves, particularly the intercostobrachial nerve (4).

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Research/Grant Support: No specific funding was provided for this investigation

Abstract 2

ANDROGENS MEDIATE SEX DIFFERENCES IN THE SPINAL PKA AND ERK SIGNALING OF CHRONIC POSTSURGICAL PAIN

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Introduction: Acute surgical pain is frequently followed by chronic postsurgical pain (CPSP). Although opioids effectively treat acute pain, prolonged opioid use in CPSP loses efficacy and is associated with dependence and tolerance. Latent sensitization (LS) is sensitized nociceptive signaling that remains tonically masked by endogenous inhibitory mechanisms, including kappa opioid receptor (KOR) signaling, after recovery from surgery.

Hypothesis: We hypothesized that the spinal androgen receptor (AR) mediates sex differences in LS by regulating protein kinase A (PKA) and downstream ERK signaling pathways after binding to testosterone.

Methods: We used a murine plantar incision model of CPSP. Mechanical and thermal sensitivity were assessed before and after incision. After resolution of hyperalgesia (21 days), LS was unmasked via intrathecal administration of the KOR antagonist LY2456302. Pharmacological inhibitors of PKA (H89, KT5720), MEK (PD98059), and ERK (SCH772984) were administered intrathecally. AR signaling was manipulated using flutamide, orchiectomy, and testosterone administration (systemic and intrathecal). We used conditional AR knockout mice ($AR^{loxP/loxP}$) crossed with PirtCre or Lbx1Cre to assess AR in the dorsal root ganglion (DRG) and spinal cord (SC) neurons, respectively.

Results: PKA inhibition prevented KOR antagonist–induced reinstatement of mechanical hypersensitivity in male but not female mice. Similarly, ERK inhibition prevented reinstatement only in males ($p < 0.05$). Pharmacological AR inhibition with flutamide or testosterone removal through orchiectomy abolished the protective male phenotype, while testosterone administration in females provided protection ($p < 0.05$). Deletion of AR in spinal cord neurons, but not DRG neurons, eliminated the protective effect from PKA and ERK inhibition. In females, testosterone administration reproduced the male phenotype in wild-type and DRG-specific knockout mice but not in spinal cord AR knockouts ($p < 0.05$).

Conclusions: Testosterone signaling through AR regulates a spinal PKA–ERK pathway that mediates latent sensitization in CPSP in a sex-dependent manner. AR activity in dorsal horn neurons is required for the protective effect observed in males.

Significance: These findings identify androgen-dependent modulation of spinal signaling pathways as a key mechanism underlying sex differences in chronic pain and suggest that targeting the AR–PKA–ERK axis may provide novel therapeutic strategies for CPSP.

Research/Grant Support: R01NS45954 (PI: BKT); R01NS146848 (PI: BKT; co-I: PB); Department of Anesthesiology and Perioperative Medicine Research Seed Award (PB); Competitive Medical Research Fund, UPMC Health System (PB)

Abstract 3

SEVOFLURANE-MEDIATED CHANGES IN FUNCTIONAL BRAIN CONNECTIVITY

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Introduction: Sevoflurane is a commonly used volatile anesthetic, but the neural correlates of its effects are not well understood. The objective of this study was to identify brain regions that are disrupted during sevoflurane-induced hypnosis.

Hypothesis: Sevoflurane affects consciousness, memory, and pain perception by disrupting functional connectivity between regions of the brain.

Methods: Thirty-four healthy volunteers (16 male, range 18-55 years, mean 29.2 years) completed resting state functional MRI (fMRI) scans under no-drug and sevoflurane conditions in an open-label observation study. Blood oxygen-level dependent weighted (TE=30 ms) images were obtained every 800 ms with 2.1 mm isotropic spatial resolution under the no-drug condition. Sevoflurane was titrated to a minimum alveolar concentration (MAC) of 0.2% while the resting state fMRI was repeated. The connectivity analysis was performed with the CONN toolbox using seed-to-voxel and ROI-to-ROI approaches using regions defined by the Harvard-Oxford atlas. Groups were thresholded with a voxel-wise threshold of $p < 0.001$ and corrected to an overall false-detection rate of $p < 0.05$. Seeds were selected a priori.

Results: The ROI-to-ROI analysis demonstrated a decrease in connectivity under the sevoflurane condition between cerebellar regions and insula cortex, anterior and posterior cingulate cortices, precentral gyrus, supplementary motor cortex, and frontal association cortices. Connectivity increased under the sevoflurane condition between frontal cortex to frontal cortex regions, frontal cortex to temporal cortex, and between the angular gyrus, posterior middle temporal gyrus, inferior frontal gyrus, posterior supramarginal gyrus, and temporooccipital middle temporal gyrus. In seed-to-voxel analyses, the anterior and posterior cingulate cortices demonstrated increased connectivity between bilateral frontal cortices and decreased connectivity between cerebellar, temporal, and occipital regions. The precuneus demonstrated increased connectivity between the left frontal cortex, bilateral temporal and parietal regions, and right cerebellar regions. There was decreased connectivity in right frontal cortex and cerebellum. The right hippocampus demonstrated decreased connectivity between regions of the right frontal and parietal cortices. The left hippocampus and right amygdala demonstrated decreased connectivity with the left precentral gyrus and inferior frontal gyrus. The left amygdala showed decreased connectivity between bilateral frontal and parietal cortices. The right and left angular gyri showed increased connectivity between large portions of the frontal, parietal, and temporal lobes.

Conclusions: The results of resting state functional connectivity analyses demonstrate numerous regions with altered connectivity under the sevoflurane condition. These regions include limbic system structures as well as frontal, temporal, and parietal association cortices.

Significance: Identifying the physiologic targets of volatile anesthetics may aid targeted pharmacologic research and clinical practice in the future. Elucidating neural mechanisms of consciousness can aid clinicians to ensure patients are adequately anesthetized during surgery.

Research/Grant Support: NIGMS R35GM146822FP00020692

Abstract 4

INTRAOPERATIVE LOW-DOSE METHADONE FOR PEDIATRIC POSTERIOR SPINAL FUSION: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

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Background: Posterior spinal fusion (PSF) for adolescent idiopathic scoliosis causes significant postoperative pain and high opioid requirements. Methadone, with dual μ- and κ-opioid agonism and NMDA antagonism, provides long-acting analgesia and may reduce perioperative opioid use. This study evaluated whether perioperative low-dose methadone (0.1mg/kg) improves postoperative pain and opioid outcomes after pediatric PSF.

Methods: In this single-center retrospective cohort study (January 2019–June 2023), pediatric patients <23 years old undergoing PSF were categorized by perioperative methadone exposure (intraoperative and/or postoperative) versus no methadone. The primary outcome was total postoperative opioid consumption (morphine milligram equivalents per kilogram, MME/kg) over postoperative days (POD) 0–3. Secondary outcomes were average daily pain scores and hospital length of stay (LOS). Inverse probability weighting (IPW) adjusted for age, sex, and protocol period.

Results: A total of 339 patients (51% no methadone, 49% methadone; mean age 14.6 ± 2.5 years; 76% female) were analyzed. Methadone patients had longer anesthesia (392 vs. 372 min, p=0.042) and surgery times (287 vs. 266 min, p=0.01). IPW-adjusted associations show postoperative opioid use was significantly higher in the methadone group on POD 0 (median 2.5 vs. 2.1 MME/kg in no methadone group; p=0.005). No significant differences were found in postoperative average pain scores (e.g., mean NRS: 2.3 vs 2.5 on POD 0, p=0.12) and LOS (3.3 vs 3.1 days, p=0.38) between methadone group and non-methadone group.

Discussion: Perioperative methadone provided comparable analgesia for pain management and recovery without prolonging hospitalization, despite higher early opioid use. Retrospective design limits causal inference, and residual confounding may persist despite propensity score-based adjustments. Further prospective trials are required.

Conclusion: Methadone remains a safe multimodal adjunct in pediatric PSF; prospective studies should refine dosing and timing to optimize analgesic benefits.

Funding: This research received no external funding. Part of Dr. Sadhasivam's effort was funded by NIH funding: U01TR003719 (PI: Sadhasivam), U01HD116257 (MPI: Sadhasivam/Chidambaran), R01HD096800 (PI: Sadhasivam), R01DA054513 (MPI: Chelly/Sadhasivam), R01DA059321 (MPI: Radhakrishnan/Sadhasivam), R44DA056280, R43HL167661, R43DA058430, R44DA055407, R41DA059303 (MPI: Sadhasivam).

Abstract 5

PSYCHIATRIC AND FUNCTIONAL BURDEN OF NEUROPATHIC PAIN COMPONENTS IN CHRONIC LOW BACK PAIN: A REGISTRY-BASED ANALYSIS

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Introduction: Low back pain (LBP) is the leading cause of disability worldwide and is frequently accompanied by psychological distress. Among individuals with chronic low back pain (CLBP), those with neuropathic pain often experience greater symptom severity and poorer treatment outcomes.

Hypothesis: Among individuals with chronic low back pain, those with neuropathic pain components, as identified by the PainDETECT scores, significantly greater psychological distress, sleep disruption, and functional impairment compared to those without neuropathic pain components, even after adjusting for, as identified by PROMIS T-scores, independent of covariates.

Methods: This retrospective analysis utilized patient-reported outcomes from the University of Pittsburgh's Patient Outcomes Repository for Treatment (PORT) registry, collected via the Collaborative Health Outcomes Information Registry (CHOIR). The cohort included 16,783 adults reporting LBP at an initial or standalone visit with valid PainDETECT scores. Participants were categorized as likely neuropathic (PainDETECT ≥ 19), intermediate (12< PainDETECT <19), and unlikely neuropathic (PainDETECT ≤ 12). Groups were compared across PROMIS domains of anxiety, depression, sleep disturbance, physical function, and positive outlook using ANOVA with post-hoc Tukey HSD. These results were then adjusted for social and demographic covariates known in literature to have associations with neuropathic pain using ANCOVA (age, sex, race, marital status, education, insurance, tobacco, alcohol, drug use, and BMI).

Results: Patients with likely neuropathic pain (vs intermediate vs unlikely neuropathic pain) reported higher mean PROMIS scores for depression (59.1 vs 54.8 vs 51.6), anxiety (60.4 vs 56.2 vs 52.7), and sleep disturbance (64.1 vs 59.4 vs 55.8), and lower scores for physical function (32.4 vs 35.4 vs 36.9) and positive outlook (46.5 vs 48.6 vs 50.5; all $p < 0.001$). In multivariable linear regression models adjusting for demographic, clinical, and psychosocial covariates, neuropathic pain status remained an independent predictor of greater psychological distress (β range = +2.6 to +6.6) and poorer functioning (β range = −3.2 to −5.8).

Conclusions: Individuals with CLBP with neuropathic pain components exhibit significantly greater psychological distress, sleep disruption, and functional impairment compared to those without neuropathic pain components, even after adjusting for demographics, socioeconomic factors, substance use, and BMI.

Significance: These findings emphasize the importance of addressing both the physical and psychosocial comorbidities associated with neuropathic components of CLBP.

Research/Grant Support: None reported.

Abstract 6

AUTOMATED ASSESSMENT OF MECHANICAL NOCICEPTION IN RODENTS

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Introduction: Over 116 million people in the U.S. are affected by acute and chronic pain, a number expected to rise with an aging population. Improved preclinical research methods are needed to better evaluate pain and analgesic efficacy. Current assays of mechanical algesia are time consuming, increase animal stress, and rely on evoked reflexive responses rather than intrinsic behaviors. These methods may misclassify supraspinal reflexes as pain and often show poor translational relevance to human pain conditions. We developed a novel self-reporting assay that prioritizes intrinsic behaviors and enables faster assessment of pain states than traditional evoked-response methods.

Hypothesis: We hypothesize that a forced-choice open field paradigm incorporating distinct surface textures would enable a behavioral assessment of pain. When given a choice between adverse and non-adverse textures, animals in a pain state are expected to spend less time on the adverse surface texture compared to their baseline and to animals receiving analgesic treatment.

Methods: Two 10.2 cm x 12.7 cm panels were designed using TinkerCad: (1) a non-adverse surface texture consisting of 1-mm-high domes resembling home-cage bedding; and (2) an adverse surface featuring alternating 4-mm and 6-mm spikes with 1-mm-diameter spike tips. The adverse texture was designed to minimize paw contact points, thereby increasing localized pressure. Two panels of each design (four total) were 3D-printed using a FormLabs Form 3B+ printer with Clear V4 resin and arranged in alternating corners of an acrylic arena with 12-inch-high walls. The arena was placed inside an IR beam-break animal tracking grid (Afasci SmartCage) to monitor position and movement. 24, 14-week-old male C57BL/6J mice received a 25-μL intraplanar injection of CFA into the left hind paw. 12 mice received pregabalin (30 mg/kg, I.P.), and 12 received an equivalent volume of saline. Each mouse was tested for 20 min, with the final 10 min analyzed to capture texture-driven behavior after initial exploration. Von Frey testing was used to confirm mechanical hypersensitivity. Texture testing was conducted on day 1, 3, 10, and 17 post-CFA injection, while Von Frey testing was performed on day 2, 4, 11, 16, and 22.

Results: Von Frey testing confirmed robust mechanical hypersensitivity following CFA injection, with pregabalin restoring thresholds to naïve levels. Von Frey testing also indicated a recovery of mechanical sensitivity by day 22 post-CFA. In the texture-based assay, CFA-injected mice showed significantly reduced occupancy of the adverse surface, with the strongest effect on day 3 and behavioral recovery observed by day 16. Pregabalin-treated mice showed increased time on the adverse texture relative to baseline and vehicle-treated mice, indicating reduced pain-avoidant behavior.

Conclusions: This self-reporting assay provides a non-invasive, low-stress measure of pain-based behavior based on intrinsic animal decision-making rather than elicited reflexes.

Significance: The texture-based self-report assay offers a clinically relevant objective behavioral measure of mechanical pain and analgesic efficacy. By eliminating reliance on evoked responses, this approach enables evaluation of novel analgesics with improved translational potential.

Research Grant Support: This work is supported in part by R01NS122830 to YX.

Abstract 7

BRAIN CHANGES WITH SEVOFLURANE AND NITROUS OXIDE DURING PERIODIC PAINFUL STIMULATION AND MEMORY PROCESSING: A FUNCTIONAL MRI STUDY IN VOLUNTEER SUBJECTS

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Introduction: Sevoflurane and nitrous oxide (N2O) are mechanistically distinct inhalational anesthetic agents with different clinical effects. While both affect cognitive function and pain perception, their systems-level brain effects during memory encoding and pain processing are poorly understood. In this study, we employ a paradigm of painful stimulation during an auditory memory encoding task to study the effects of sevoflurane and N2O using 3 T fMRI.

Hypotheses: 1) Sevoflurane and N2O will decrease ratings of pain intensity and unpleasantness and decrease pain-related activation in the somatosensory and affective components of the pain processing neuromatrix. 2) Both agents will correlate with decreased memory performance and decreased memory-encoding activation.

Methods: This data is from two IRB-approved, pre-registered, single-arm, open-label mechanistic neuroimaging clinical studies (NCT06702631, NCT06044740). Healthy adults were recruited, screened for eligibility, and compensated for participation. During fMRI, subjects listened to 35 words. Twelve of the 35 words were accompanied by a 2 s painful shock. Blood oxygen-weighted images of this task were obtained at 3T. After the no-drug baseline, this experimental paradigm was repeated under either 0.5% sevoflurane (n=31) or 70% N2O (n=21). Pain intensity and unpleasantness ratings were recorded after painful stimulation in both conditions. The next day, participants underwent drug-free recognition testing. Task performance was quantified using d' (0=chance, units ≈ SD). Behavioral data were analyzed with paired t-tests. FMRI analysis was performed with FSL 6.

Results: Next-day memory performance and ratings of pain intensity and unpleasantness decreased under both drugs. FMRI signatures of memory performance at baseline included bilateral activation in the anterior cingulate cortex (ACC), lateral prefrontal and parietal cortices, and precuneus. Painful stimulation produced baseline activation in the right primary somatosensory cortex (S1), bilateral amygdala, and insula. During memory encoding, sevoflurane was associated with bilateral decreased temporal lobe activation and bilateral increased activation in the ACC and prefrontal cortex. Memory encoding under N2O was associated with decreased bilateral temporal lobe activation. Sevoflurane was associated with decreased pain activation in the bilateral insula, as well as a small area of increased activation in the left S1. Under N_2O, painful stimulation was associated with widespread decreased activation, including in the bilateral insula, anterior and posterior cingulate, prefrontal and parietal cortices, S1, and cerebellum.

Conclusions: Sedative doses of sevoflurane and N2O impaired memory and reduced auditory cortex activation. Both agents also decreased pain-related activation in the posterior insula, a key region in pain processing, consistent with the reduction in pain reported by subjects. N2O was associated with more widespread decreases in brain activation during pain.

Significance: Upon completion of both projects, we will determine behavioral and neural differences between sevoflurane and N2O anesthesia for memory and experience of pain.

Research/Grant Support: NIGMS R35GM146822 (PI: Keith Vogt, MD PhD)

Abstract 8

REFINING ECOLOGICAL MOMENTARY ASSESSMENT FOR PHANTOM LIMB PAIN

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Introduction: Phantom limb pain (PLP) affects most people with limb amputation, but evidence for efficacy of treatments is inconsistent and inconclusive. To better inform PLP treatment, improved assessment methods are needed. Ecological momentary assessment (EMA) is a systematic, real-time method for measuring highly variable outcomes and predictive factors for those outcomes. Our goal is to use EMA to identify person-specific factors affecting PLP to inform personalized treatment.

Hypothesis: We hypothesized that EMA and causal modeling would identify stable and meaningful relationships between PLP intensity and other measured factors (e.g., sleep).

Methods: This longitudinal, observational study includes two phases. In the first phase, individuals with lower limb amputation and PLP were recruited. Participants received a text notification to complete an online survey three times per day for 40 days. These EMA surveys measured current PLP and potentially associated factors (e.g., sleep, activity, mood). Causal modeling was used to analyze individual datasets and identify person-specific factors predicted to cause PLP. In the second phase, in addition to EMA surveys, participants will use wearable devices to measure sleep, activity, and other objective factors that may be predictive of PLP. Participant feedback on the data collection process and perception of personalized results will be obtained through semi-structured interviews.

Results: Seventeen participants (10 male, mean age: 51.7) completed the first phase of the study with a mean survey response rate of 89.3%. Causal models with face validity were produced using the EMA data. Most factors predicted to affect PLP were unique to individual participants. Introducing wearable devices in the second phase of the study is expected to increase data accuracy and consistency, improving causal modeling.

Conclusions: EMA and causal modeling are feasible for identifying factors affecting PLP. PLP factors are largely person-specific. Incorporating wearable devices in conjunction with surveys will aim to improve and refine data collection and results. Participant feedback during interviews will inform future implementation work.

Significance: Individualized assessment of PLP is necessary for effective clinical care. Identification of factors affecting PLP can provide information for evidence-based, patient-specific treatment recommendations through a precision medicine approach.

Research/Grant Support: Dr. Falbo was supported by NIH training grant F31NS134186 (PI: Kierra Falbo) and NIH training grant T32GM075770 (PI/PD: Yan Xu).

Abstract 9

POST-OPERATIVE PAIN AFTER INTRAOPERATIVE METHADONE IN CARDIAC SURGERY IN ELDERLY: A PROSPECTIVE COHORT

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Introduction: Short-acting opioids are commonly used for post-operative pain management after cardiac surgeries and can lead to significant adverse events. In this context, methadone, a long-acting opioid, is proposed to induce longer analgesia and mitigate the adverse clinical outcomes. This study aims to analyze the quality of analgesia and the incidence of adverse events in elderly patients undergoing cardiac surgery with intraoperative methadone use.

Hypothesis: Intraoperative methadone use can decrease post-operative pain for elderly patients undergoing cardiac surgery.

Methods: This study was approved by the University of Pittsburgh's IRB (STUDY23020064). This is a prospective cohort of 109 patients over 60 years of age undergoing cardiac surgery and receiving intraoperative methadone (0.1 mg/kg) at induction and at sternal closure. Pain was assessed using numeric rating scale (NRS) scores from post-operative day 0 to day 3 (POD0-3). Post-operative nausea and vomiting (PONV), respiratory depression (RD), delirium, excessive sedation, chronic post-surgical pain (CPSP), and post-discharge opioid use were evaluated. Delirium was defined as positive CAM. CPSP was defined as NRS ≥4. Post-discharge opioid exposure was quantified using cumulative prescribed morphine milligram equivalents (MME), derived from the Pennsylvania Prescription Drug Monitoring Program data. Patients who died (3) prior to follow-up were excluded from post-discharge analyses. Proportions are reported with exact (Clopper–Pearson) 95% confidence intervals.

Results: Median pain (IQR) scores at rest were 0 (0–3) on POD0 (n=66), 4.2 (2.8–6) on POD1 (n=93), 4 (2–5.3) on POD2 (n=94), and 3.3 (2–5) on POD3 (n=93). Median movement (IQR) scores were 0 (0–2) on POD0 (n=61), 7 (4–8) on POD1 (n=92), 6 (3–7) on POD2 (n=90), and 5 (4–7) on POD3 (n=89). The incidence rates were as follows: PONV was 45.9% (36.3%-55.7%); RD was 8.3% (3.8%-15.1%); delirium was 12.8% (7.2%-20.6%); excessive sedation was 24.8% (17%-34%); CPSP was 11.3% (6%-18.9%) at 3 months post discharge and 6.6% (2.7%-13.1%) at 6 months, outpatient opioid prescription frequency at 3 months post discharge was 49.1% (39.2%-59%). Post-discharge cumulative prescribed opioid mean (± SD) was 37.5 (± 54.69) MME.

Conclusion: As a long-acting opioid, intraoperative methadone has shown promise as an alternative for postoperative pain management, especially on POD0. On the other hand, it can potentially be associated with significant increase in the incidence of PONV and persistent opioid use.

Significance: Intraoperative methadone is a viable option for multimodal analgesia for cardiac surgeries in elderly patients. However, the power of the study was limited due to the small cohort. To address this limitation, a follow-up study with a larger cohort has been planned.

Research/Grant Support: Internal funding (PI: Dr. Senthil Sadhasivam MD, MPH, MBA, FASA).

Abstract 10

CHRONIC LOW BACK PAIN MAY BE ASSOCIATED WITH INCREASED MECHANICAL DETECTION THRESHOLD AT AURICULAR ACUPOINTS

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Introduction: Although auriculotherapy (AT) can reduce pain, the factors that optimize its personalized application in pain management are not fully understood. Previous work demonstrated that painful body areas have corresponding pathologically sensitized ear acupoints (1); however, due to methodological limitations, including noncalibrated test stimuli, it remains unclear whether ear acupoint sensitivity is associated with pain or predicts treatment response (2).

Hypothesis: We hypothesize that chronic low back pain in patients may be associated with different mechanical detection threshold at auricular acupoints relative to pain free volunteers.

Methods: To address this gap, we conducted a preliminary interim analysis to evaluate whether ear acupoint sensitivity is associated with chronic low back pain (LBP). Mechanical Detection Thresholds (MDT) were measured using calibrated Von-Frey filaments at the Low Back ear acupoint, predicted to be sensitized in LBP, and at control ear acupoints corresponding to nonpainful body areas (Shoulder, Thumb). We enrolled pain-free control participants (n=17, 12 F, 5 M, mean age=42.6) and LBP patients (n=7, 3 F, 4 M, mean age= 38.0, mean pain intensity 4.3/10 SD= 2.4).

Results: In a repeated-measures ANOVA of log-transformed MDTs, LBP patients showed higher thresholds (reduced sensitivity, $F=8.798$, $p=0.008$, $\eta^2=0.169$) than pain free controls across all ear acupoints, after controlling for age and sex.

Conclusions: Although sensory abnormalities may exist at ear acupoints in LBP, our small LBP sample (n=7) showed reduced touch detection sensitivity at both Low Back and control acupoints.

Significance: Contrary to prior work showing more sensitive acupoints corresponding to painful body areas, our preliminary analysis suggests reduced sensitivity in LBP, justifying continued data collection to clarify sensory abnormalities and their relevance to personalized AT.

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Abstract 11

SEX-SPECIFIC EFFECTS OF *MALAT1* AND NEUROINFLAMMATION IN ALCOHOL CONSUMPTION

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Introduction: Alcohol activates the neuroimmune system, triggering inflammatory signaling thought to promote alcohol consumption and contribute to alcohol use disorder (AUD). However, the molecular mechanisms linking neuroinflammation to drinking behavior remain unclear. *Malat1* is a widely expressed, evolutionarily conserved long non-coding RNA that promotes pro-inflammatory signaling, including in the central nervous system. *Malat1* is upregulated in post-mortem brains from AUD subjects and rodents chronically exposed to alcohol, yet its causal role in regulating alcohol consumption remains unexplored.

Hypothesis: We hypothesized *Malat1* regulates immune-induced increases in alcohol intake.

Methods: To assess whether modulation of *Malat1*-associated neuroinflammatory signaling alters alcohol intake, tamoxifen-inducible *Malat1* homozygous floxed, hemizygous CreERT2 (*Malat1* global KO) mice and Cre negative littermate controls (WT) underwent ten days of baseline two-bottle choice (2BC; 10% v/v), followed by ten additional days of drinking post-treatment. One cohort received a single lipopolysaccharide (LPS; 1 mg/kg, i.p.) injection to induce inflammation before this period; another received daily quercetin (30 mg/kg, i.p.), an anti-inflammatory compound reported to regulate *Malat1* function and attenuate alcohol reward, prior to each post-treatment session. A subset of mice from each group was monitored with sipper devices to characterize temporal drinking patterns.

Results: LPS increased alcohol intake in females regardless of genotype. Quercetin produced a treatment-by-genotype interaction in females, with quercetin-treated *Malat1* global KO females, but not WTs, showing elevated alcohol preference. Neither treatment altered male drinking, though *Malat1* global KO males consistently consumed more alcohol than WT controls.

Conclusions: Females are more sensitive to inflammation-induced alcohol intake, and *Malat1* may differentially mediate alcohol intake in a sex-specific manner.

Significance: Our studies are the first to causally test *Malat1*'s role in mediating inflammation-induced alcohol intake, elucidating its sex-specific effects on drinking.

Research/Grant Support: NIAAA F31 AA032172 (PI: Daniela V Gil, BS), NIAAA U01 AA020889 (PIs: Sean P Farris, PhD; Gregg E Homanics, PhD), NIAAA R01 AA030257 (PI: Sean P Farris, PhD)

Abstract 12

ANDROGEN SIGNALING MEDIATES SEX DIFFERENCES IN THE INTRACELLULAR SIGNALING OF ACUTE POSTSURGICAL PAIN

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Introduction: Acute postsurgical pain (APSP) remains a major global health challenge. More than 310 million surgeries occur worldwide each year, and nearly 80% of patients experience postoperative pain, with about 75% reporting moderate to severe intensity. Emerging evidence also indicates that biological sex significantly influences pain prevalence, severity, and treatment outcomes. Understanding sex-specific pathways that regulate APSP is critical for developing more effective and personalized pain management strategies. Our previous data reveal that in a mouse plantar incision model of postsurgical pain, intrathecal administration of pharmacological inhibitor of Ras-associated protein-1 (Rap1) (GGTI) but neither mitogen-activated protein kinase (MEK) (PD98059), and extracellular signal-regulated kinases (ERK) (SCH772984) reversed mechanical and heat hypersensitivity in females. By contrast, GGTI, PD98059, and SCH772984 all prevented hypersensitivity in males.

Hypothesis: We tested the underlying mechanisms of these sex differences in APSP by targeting androgen receptor (AR) signaling at two key sites of pain modulation: central terminals of dorsal root ganglion (DRG) neurons and spinal cord dorsal horn (SC) neurons.

Methods: To determine site of action, we crossed AR floxed ($AR^{loxP/loxP}$) mice with either $Pirt^{Cre}$ or $Lbx1^{Cre}$ mice to delete AR in DRG or SC neurons, respectively. Selective deletion was confirmed by fluorescence in situ hybridization for AR. Next, we implanted placebo or testosterone pellets subcutaneously in female DRG- or SC-specific conditional knockout mice. Two weeks after implantation, we performed plantar incision and tested the effects of ERK inhibitor SCH772984 in wildtype $AR^{loxP/loxP}$, spinal ($AR^{loxP/loxP}$; $Lbx1^{Cre}$) and DRG-specific ($AR^{loxP/loxP}$;$Pirt^{Cre}$) knockout female mice.

Results: ERK inhibitor SCH772984 prevented incision-induced mechanical and heat hypersensitivity in $AR^{loxP/loxP}$ females implanted with testosterone but not placebo pellets. Spinal ($AR^{loxP/loxP}$; $Lbx1^{Cre}$) but not DRG-specific ($AR^{loxP/loxP}$;$Pirt^{Cre}$) deletion prevented SCH772984-induced reversal of hypersensitivity, indicating a spinal rather than sensory neurons site of action. SC-specific but not DRG-specific AR deletion abolished this effect.

Conclusions: We conclude that testosterone acts at spinal androgen receptors to sex-dependently maintain MEK → ERK signaling components of APSP.

Significance: Our findings promote spinally directed AR agonists as novel targets for the development of a new pharmacotherapy for APSP.

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Abstract 13

NUCLEUS ACCUMBENS NEUROIMMUNE AND SYNAPTIC REMODELING TRANSCRIPTIONAL SIGNATURES IN ALCOHOL USE DISORDER

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Introduction: Alcohol Use Disorder (AUD) is a chronic, relapsing condition affecting 400 million individuals worldwide. Repeated episodes of heavy alcohol use induce widespread alterations in the immune system alongside synaptic remodeling. The nucleus accumbens (NAc) is a key brain region that mediates initiation and escalation of alcohol consumption. Here, we examined gene expression alterations in the NAc of postmortem brains from AUD subjects.

Hypothesis: Individuals with AUD have significant changes in NAc immune -and synaptic-transcript expression compared to control subjects, and these immune- and synaptic-changes contribute to continued alcohol drinking.

Methods: Bulk RNA-sequencing was performed on human postmortem NAc samples from male subjects with AUD (n=9) and matched male control subjects (n=9). Differential expression analyses were performed and genes were considered differentially expressed at $p<0.05$ and $|log2FC|>0.25$. Functional pathway enrichment was performed using EnrichR.

Results: We identified 1314 differentially expressed genes (DEGs) that met both criteria. Functional enrichment of the top 500 DEGs revealed that pathways involved in regulation of acute inflammatory responses, responses to cytokines, regulation of the blood-brain barrier, and leukocyte migration were the most enriched (Gene Ontology Biological Processes). Additional analysis shows key immune transcripts *IL6, IL1R2, IFNG, CCL3* (cytokines), *MIR146B* (immune *lncRNA*), *CD33*, and *ICAM1*, and key synaptic remodeling transcripts *SLC7A2, GADD45A, HDAC9, C1QL4, ST8SIA2* are among the top DEGs.

Conclusions: Individuals with AUD show significant changes in NAc immune- and synaptic- gene expression, suggesting neuroimmune changes and synaptic remodeling contribute to continued alcohol consumption. Ongoing analyses are performing cell type deconvolution to examine cell-type specific contributions to NAc AUD etiology, with a focus on the central nervous system resident immune cells, microglia.

Significance: Chronic alcohol consumption causes increased inflammation in the brain, further driving alcohol consumption and contributing to comorbid symptoms (e.g., chronic pain, anxiety, stress), yet no FDA-approved medication directly addresses neuroinflammatory mechanisms of alcohol. Transcriptomic results from AUD human postmortem brains are *necessary* to inform future gene targets for designing therapies to treat excessive alcohol use.

Research/Grant Support: NINDS T32NS141747 (Awarded to Tori Keefauver; PI: Stephen Meriney); NIAAA U01AA020889 (PI: Sean Farris); NIAAA R01AA030257 (PI: Sean Farris)

Abstract 14

PAIN-PROCESSING PARABRACHIAL NEURONS IN AWAKE MICE ARE SENSITIZED TO MECHANICAL STIMULI DURING ACUTE WITHDRAWAL FROM CHRONIC ALCOHOL

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Introduction: Alcohol use disorder (AUD) and pain are comorbid. We recently found that exposure to chronic (4-week) intermittent ethanol vapor (CIEV) is associated with chronic alcohol withdrawal induced pain (CAWIP) in male and female C57BL/6J (B6J) mice. The molecular circuitry that underlies CAWIP is poorly understood. We begin with the analysis of the activity of three regions: 1) The lateral parabrachial nucleus (LPBN), a critical brainstem hub that integrates inputs from the spinal cord dorsal horn with inputs related to critical survival needs through the Y1 receptor for neuropeptide Y (NPY); 2) The arcuate nucleus of the hypothalamus (Arc), which sends projections to and releases NPY in LPBN to inhibit Y1 neurons; and 3) the central nucleus of the amygdala (CeA), a primary projection target of LPBN neurons that are implicated in alcohol addiction.

Hypothesis: We hypothesized that withdrawal from chronic alcohol exposure is associated with increased activity of PBN and CeA neurons and decreased activity of Arc neurons.

Methods: B6J mice were exposed to CIEV or Air control conditions (16 hrs ON/8 hrs OFF, 4 days/wk, 4 wk) to induce mechanical hypersensitivity at the hindpaws. During the 24 hr withdrawal period, stimulus-evoked neuronal activity in PBN, Arc, and CeA was assessed with the immediate early gene expression of Fos. Mice were anesthetized (1min @ 3% iso, 1% during stimulation) and their left hind paw was stimulated with either a light brush or a noxious pinch 3 x 20 sec, each spaced 1min apart. 90 minutes after stimulation, brain tissue was taken for Fos immunohistochemistry. Arc sections were co-stained with NPY antibody.

Results: CIEV increased Fos expression in the right PBN ($p<0.05$) to an equal extent after brush or noxious pinch. We also observed no increases in mechanically evoked Fos in the left PBN ($P>0.05$). However, we observed an increase in PBN Fos expression in the CIEV mice compared to air mice. Fos expression in the Arc was decreased in the CIEV mice compared to the air group. Lower Fos expression was measured in the CeA in CIEV mice compared to air mice. Mean fluorescence intensity of Arc NPY was similar between CIEV and air-treated mice.

Conclusions: Our studies indicate that withdrawal from CIEV increases stimulus-evoked activity of PBN neurons but not CeA neurons, and decreases the activity of Arc neurons. Significance: Alcohol-induced dysfunction of the nociceptive circuit may underlie the hypersensitivity phenotype we see in our laboratory mice during withdrawal from CIEV. Future studies will focus on manipulations of the Arc→PBN→CeA pathway to reduce pain.

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Abstract 15

GREEN LIGHT FOR POST-OPERATIVE WELLNESS (GLOW): A RANDOMIZED CONTROLLED TRIAL IN ADULT PATIENTS UNDERGOING ABDOMINAL SURGERY

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Introduction: Light therapy has shown promise as a non-pharmacologic pain management strategy in multiple debilitating pain conditions including fibromyalgia and migraine. Additional potential benefits relevant to post-operative recovery include improved sleep, mood, and immune response. Here we test a bright green light intervention, hoping to harness the circadian benefits of bright light and the pain modulating potential of green light.

Hypothesis: Post-operative patients exposed to bright green light will have less pain and better patient-reported measures of recovery than those exposed to a dim white light control.

Methods: Eligible participants scheduled for abdominal surgery at a single academic tertiary care hospital are enrolled pre-operatively. Following surgery, participants are randomly allocated 1:1 between two light conditions [bright green light (1,400 +/- 50 lux, peak 505 nm) and dim white light (100 +/- 50 lux, full-spectrum)], stratified by approach (open or minimally invasive). The assigned light intervention is administered at bedside for 4 hours daily on post-operative days (POD) 1-3 or until hospital discharge, whichever comes first. The primary outcome is incisional pain with movement (strong cough), reported using an 11-point numerical rating scale (NRS). Secondary pain outcomes include incisional pain at rest (NRS) and opioid requirements (oral morphine equivalents). Additional secondary outcomes include patient-reported measures of sleep, depression, and anxiety (PROMIS, Patient-Reported Outcomes Measurement Information System); overall post-operative recovery (QOR-15, Quality of Recovery-15); and hospital length of stay.

Results: The GLOW trial launched in January 2026, and 162 patients scheduled for abdominal surgery have been screened to date. Of the 27 eligible patients approached, 15 (56%) provided consent to participate. Of the 11 who have undergone surgery to date, there has been 1 withdrawal and 1 screen failure, with 9 completing study interventions and surveys [(33% open approach, 64% female, 100% White, mean age 58 (range 33-71) years]. On average, participants received 2.78 (range 2-3) days of light therapy, for an average of 189 (range 172-240) minutes per day. Only 1 symptom possibly related to light exposure has been reported (headache), and there have been no safety issues or nursing concerns.

Conclusions: A randomized controlled trial of green light therapy for post-operative pain control and wellness is highly feasible and acceptable in patients undergoing abdominal surgery at our academic tertiary-care hospital.

Significance: Pending accrual of the target study population (n = 60), green light therapy may be a low-risk, low-cost adjunct to improve multiple aspects of post-operative recovery.

Research/Grant Support: Shadyside Hospital Foundation; T32GM075770 (PI: Yan Xu)

Abstract 16

PERIPHERAL MACROPHAGES DO NOT CONTRIBUTE TO NEUROPATHIC PAIN IN MULTIPLE SCLEROSIS

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Introduction: Multiple sclerosis (MS) is a chronic illness characterized by the loss of myelin in the central nervous system. Individuals with MS are commonly affected by chronic neuropathic pain and musculoskeletal pain. The mechanisms of multiple sclerosis-associated central neuropathic pain (MSNP) are poorly understood. One clue is microglial proliferation in the spinal cord of humans and rodent MS models, hinting that neuroinflammation may cause MSNP.

Hypothesis: We recently found that spinal microglia maintain MSNP, using CX3CR1CreER chemogenetic interventions. However, CX3CR1 is also expressed in macrophages. Here we used an interventional strategy to deplete macrophages in our mouse model of MSNP.

Methods: We use a model in female C57Bl/6 mice called experimental autoimmune encephalomyelitis without pertussis toxin (EAE-nPTX) to induce MS-like symptoms including pain-like behavior. To do this, we injected a total of 100µL of a homogenized solution of 10µL MOG35-55 and 50µL CFA/MTB, and 40µL of 1x PBS into each mouse subcutaneously (50µl of the 100µl solution gets injected into each flank totaling 100µl of solution into each mouse)(n=8). This solution was injected again seven days later. Control mice received 100µl (50µl in each flank) of homogenized CFA/PBS (10mg/mL)(n=8). 3 wk later, mice received intravenous injections of either liposomal encapsulated chlodronate (LEC) (50µL/10µL, i.v. 100µl/10g) for microglial / macrophage depletion (n=8), or control liposome (n=8). We established four groups; 1) EAE-nPTX that received LEC (n=4); 2) CFA/PBS mice that received LEC (n=4); 3) EAE-nPTX mice that received control liposomes (n=4); and 4) CFA/PBS mice that received control liposomes (n=4). Throughout the study, we tracked pain-related behaviors including mechanical hypersensitivity (von Frey) and cold hypersensitivity (evaporative acetone to plantar hind paw). Behavior was measured before EAE-nPTX induction and then 7, 14, 19, 21, 23, and 26 d later.

Results: EAE-nPTX mice developed greater mechanical and cold hypersensitivity as compared to control mice. Our initial studies found that intrathecal LEC decreased hypersensitivity in EAE induced mice. By contrast, our newest results indicate that intravenous LEC did not change mechanical hypersensitivity in EAE-nPTX mice, as follows: Group 1(mean +/- SEM): D21: 0.2 +/-0.1, 96hr post (initial) injection: 0.6 +/-0.1. Group 2 (mean +/- SEM): D21: 0.6 +/- 0.1, 96hr post (initial) injection: 0.8 +/- 0.1. Group 3 (mean +/- SEM): D21: 0.2 +/-0.2, 96hr post (initial) injection: 0.2 +/- 0.2. Group 4 (mean +/- SEM): D21: 0.8 +/- 0.396hr post (initial) injection: 1.0 +/- 0.2

Conclusion: Spinal microglia but not peripheral macrophages are necessary for MSNP. Future studies will include a naive (uninjured) group and will also increase the number of animals. Furthermore, we will perform immunocytochemistry to confirm demyelination and macrophage depletion in spinal cord tissues.

Significance: These studies point to spinal macrophages as a selective target for the treatment of MSNP.

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Abstract 17

BEHAVIORAL SIGNS OF CHRONIC PAIN AFTER RESECTION OF LOWER LUMBAR SPINOUS PROCESSES

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Introduction: Low back pain (LBP) is the leading cause of years lived with disability worldwide.[1] Treatments are often ineffective or limited by side effects. Until recently, preclinical rodent models of cLBP were invasive, technically difficult, and/or associated with minimal signs of pain.[2] To accelerate our understanding of *in vivo* chronic LBP mechanisms, we further characterized an exciting new model of LBP associated with lumbar spine instability (LSI) with an intact nervous system. Prior studies with the LSI model involved resection of the three lower lumbar spinous processes in a single sex (male) and resulted in lumbar degeneration and mechanical hypersensitivity at 16 weeks post-surgery.[3-4]

Hypothesis: LSI surgery leads to mechanical hypersensitivity in both sexes, which is maintained at 16 weeks post-surgery.

Methods: Male and female C57BL/6 mice (19 weeks; The Jackson Laboratory) underwent LSI surgery (n=13 per group).[3-4] LSI is induced by simple resection of the L3-L5 spinous processes, resulting in severe lumbar degeneration within 16 weeks. Sham mice (n=10 per group) underwent dorsal skin incision only. The 50% mechanical threshold to hind paw withdrawal was determined weekly from baseline until week 4 post-surgery using an up-down method[5] with eight von Frey filaments (0.008-6g, Stoelting), and then repeated every 2 weeks until 16 weeks post-surgery. Data were analyzed with 2-factor ANOVA followed by Sidak's multiple comparisons test (GraphPad Prism).

Results: Compared to Sham surgery, LSI increased mechanical hypersensitivity at week 6 in both males and females. This peaked at 16 weeks (females: 0.349g, $p<0.01$; males 0.243g, $p<0.01$).

Conclusions: Our data indicate that LSI leads to the development of mechanical hypersensitivity in male and female mice, starting at 6 weeks after surgery. Hypersensitivity continued to increase through 16 weeks. Future work will evaluate behavioral signs of the affective dimension of pain, correlate these results to severity of lumbar spine degeneration, evaluate the activity of neurons in the dorsal horn of the spinal cord, and test the responsiveness of mechanical hypersensitivity to conventional analgesics such as ketorolac.

Significance: The LSI model is technically feasible and demonstrates robust mechanical hypersensitivity, making this model far superior compared to previous models of LBP.

Research/Grant Support: NIH training grant T32GM075770, PI/PD: Yan Xu

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Abstract 18

OPIOID USE DISORDER DURING PREGNANCY: DIFFERENCES IN GENETIC VARIATIONS AND RNA EXPRESSIONS-AN OBSERVATIONAL COHORT STUDY

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Introduction: Despite the high prevalence of exposure to opioids, little is known about the impact of opioids on pregnancy and risk factors for opioid misuse. There is an unmet need for a multi-genic and psychological comprehensive risk model to identify mothers at high-risk for opioid use disorder (OUD).

Hypothesis: This study aimed to identify the multi-genic signatures that serve as genetic predictors for predisposition to developing opioid use disorder in pregnancy.

Methods: We conducted an observational cohort study including 99 pregnant women receiving medication for opioid use disorder and 104 control pregnant women across two clinical sites from 2018-2023. Peripheral venous blood was extracted and analyzed for pharmacogenomic and differential gene expression accounting for OUD status, adjusted for maternal age, race, smoking during pregnancy, maternal health history, study site, and baseline diagnosis of depression and anxiety.

Results: Four loci showed significant associations with OUD at the predefined significance threshold ($P < 5.32 \times 10^{-4}$). Three of these loci were located within the ADH1A, NFKBIL1, and CYP2A6 genes, while the fourth was in the intergenic region between SNRNP40 and NKAIN1. However, these associations were no longer statistically significant after adjusting for psychiatric comorbidities. Among the candidate genes examined, CYP2B6, COMT, and SLC22A1 showed the strongest associations with OUD, although none reached the significance threshold. After accounting for psychiatric diagnoses, the association signals for CYP2B6 and OPRM1 became stronger, but still did not reach statistical significance. Transcriptomic analysis further identified 326 genes that were differentially expressed between mothers with OUD and unaffected controls. Of these, 268 genes were significantly enriched in biological processes related to chromatin assembly and mitochondrial energy metabolism.

Conclusions: Our study provided insights into the genetic differences associated with opioid use disorder including novel biological processes linking chronic opioid exposure with cellular metabolic and epigenetic dysregulation impacted by comorbid psychiatric history.

Significance: Investigating the genetic component of OUD identifies high-risk genetic signatures which aids future clinical applications for screening and personalized medicine including confounding psychiatric factors of addiction etiology.

Research/Grant Support: NICHD 1R01HD096800-01 (PI: Senthilkumar Sadhasivam, MD, MPH, MBA, FASA)

Abstract 19

CONNECTIVITY BETWEEN SENSORY AND MOTOR REGIONS WHILE WALKING DIFFERS BY PAIN LEVEL IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Introduction: Knee osteoarthritis (KOA) is a common condition involving tibio-femoral joint degeneration causing pain with weightbearing activities like walking. While neuroimaging studies have revealed changes in brain activity at rest in those with KOA, little is known about brain activity during movement-evoked pain (MEP). This study assessed changes in functional connectivity of patients with KOA during the six-minute walk test (6MWT) using functional near-infrared spectroscopy (fNIRS).

Hypothesis: Brain activity in the prefrontal cortex and sensorimotor regions while walking will differ based on presence of MEP.

Methods: Activity in the prefrontal cortex and sensorimotor cortex was measured using fNIRS during the 6MWT, a validated physical function test measuring distance traveled while walking for six minutes. Functional connectivity differences between the last and first two minutes of the test were calculated and contrasted between groups, accounting for cardiopulmonary noise using short-separation channels. KOA patients were divided based on presence or absence of MEP during the test (MEP+, n = 20; MEP-, n = 29) and based on average pain over the last day (low, n = 25; high, n = 29). In addition, a control group also completed the 6MWT (n = 27). To further account for physiological noise due to walking, permutation testing was performed by randomizing group assignment over 10,000 iterations.

Results: When comparing the change in brain activity over the course of the walk test between groups, the MEP+ group displayed a larger change in functional connectivity within the left premotor cortex relative to control participants and a smaller change in functional connectivity between the left premotor cortex and the left dorsolateral prefrontal cortex compared to the MEP- group ($p_{adj} < 0.001$). Patients in the MEP- group displayed less change in functional connectivity in the left primary sensory cortex than controls. When divided by average pain intensity, there was no difference in functional connectivity change during walking between any of the groups.

Conclusions: In addition to regions associated with motor and sensory functions, brain regions associated with the affective aspect of pain displayed differences between groups in connectivity after walking, but only when grouped by presence of MEP.

Significance: Presence of MEP during a functional task is more relevant to neural activity during that task than average pain levels collected at rest.

Research/Grant Support: NINDS K23NS123429 (PI: Benedict Alter, MD, PhD), NIH T32GM075770 (PI: Yan Xu)

Abstract 20

BAYESIAN DEEP LEARNING AUTOREGRESSIVE MODELING FOR MULTIOUTPUT INFERENCE ON ICU TIMESERIES WITH MISSING DATA

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Introduction: The intensive care unit (ICU) is an environment where not only is a large amount of data per patient collected, but where sudden, catastrophic changes can occur. Predicting these outcomes (death, serious organ failure, etc.) would be of great importance to improve clinical outcomes. However, moving from laboratory settings to clinical practice can prove challenging when acquired data becomes noisier and often large swaths are missing. Deep learning approaches incorporating Bayesian strategies can potentially handle these noisy, sparse systems and make properly calibrated predictions even on data that is difficult to use and interpret.

Hypothesis: Development and training of a Bayesian deep learning LSTM model to handle complex, noisy, and sparse real-world ICU data is a feasible step towards a larger-scale high-accuracy predictive model.

Methods: Using 12 subjects from the MIMIC-IV ICU waveform dataset, we trained an autoregressive multi-output predictive Bayesian LSTM model using a Flipout approximation to approximate Bayesian priors in the deep learning model. We performed a 3-fold cross validation and recorded the performance of the model across those 3 folds.

Results: Across the 3-fold cross validation, we achieved a balanced accuracy of predicting sepsis, mortality, cardiac arrest, and AKI of 0.75±0.21. In regards to the feasibility of the timeseries modeling and analysis, the autoregressive segment of the model achieved a mean absolute error across cross-validation folds of 0.40±0.15.

Conclusions: The accuracy scores greater than chance and a modestly low mean squared error suggest that there is signal present in the data that this modeling approach can detect, even in cases where the input data is noisy or missing.

Significance: With the feasibility of developing and training a Bayesian LSTM and modest ability to predict clinically useful targets demonstrated, this study serves as an indicator that the planned approach has merit, warranting further model development.

Research/Grant Support: NSF ACCESS Postdoc Supercomputing Grant MED250003 (PI: Cooper Mellema, MD-PhD)

Abstract 21

CHEMOGENETIC ACTIVATION OF DORSAL HORN NEURONS THAT EXPRESS THE MU OPIOID RECEPTOR INDUCES NOCICEPTIVE BEHAVIORS IN MICE

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Introduction: Mu opioid receptors (MORs) are inhibitory G protein–coupled receptors that mediate the analgesic effects of opioids by suppressing neuronal excitability in dorsal horn neurons. MORs on dorsal horn neurons are the primary target of intrathecal or epidural opioid analgesic drugs. MOR constitutive activity (MORCA) provides endogenous analgesia by opposing latent pain sensitization. Despite the well-established analgesic role of MORs, the contribution of spinal MOR-expressing neurons to pain and its control has not been extensively studied. Since MOR activation inhibiting neuronal activity reduces nociceptive signaling, we hypothesized that spinal MOR-expressing neurons may have a pronociceptive function.

Hypothesis: Spinal MOR-expressing neurons may have a pronociceptive function.

Methods: To test this, we injected AAV8-hSyn-DIO-hM3D(Gq)-mCherry (Gq virus) or AAV8-hSyn-DIO-mCherry (control virus) into the left L3–L4 lumbar spinal cord of Oprm1Cre mice. Twenty-one days later, we administered clozapine-N-oxide (CNO; 3 mg/kg, i.p.) or saline control (Sal), and then evaluated: 1) mechanical (von Frey), cold (acetone test), and heat (hotplate) sensitivity at the plantar hindpaw; 2) motor coordination (accelerating rotarod); and 3) spontaneous behaviors that indicate nociception (abdomen biting and face wiping) and itch (back biting and scratching).

Results: We found that chemogenetic activation of spinal MOR-expressing neurons induces mechanical ($F(3,90)=7.9$, $p<0.0001$; Drug) and cold hypersensitivity ($F(3,90)=11.42$, $p<0.0001$; Drug), but did not change heat sensitivity ($F(3,90)=1.31$, $p=0.27$; Drug) or motor coordination ($F(1,4)=0.39$, $p=0.56$; Drug). Next, chemogenetic activation increased abdomen-biting behavior (Gq CNO vs mCherry CNO control, $p<0.05$) but did not change face wiping, back biting, or scratching behaviors ($p>0.05$). Furthermore, we found that CNO induced abdomen biting ($p<0.05$) in Gq mice but not mCherry control mice ($p>0.05$). CNO did not change face wiping, back biting, or scratching responses in Gq mice as compared to mCherry controls ($p>0.05$).

Conclusion: We conclude that spinal MOR-expressing neurons are pronociceptive.

Significance: These findings support a pronociceptive role for spinal MOR-expressing neurons and demonstrate that activation of these neurons induces nociceptive behaviors in mice.

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Abstract 22

SEX DIFFERENCES IN PROTEIN KINASE A SIGNALING OF LATENT POSTSURGICAL PAIN

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Introduction: Latent sensitization (LS) is a long-lasting "silent" pain state masked by tonic kappa-opioid receptor (KOR) signaling in the spinal cord and is studied in mice as a model of chronic postsurgical pain (CPSP). Protein kinase A (PKA) is a cAMP-dependent serine/threonine kinase implicated in multiple forms of chronic pain. For example, blockade of adenylyl cyclase or PKA reverses nerve injury-induced hypersensitivity and reduces spinal pCREB expression. Our prior work demonstrated that preadministration of the PKA inhibitor H89 prevented KOR antagonist-induced reinstatement of mechanical hypersensitivity in male but not female mice, suggesting sexually dimorphic engagement of spinal PKA in CPSP.

Hypothesis: Spinal PKA signaling is both necessary and sufficient to drive LS reinstatement selectively in male but not female mice.

Methods: Adult male and female C57BL/6 mice underwent plantar incision surgery. At Day 21, after resolution of initial hypersensitivity, mice received intrathecal 6BNZ (PKA activator) or saline, followed by immunohistochemical quantification of FOS expression in spinal dorsal horn laminae I-II. In a separate cohort, mice received intrathecal KT5720 (100 or 500 ng) prior to KOR antagonist LY2456302 (10 μg). Mechanical thresholds were assessed via von Frey filaments and thermal sensitivity via paw withdrawal latency.

Results: 6BNZ induced mechanical hypersensitivity in males but not females. 6BNZ significantly increased touch-evoked spinal FOS expression in 21-day post-incision males but not females ($p<0.05$), indicating sex-dependent recruitment of dorsal horn neurons. Because H89 inhibits numerous other kinases including AKT, RSK, AMPK, and ROCK, we confirmed these findings using KT5720, a more potent and selective PKA inhibitor. Preadministration of KT5720 at either dose prevented KOR antagonist-induced mechanical and heat hypersensitivity in males but not females.

Conclusions: Spinal PKA signaling is both necessary and sufficient to drive LS reinstatement selectively in males, confirming that only males recruit PKA to maintain CPSP.

Significance: These findings identify spinal PKA as a sexually dimorphic mediator of chronic postsurgical pain, highlighting the importance of sex as a biological variable in pain research and suggesting PKA as a potential target for the development of male-specific analgesic strategies.

Research/Grant Support: Department of Anesthesiology and Perioperative Medicine Research Seed Award to PB Competitive Medical Research Fund of the University of Pittsburgh Medical Center Health System to PB; R01NS146848 (co-I – PB; PI – BKT).

Abstract 23

CHEMOGENETIC ACTIVATION OF DORSAL HORN NEURONS THAT EXPRESS THE KAPPA OPIOID RECEPTOR INDUCES PAIN- AND ITCH-RELATED BEHAVIORS IN MICE

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Introduction: κ-opioid receptors (KOR) are expressed on sensory and spinal cord dorsal horn (DH) neurons that relay the transmission of pain signals from the periphery to the brain. Our previous publications demonstrate that intrathecal administration of KOR agonists alleviate both acute and chronic pain, presumably by acting at DH neurons that express KOR. However, the function of these KOR-expressing neurons remains poorly defined.

Hypothesis: Since KOR is coupled with inhibitory G proteins, we hypothesized that the function of KOR-expressing neurons is pronociceptive.

Methods: To test our hypothesis, we injected AAV8-hSyn-DIO-mCherry (control virus) or AAV8-hSyn-DIO-hM3D(Gq)-mCherry (Gq virus) into the L3-L4 spinal cord of *Oprk1*^{Cre} mice. 21 days later, we administered clozapine-N-oxide (CNO; 3 mg/kg, i.p.) or saline control and then evaluated: 1) mechanical (von Frey), cold (acetone test), and heat (hotplate) sensitivity at the plantar hind paw; 2) motor coordination (accelerating rotarod); and 3) spontaneous behaviors that indicate nociception (abdomen biting and face wiping) and itch (back biting and scratching).

Results: Our data reveal that CNO significantly increased both mechanical ($F_{(12,120)}$ = 3.3, p=0.0003; Drug x Time) and cold sensitivity ($F_{(12,120)}$ = 8.3, p<0.0001; Drug x Time) in Gq mice but not in mCherry mice. However, we did not see any changes in heat sensitivity (p=0.98) for either Gq or mCherry mice. Similarly, CNO did not change time spent on rotarod in either strain (p=0.53). CNO induced abdomen biting in mice that express the Gq virus (Sal: 147.57 ± 24.29; CNO: 371.07 ± 95.97) but not in those that express the control mCherry virus (Sal: 243.71 ± 48.90; CNO: 198 ± 24.12). There was no significant difference in face wiping (p>0.05). CNO induced back biting in Gq mice (Sal: 240.71 ± 34.60; CNO: 463.5 ± 43.51) but not in mCherry control mice (Sal: 332.71 ± 59.76; CNO: 322.5 ± 62.59). CNO induced scratching in Gq mice (Sal: 37 ± 17.93; CNO: 248.5 ± 144.86) but not mCherry control mice (Sal: 58.92 ± 12.79; CNO: 32.29 ± 9.48).

Conclusions: Together, our data reveal that spinal KOR-expressing neurons are sufficient to drive hyperalgesia, nocifensive, and itch-related behaviors.

Significance: Researchers could alleviate chronic pain and identify a therapeutic target by inhibiting spinal KOR-expressing neurons under injury conditions.

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Abstract 24

LONG NONCODING RNA *GAS5* MODULATION OF THE STRESS-RELATED PHENOTYPES OF CHRONIC INTERMITTENT ETHANOL EXPOSURE

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Introduction: The long noncoding RNA growth arrest specific 5 (*Gas5*) is differentially methylated in blood and brain of individuals with alcohol use disorder (AUD) and has multiple proposed functions, including immune- and glucocorticoid signaling modulation. In mouse, we previously observed a male-specific increase in nondependent voluntary ethanol consumption following *Gas5* knockdown (KD) in medial prefrontal cortex (mPFC) in the two-bottle choice (2BC) assay as well as persistent downregulation of mPFC *Gas5* following chronic intermittent ethanol vapor (CIEV) exposure. The current study sought to further characterize the role of mPFC *Gas5* in the behavioral phenotypes post-CIEV exposure.

Hypothesis: We hypothesize mPFC *Gas5* modulates CIEV-induced escalation of ethanol consumption and stress-related behaviors during ethanol abstinence.

Methods: We performed cranial stereotaxic infusions of an adeno-associated virus for mPFC *Gas5* KD in male mice on a C57BL/6J background and exposed these mice to five cycles of CIEV-2BC to simultaneously induce ethanol dependence and measure escalation of ethanol consumption. Beginning 72 hours after a sixth cycle of CIEV, we tested a battery of stress-related behaviors during ethanol abstinence, including the open field test (OFT) and the elevated plus maze (EPM), sucrose preference, sucrose splash, and stress-induced hyperthermia (SIH) assays. We also measured peak serum corticosterone (CORT) at seven and 28 days after CIEV to probe hypothalamic-adrenal-pituitary (HPA) axis dysfunction.

Results: *Gas5* KD in mPFC did not alter escalation of ethanol consumption, but modulated CIEV effects on select stress-related behaviors during ethanol abstinence. In the OFT, *Gas5* KD in air controls mimicked the stress-like phenotype of CIEV, measured by decreased entries and time spent in the inner zone, whereas *Gas5* KD attenuated this phenotype in CIEV mice. In the EPM, CIEV resulted in decreased stretch-attend postures, which was ablated in *Gas5* KD CIEV mice, suggesting *Gas5* KD reversed CIEV impairment of risk assessment behavior. No effects of CIEV nor mPFC *Gas5* KD were observed in the sucrose preference, sucrose splash, or SIH paradigms. Peak serum CORT increased in CIEV mice seven days into abstinence, with no effect of *Gas5* KD. However, 21 days into abstinence, CIEV mice with *Gas5* KD had persistently increased peak serum CORT, while CIEV controls returned to levels resembling air controls.

Conclusions: These findings suggest mPFC *Gas5* modulates stress-related phenotypes of abstinence from chronic ethanol exposure, specifically anxiety-like and risk-assessment behaviors as well as HPA axis dysfunction.

Significance: AUD research almost exclusively focuses on protein-coding genes, and existing AUD medications target behavioral outcomes, not AUD pathogenesis. By examining the functioning of a noncoding RNA in ethanol-related phenotypes, this work may lead to more effective treatments for AUD and comorbid stress-related disorders.

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Abstract 25

INTRA-OPERATIVE METHADONE AND CYP2B6 PHENOTYPING IN CARDIAC SURGERY

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Introduction: Elderly patients who undergo major cardiac surgery are at a higher risk for opioid-related adverse events (ORADEs), mortality and morbidity; adequate post-operative pain management is paramount. Recently, intraoperative methadone in cardiac anesthesia has been shown to reduce post-operative pain and opioid usage, but the genetic factors that influence its metabolism need to be explored. The CYP2B6 gene encodes an enzyme that facilitates opioid metabolization. This study aims to explore how CYP2B6 phenotypes may impact the analgesic efficacy and adverse effects of methadone.

Hypothesis: We hypothesized that the CYP2B6 phenotype could identify patients at risk for poor pain relief and ORADEs.

Methods: This was a prospective single-arm observational pilot study approved by the University of Pittsburgh Institutional Review Board (STUDY23020064). Patients over the age of 60 years old (n=91) undergoing cardiac surgery who were expected to receive both an induction and sternal closure dose of intraoperative methadone (0.1mg/kg/dose) were recruited. Written informed consent was obtained from all subjects. Blood samples were collected prior to the start of the procedure for pharmacogenetic analysis. Genotypes for the CYP2B6 gene were included and due to the high polymorphic activity of this gene, patients were classified into the following phenotypic classes based on opioid metabolism rate: poor, intermediate, normal, rapid, and ultra-rapid. No ultra-rapid metabolizers were identified in our enrolled patient population. Quality of analgesia and ORADEs were co-primary outcomes. Quality of analgesia was evaluated using numerical pain scores (0-10) in the first 72h post-surgery. ORADEs include post-operative nausea and vomiting (PONV), sedation, chronic post-surgical pain (CPSP), and opioid use up to three months post-discharge.

Results: In this ongoing prospective study of 91 subjects, less than 10% of subjects were poor and rapid metabolizers, while 58% were normal, and 34% were intermediate metabolizers. We did not observe a statistically significant correlation between CYP2B6 phenotypes and clinical outcomes including ORADEs and pain scores, possibly due to small sample size.

Conclusions: This ongoing study did not show a statistically significant correlation between CYP2B6 phenotypes and postoperative opioid and pain outcomes. The lack of correlation may be due to the infrequency of poor and rapid metabolizers in our enrolled patient population. A follow-up study with a larger cohort has been planned to better delineate this relationship.

Significance: These findings will help us build machine learning models that personalize methadone dosing and other analgesics to reduce adverse outcomes.

Research/Grant Support: Internal Funding (PI: Dr. Senthil Sadhasivam, MD, MPH, MBA, FASA)

Abstract 26

TRANSVERSUS ABDOMINIS PLANE BLOCKS FOR CHRONIC ABDOMINAL PAIN: PATIENT AND PROCEDURAL FACTORS ASSOCIATED WITH TREATMENT RESPONSE

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Introduction: Chronic abdominal pain (CAP) is increasingly prevalent and a common complaint seen by pain physicians. Transversus abdominis plane (TAP) blocks have recently emerged as a treatment option for CAP, but predictors of treatment response remain unclear. Prior studies have suggested factors such as BMI, neuropathic symptoms, and comorbidities may play a role in predicting success of TAP blocks but were limited by small sample sizes.

Objective: To evaluate patient and procedural predictors of TAP block response in a larger cohort.

Methods: A retrospective study of 187 patients with CAP who underwent TAP blocks at UPMC Pain clinics was conducted. Patients were classified as responders or non-responders at 3 months based on meeting criteria of either ≥30% pain reduction, ≥5-point improvement in PROMIS physical function, or global impression of improvement. Demographic, clinical, and procedural variables were then analyzed.

Results: Eighty patients were found to be responders to treatment, and 107 patients were found to be non-responders. Responders had significantly fewer pain regions on body maps at baseline and 3 months. No differences were observed in age, sex, BMI, pain duration, or comorbidities (fibromyalgia, anxiety, depression). Procedural factors including steroid use, anesthetic volume, number of blocks, and laterality were not associated with outcomes.

Conclusions: This study's findings suggest TAP blocks may be effective for chronic abdominal pain independent of previously identified patient factors. Notably, the number of pain body regions was associated with treatment efficacy, as patients with fewer body regions involved were more likely to benefit from TAP blocks. These findings suggest that patients with widespread pain, even with abdominal pain present, may demonstrate reduced responsiveness to TAP blocks and warrant further investigation.

Significance: This study provides clinically relevant insight into patient selection for transversus abdominis plane (TAP) blocks in chronic abdominal pain. Treatment response was more strongly associated with pain distribution than with demographic, psychosocial, or procedural factors, as patients with fewer involved body regions were more likely to benefit. These findings support the use of pain body mapping to identify appropriate candidates and suggest TAP blocks may be most effective for patients with localized rather than widespread pain, improving patient selection and counseling.

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Abstract 27

RESISTANCE TO AXIAL STRETCH AFTER RESECTION OF LOWER LUMBAR SPINOUS PROCESSES

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Introduction: Chronic low back pain (CLBP) is the leading cause of years lived with disability, and its prevalence is expected to rise to approximately 843 million cases worldwide by 2050.[1] A new mouse model of lumbar spine instability (LSI) involves resection of the three lower lumbar spinous processes at 19 weeks of age. Within 16 weeks of surgery, LSI leads to severe lumbar degeneration and the onset of stimulus-dependent behaviors such as mechanical hypersensitivity.[2]

Hypothesis: Our goal was to determine if LSI is associated with behavioral readouts of CLBP. One clue comes from the laboratory of Laura Stone, who evaluated a genetic mouse model of disc degeneration and CLBP with a tail suspension assay of axial stretch. This mouse model exhibited decreased duration of time spent immobile, decreased time spent fully extended, increased time spent rearing, and increased time self-supported. [3,4] We predicted similar behavioral readouts of CLBP in the LSI model.

Methods: Male and female C57BL/6 mice (19 weeks; The Jackson Laboratory) underwent LSI (n=8 per group).[2] Sham mice (n=7 per group) underwent dorsal skin incision only. 16 weeks after surgery, a 3-min tail suspension assay was administered. Video recordings of time spent in (1) immobility, (2) full extension, (3) scrunched, (4) rearing, and (5) self-supported were analyzed by an observer blinded to experimental condition.[3,4]

Results: Compared to Sham females, LSI females demonstrated increased duration of time self-supported (94s ± 14s vs 134s ± 12s, $p<0.05$, unpaired t-test). Male Sham and LSI mice did not differ in any outcome measure.

Conclusions: Our data indicate that LSI female but not male mice develop resistance to gravity-induced axial stretch. Future work will evaluate the temporal profile of behaviors during axial stretch, determine severity of lumbar spine degeneration, and further evaluate sex-based differences including imaging to assess for structural lesions.

Significance: These findings support notions that CLBP varies in prevalence and severity between males and females. Our findings highlight the necessity to approach pain management and treatment differently when inevitably applied to human subjects.

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Abstract 28

NOVEL INTRAUTERINE TARGETING OF VEGF SIGNALING ALLEVIATES PELVIC TACTILE ALLODYNIA IN A MOUSE MODEL OF ENDOMETRIOSIS

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Introduction: Endometriosis (EM) impacts an estimated 9 million women in the US. EM patients have debilitating chronic pelvic pain (CPP), and current hormone targeting therapies have adverse side effects or offer temporary relief. Thus, there is a need for new non-hormonal therapies. Our previous data revealed, for the first time, that patients with EM-associated CPP (EM-CPP) have an elevated number of mast cells (MCs) that co-label with vascular endothelial growth factor (VEGF) in endometrial and lesion biopsies. We observed similar levels of MCs co-labeling with VEGF in the uterine tissue of our EM mouse model that develops evoked pain-like behaviors referred to as pelvic tactile allodynia.

Hypothesis: Here, we test the hypothesis that pelvic tactile allodynia in EM mice results from VEGF signaling in uterine lesions and that a new intrauterine (i.u.) delivery route targeting VEGF can blunt pelvic tactile allodynia.

Methods: To induce our EM model, we first utilized C57BL/6J donor mice (6-8 weeks old) that received a subcutaneous injection of estradiol benzoate (10µg), and 4 days later, each uterine horn was excised and placed in Hank's Balanced Salt Solution (HBSS) and minced. Then, recipient mice received an intraperitoneal (i.p.) injection of either HBSS (500µl; "shams") or HBSS+ donor mice minced uterine horn (500µl; "EM mice").

Results: To establish the relevance of MC-derived VEGF to pelvic pain in our EM model, we conducted triple immunofluorescence and found that the MCs expressing VEGF are adjacent to CGRP+ afferents in the uterine tissue of EM mice but not sham controls. To assess pelvic tactile allodynia, von Frey (vF) testing was performed on day 28. Then, sham and EM mice received either i.u. VEGF-neutralizing antibody (anti-VEGF; 1mg/kg) or i.u. IgG (1mg/kg), and vF thresholds were assessed at 3, 9, 18, and 36 hrs. In a separate cohort, we injected the uterine horn (10 µL) with CTB555 to backlabel lumbosacral DRGs and assess changes in neuronal activation (p-ERK expression). In sham mice, neither i.u. IgG nor i.u. anti-VEGF altered mechanical thresholds or p-ERK in DRGs. In EM mice, i.u. anti-VEGF reversed mechanical hypersensitivity and decreased p-ERK expression in DRGs after 9 hrs, but not after i.u. IgG treatment.

Conclusions: These findings demonstrate that in EM mice, 1) MCs expressing VEGF are adjacent to peptidergic afferents, and 2) i.u. delivery of anti-VEGF reverses pelvic tactile allodynia and neuronal activity.

Significance: This study suggests that i.u. delivery of VEGF-neutralizing antibodies is a new potential therapeutic approach to alleviate EM-CPP.

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Abstract 29

MICROELECTRODE ARRAYS WITH INTEGRATED ENZYME-BASED BIOSENSORS FOR REAL-TIME GLYCINE DETECTION IN THE CENTRAL NERVOUS SYSTEM

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Introduction: Glycine is a versatile neurotransmitter which functions as a synaptic regulator and as a direct inhibitory neurotransmitter in the central nervous system (CNS). Glycine is utilized and regulated by both neurons and astrocytes in the CNS for both excitatory and inhibitory signaling via glycine receptors (GlyR), glycine transporters (GlyT), and N-methyl-D-aspartate receptors (NMDAr). In excitatory neurotransmission glycine acts as a co-agonist on NMDA receptors. At inhibitory synapses glycine binds chloride permeable GlyRs producing neuronal polarization and synaptic inhibition which is a key regulator of pain signaling in the spinal cord. Dysfunction of the glycinergic system in the spinal cord has been linked to dis-inhibition of pain signaling in the development of chronic pain. Glycinergic activity is not limited to the spinal cord as histological studies have verified that GlyRs are abundant in the spinal cord, midbrain, hippocampus, and prefrontal cortex which implies additional functions of glycine neurotransmission beyond pain signaling. However, the full scope of glycine function in the CNS has yet to be fully understood and is limited by current sensing technologies. Therefore, there is a need for new tools and technologies which can detect real-time changes in extracellular glycine from intact neural tissues. In recent years, new enzymatic based approaches have been utilized with next-generation microelectrode arrays to provide real-time detection of glutamate, GABA, and glucose in the brain.

Hypothesis: We hypothesize that the enzyme glycine oxidase (GlyOx) can be functionalized onto the surface of implantable microelectrodes arrays (MEAs) to enable real-time amperometric detection and quantification of glycine in the extracellular space of intact tissues.

Methods: Here, we present a flexible polymer microelectrode array (MEA) integrated with GlyOx to enable real-time amperometric detection of glycine both in-vitro and in-vivo as a GlyOx biosensor. Functionalized MEAs and injection canulae were implanted into mice brains to span the prefrontal and infralimbic cortices in an acute experimental procedure. Detection of local glycine was confirmed via canula injection of GlyT1 antagonist bitopertin as well as individual injections of GABA, glutamate, glycine, and KCl.

Results: By utilizing our GlyOx biosensors, we have successfully achieved detection of glycine with a limit of detection of 3.06μM. Using selective enzyme functionalization, we also achieved simultaneous real-time detection of GABA (GABAse), glutamate (glutamate oxidase), and glycine from anesthetized mice following injection of pharmaceutical agents as well as individual neurotransmitter solutions.

Conclusions: Our GlyOx functionalized MEAs enable real-time monitoring of glycine within intact neural tissues with high specificity and accuracy.

Significance: The ability to detect glycine in real-time enables further study and characterization of the roles of glycine in the context of pain sensing in health and disease for the development of new therapies for the monitoring and treatment of chronic pain.

Research / Grant Support: NIH R01NS136622 (PI: Tracy Cui), NIH T32GM075770 (PI: Yan Xu)

Abstract 30

MULTIGENIC AND PSYCHOSOCIAL RISK FACTORS FOR RELAPSE IN PREGNANT WOMEN WITH OPIOID USE DISORDER

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Introduction: With rising rates of drug overdose deaths during pregnancy, identifying genetic and psychosocial risk factors is critical for developing predictive models and reducing maternal mortality. This study evaluates multigenic signatures associated with relapse and characterizes relapse patterns and substances used among pregnant women with Opioid Use Disorder (OUD).

Hypothesis: We hypothesized that genetic variants in opioid metabolism pathways and psychosocial factors contribute to relapse during pregnancy. Integrating these factors can help improve the identification of women at higher risk of relapsing.

Methods: We conducted a multi-site prospective study of 85 pregnant women (≥16 weeks gestation) with OUD receiving Opioid Replacement Therapy (ORT). Relapse was defined as use of any illicit drugs, non-prescribed opioids, or cannabinoids; assessed at 3 timepoints - Enrolment, throughout pregnancy, and at delivery using urine drug screens, EMR documentation, and self-reported surveys. Maternal blood samples were genotyped using a genome-wide SNP array. Variants within candidate genes involved in opioid metabolism (CYP3A4, CYP2B6, FAAH), transport (ABCB1, ABCC3, ADRB2, SLC22A1), receptors (OPRM1), and signaling (COMT) were extracted and underwent standard quality control. Associations between relapse and clinical variables were assessed using χ^2, Fisher's exact, and Wilcoxon rank-sum tests. Single-variant association testing was conducted using PLINK-glm command under an additive genetic model. All models included the first derived latent factor as a covariate to reduce confounding. Gene-based associations were evaluated using SKAT with correction for multiple testing.

Results: Among 85 mothers, 39 relapsed at enrollment and 45 during pregnancy, while 22 relapsed at delivery. The most common substance combinations were opioids + illicit drugs (cocaine), THC only and illicit drugs only. Depression was significantly associated with relapse at enrollment (p=0.009) and during pregnancy (p=0.044), while PTSD showed a borderline association at enrollment. Single-variant testing revealed a variant in SLC15A2 associated with relapse at enrollment ($p \approx 1.1 \times 10^{-4}$), an intergenic variant in CD28/CTLA4, and an intronic variant in PHLDB2/PLCXD2 significantly associated with relapse during pregnancy ($p \approx 2.9 \times 10^{-4}$ and 3.5×10^{-4}, respectively), remaining significant after psychiatric adjustment. Gene-based analyses revealed the strongest signal for ABCB1 during pregnancy.

Conclusions: We identified numerous genetic signatures and psychiatric comorbidities significantly associated with relapse during pregnancy.

Significance: Insights will support early clinical intervention and the development of personalized treatment strategies.

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Abstract 31

COMPARATIVE PERIOPERATIVE OUTCOMES FOLLOWING DIFFERENT SURGICAL AND REGIONAL ANESTHETIC APPROACHES IN TWO INFANTS WITH TYPE-H TRACHEOESOPHAGEAL FISTULA: A CASE SERIES

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Introduction: Congenital H-type Tracheoesophageal fistulas (H-type TEF) are a rare form of TEF, accounting for 4-5% of TEF abnormalities, that pose unique challenges for diagnosis due to the absence of esophageal atresia. Surgical repair may be performed through a cervical or thoracic approach depending on the location of the fistula. Effective perioperative pain management is essential in the neonatal population to reduce opioid administration and respiratory depression and potentially avoid long-term damage on the developing neonatal nervous system. However, limited literature compares surgical approaches or describes the role of perioperative anesthetic techniques.

Hypothesis: Regional anesthetic techniques, specifically superficial cervical plexus nerve block for cervical repair and caudal thoracic epidural for transthoracic repair, can be effectively applied to H-type TEF repair and may reduce perioperative opioid requirements.

Methods: We present two infants diagnosed with H-type TEF who underwent different surgical and regional anesthetic approaches. Case 1 underwent a cervical approach H-type TEF repair with placement of a right superficial cervical plexus nerve block for perioperative analgesia. Case 2 underwent a transthoracic approach H-type TEF repair with placement of a caudal thoracic epidural. Perioperative outcomes include time to extubation, total opioid administered, postoperative respiratory status, pain scores assessed by the Neonatal Pain, Agitation and Sedation Scale (N-PASS), feeding progression, length of stay in the intensive care unit (ICU), and perioperative complications.

Results: Both patients were extubated on postoperative day (POD) 0. Case 1 required less postoperative morphine over the first 24 hours (0.3 mg/kg vs 0.75 mg/kg in Case 2) but had a longer postoperative hospitalization (22 vs 8 days). Case 1 developed right vocal cord paralysis resulting in silent aspiration requiring gastrostomy tube placement. Case 2 experienced a small anastomotic leak and was managed with thickened feeds.

Conclusions: These cases demonstrate the use of different regional anesthesia techniques tailored to the chosen surgical approach for H-type TEF repair and highlight the potential role of regional anesthesia in perioperative management. Further investigation is needed to determine the optimal perioperative analgesia for specific H-type TEF repair surgical approaches.

Significance: Given the rarity of H-type TEF and limited literature on perioperative anesthesia, these cases contribute clinical guidance on the use of regional anesthesia techniques tailored to a specific surgical approach, with implications for opioid sparing in neonates.

Research/Grant Support: None. There are no sources of funding support or financial disclosures.

Abstract 32

CHARACTERIZING GRIMACE BEHAVIOR AND MICROGLIA MORPHOLOGY IN A MOUSE MODEL OF CHRONIC ALCOHOL WITHDRAWAL-INDUCED PAIN

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Introduction: Alcohol Use Disorder (AUD) is a highly prevalent disease that causes deterioration of health and a steep socioeconomic cost. Individuals with AUD often report symptoms of chronic pain and many continue consuming alcohol to combat these symptoms, especially during withdrawal. Alcohol has deleterious effects on the neuroimmune system that cause aberrant inflammation and increased sensitivity to painful stimuli. However, the neurobiological connection between AUD and chronic pain remains ill-defined. Microglia are the primary immune cells in the central nervous system and mediate neuroinflammation associated with alcohol consumption and pain responses; however, few studies have looked at these effects in combination. Thus, we sought to investigate the role of microglia in chronic alcohol withdrawal-induced pain (CAWIP).

Hypothesis: We hypothesized that exposure to chronic intermittent ethanol vapor (CIEV) would lead to heightened spontaneous nociception (*i.e*. grimacing) and changes in microglial morphology indicative of a reactive phenotype.

Methods: Animals underwent 5 w of exposure to CIEV or ambient air (control group) allowing for clinically relevant blood alcohol levels (150-250 ng/dL) in our CIEV group. 24 h after the last CIEV exposure, animals were video recorded for 30 m and videos were uploaded and scored using PainFace technology. PainFace uses machine learning to measure action units (*i.e.* orbital tightening) and results in a final grimace score indicative of spontaneous nociception. Brains were collected and cortical microglia were traced using Microscopy Image Analysis Software to measure differences in microglia morphology. As a positive control, a separate cohort of mice were injected with lipopolysaccharide (LPS; 1.0 mg/kg) to induce innate immune activation, and grimacing behavior and microglia morphology was measured 24 h post-injection.

Results: PainFace software showed increased grimacing behavior in mice 24 h into withdrawal compared to air controls, representative of CAWIP. Grimacing behavior was negatively correlated with territory occupied by microglia in the cortex showing increased microglial reactivity, typical of a pro-inflammatory state. LPS treatment led to increased grimacing behavior and reductions in territory occupied by microglia compared to saline treatment, similar to mice undergoing withdrawal from CIEV.

Conclusions: These data indicate an association between microglia reactivity and CAWIP, such that alcohol may increase microglia reactivity leading to heightened inflammation and increased spontaneous nociception.

Significance: Alcohol use and chronic pain are highly comorbid and continued alcohol use is often used to combat symptoms of pain. These studies identify a role for microglia in the genesis of CAWIP and may further be investigated as a therapeutic target.

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Abstract 33

MINIMIZATION OF SYSTOLIC ANTERIOR MOTION IN ROBOTIC MITRAL VALVE REPAIR

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Introduction: Systolic anterior motion (SAM) is a complication of mitral valve repair (MVR) with an incidence rate of 4-13%. Various transesophageal echocardiography (TEE) measurements have been identified as risk factors in the prediction of SAM. Most of these parameters were studied on patients undergoing a conventional MVR approach and have not been examined in the context of robotic MVR.

Hypothesis: We hypothesize that patients who develop SAM after robotic MVR have predictable characteristics that can be stratified by TEE.

Methods: From September 2021 to August 2025, 197 patients underwent isolated robotic MVR at our institution. Using TEE, structural measurements of previously published predictors of SAM were discussed with the surgical team prior to the start of the case. These risk factors included position of the coaptation point (AL/PL ratio), anterior and posterior leaflet heights (AL, PL), aorto-mitral angle, coaptation to basal septum distance (C-sept) and basal septum and ventricular sizes. For simplicity, low risk consisted of 0-3 risk factors and high risk consisted of 4-7 risk factors. Surgical outcomes were compared between low and high-risk groups. Post-hoc TEE measurements were also compared between patients who developed SAM and patients who did not. Univariable association between various TEE measurements and SAM were evaluated using Firth logistic regression.

Results: The incidence of SAM in 197 patients who underwent robotic MVR was 3.5% (n = 7). Of those patients who developed SAM, 2 had valve replacements and 5 were managed with volume administration, esmolol, and afterload augmentation. Univariate firth logistic regression found associations with the development of SAM: aorto-mitral angle (OR 0.95, CI 0.9 - 0.99), C-sept distance (OR 0.78, CI 0.64-0.93) and left ventricular end systolic diameter (LVESD) (0.72, CI 0.57-0.87). Furthermore, patients with higher documented SAM risk factors were also associated with the likelihood of developing SAM (OR 2.35, 1.27-4.83). Predictably, there were group differences in risk factors in the high (N = 89) and low (N = 108) SAM risk patients that surgeons were aware of intraoperatively. However, there were no significant differences in surgical complexity as measured by both Fujita Complexity Score and Mitral Valve Complexity score. While not statistically significant, the high SAM risk group trended towards higher mitral valve repair time with a larger annuloplasty band compared to commissure-commissure diameter. The high SAM risk group was also observed to contain 100% of patients with SAM.

Conclusions: The evaluation of certain TEE parameters, notably C-sept, aorto-mitral angle and LVESD can be more important for the association of SAM in robotic MVR. Careful discussion of patients at high risk of SAM may allow robotic MVR to be completed with an overall lower SAM incidence than reported in literature, especially using a simple risk stratification strategy.

Significance: Surgical adjustments preventing SAM in robotic MVR may be informed by interdisciplinary TEE risk stratification.

Research/Grant Support: None

DEPARTMENT OF CRITICAL CARE MEDICINE

Oral Abstract O2

DEVELOPING PARSIMONIOUS MODELS OF ACUTE BRAIN DYSFUNCTION FOR CRITICALLY ILL CHILDREN IN THE PEDIATRIC INTENSIVE CARE UNIT (PICU): LEVERAGING EXPERT KNOWLEDGE AND CAUSAL STRUCTURE LEARNING

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Introduction: Among PICU survivors who suffered acute brain dysfunctions (ABD), 35% receive a new neurocognitive diagnosis. To mitigate these harms, clinicians need to identify at-risk patients as early as possible. Predictive models might help, but their adoption in critical care has been limited by concerns about model transparency and reliability. This study addresses these challenges by leveraging clinician expertise and causal structure learning (CSL) to develop more parsimonious and clinically aligned models for predicting ABD.

Hypothesis: Integrating clinician-elicited knowledge with CSL algorithms may enable us to (1) identify potential causes of ABD and (2) facilitate the development of predictive models using a limited set of biomarkers without substantial loss in performance.

Methods: We labeled 18,568 PICU encounters from UPMC Children's Hospital (2010–2022) using a validated ABD computable phenotype. We elicited knowledge from four clinicians to construct a consensus directed acyclic graph (DAG) representing causal relationships among factors associated with ABD. We applied two CSL algorithms, GOLEM and PC-MB, to estimate plausible causal relationships. The resulting DAGs were compared with and integrated into the clinician consensus DAG to produce enriched variations. Using these variations, we trained XGBoost models on biomarkers identified as potential causes of ABD. We evaluated performance using the area under the precision-recall curve (AUPRC).

Results: The clinicians' consensus DAG (Fleiss' Kappa = 0.62) identified 16 biomarkers as potential causes of ABD. The PC-MB algorithm showed 78% concordance with clinician consensus; GOLEM showed 46%. Together, these algorithms identified seven biomarkers not included in the consensus: BUN, creatinine, dobutamine, glucose, potassium, PTT, and SpO2. The model trained on the intersection of the consensus and PC-MB DAGs achieved an AUPRC of 0.79 with 14 biomarkers. In comparison, the control model used all of the 45 available biomarkers to achieve an AUPRC of 0.81. An additional model created without medications and restricted to vitals and laboratory results (11 biomarkers) achieved an AUPRC of 0.77.

Conclusions: CSL, guided by expert knowledge, identified biomarkers that clinicians had initially overlooked, suggesting that this hybrid approach may deepen our understanding. We used these factors to build causally informed predictive models that are consistent with PICU clinicians' reasoning. Our best model used 14 biomarkers and performed comparably to a model using all 45, indicating that many of these biomarkers are not essential for predicting ABD. The performance of the constrained model trained solely on vitals and laboratory results suggests that readily available bedside data may retain sufficient predictive value for clinical applications.

Significance: The hybrid expert-CSL approach may be generalizable to other domains where model transparency and clinical alignment are essential. Models built on routinely collected vitals and laboratory values achieve competitive performance, suggesting the possibility of building flexible models using information commonly collected in PICUs. By producing parsimonious models that rival high-dimensional alternatives, these findings support a pathway toward bedside clinical decision-support tools that may be transparent enough to earn clinicians' trust while remaining practical to implement.

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Abstract 34

EARLY NEURODEGENERATION IN AN EXPERIMENTAL MODEL OF PEDIATRIC CARDIAC ARREST IS SEX DEPENDENT

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Introduction: Neonatal and adult models producing focal hypoxic-ischemic brain injury (i.e. stroke) show sex-dependent neurodegeneration, with males being more vulnerable. Whether sex differences also occur in models of global ischemia, such as seen after cardiac arrest, is unknown.

Hypothesis: Like focal ischemia, males would have more neurodegeneration than females after asphyxial cardiac arrest (ACA) in juvenile postnatal day 17 (PND17) rats.

Methods: Anesthetized male and female PND17 Sprague-Dawley rats (n=6/sex/group) were endotracheally intubated and mechanically ventilated and femoral arterial and venous catheters placed. Vecuronium was administered i.v. and ventilation was discontinued to induce ACA. After 14 minutes, return of spontaneous circulation was achieved with chest compressions, epinephrine, and resuming ventilation. Neurological Deficit Scores (NDS) were recorded on days 1-7 then rats were sacrificed by perfusion fixation. Brains were paraffin-embedded and 10 micrometer coronal sections that included the dorsal hippocampus were processed for histological evaluation using H&E and Fluoro-Jade B (FJB) staining, and Iba1 immunohistochemistry.

Results: ACA resulted in significant neurodegeneration in the selectively vulnerable CA1 hippocampus at 7 days in both male and female rats compared with naïve animals assessed by H&E and FJB as indicators of neuronal survival and neurodegeneration, respectively; neuroinflammation assessed by Iba1 staining of reactive microglia; and worse neurobehavioral outcomes (NDS) on day1-2 (ANOVA; all $p< 0.05$). Compared with males, female rats showed increased neurodegeneration using FJB staining (37±16 vs. 17±16 FJB+ neurons/mm) and increased neuroinflammation using Iba1 immunohistochemistry (40±14 vs. 21±17 Iba1+ cells/mm) (mean±SD, both $p<0.05$). Female rats also demonstrated reduced CA1 neuronal survival using H&E staining (63±28 vs. 82±22 neurons/mm), although this difference was not statistically significant ($p=0.3$). There was no sex difference in NDS.

Conclusions: Contrary to our initial hypothesis, juvenile female rats had increased neurodegeneration and neuroinflammation compared with male rats 7 days post-injury. These findings warrant additional studies with larger sample sizes to verify sex-dependent differences in vulnerability to global hypoxia-ischemia produced by ACA, and long term histologic and behavioral outcome assessments to determine if this vulnerability is enduring.

Significance: These findings challenge existing paradigms derived from focal ischemia models and suggest that sex-specific vulnerability to brain injury may differ in global ischemia after pediatric cardiac arrest. Understanding these differences may be critical for developing targeted neuroprotective strategies.

Abstract 35

DEVELOPMENT AND REFINEMENT OF A MACHINE LEARNING-BASED NEONATAL MORTALITY RISK ADJUSTMENT MODEL ACROSS LEVELS OF CARE

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Introduction: Meaningful comparison of outcomes across centers requires accounting for differences in population characteristics that crude mortality rates alone cannot capture. Neonatology lacks the robust, widely adopted risk assessment frameworks established in adult and pediatric critical care. This work addresses that gap by applying machine learning to EHR-derived data to develop a modern neonatal mortality risk adjustment tool.

Hypothesis: A machine learning model trained on multicenter EHR-derived data within the first 24 hours of admission will outperform the Score for Neonatal Acute Physiology-II (SNAPPE-II) in prediction of in-hospital neonatal mortality.

Methods: A multicenter retrospective cohort of 21,849 neonates admitted to UPMC NICUs between 2016-2023 was derived from the EHR data warehouse. Extracted variables included demographics, perinatal risk factors, vital signs, and lab results. A 70/30 split was used for training and validation of a supervised XGBoost mortality risk tool. Model performance assessed using AUROC, AUPRC, Brier score, and calibration plots. The model was subsequently retrained and recalibrated using level IV data only (n = 4,097) to improve performance in the clinically distinct subgroup. Performance compared to a modified SNAPPE-II.

Results: The combined model achieved an AUROC of 0.967, AUPRC of 0.566, and a Brier score of 0.010 across the full validation cohort. This outperformed the modified SNAPPE-II (AUROC 0.808, AUPRC 0.237, Brier score 0.014) with good calibration confirmed by GiViTI analysis ($p = 0.358$). Performance was particularly strong in the level III subgroup (AUROC 0.974, AUPRC 0.630, Brier score 0.008). However, the combined model demonstrated markedly poor performance in the level IV subgroup (AUROC 0.474, AUPRC 0.028, Brier score 0.092). The retrained quaternary model achieved an AUROC of 0.928, AUPRC of 0.247, and Brier score of 0.022, representing statistically significant improvements over both the combined model and modified SNAPPE-II in this population ($p < 0.05$).

Conclusion: These models demonstrate promising improvement over existing neonatal mortality risk adjustment strategies, with population-specific recalibration further improving performance in complex quaternary settings. External validation is needed to confirm generalizability before broad clinical adoption.

Significance: Open-source, EHR-compatible neonatal mortality risk models built on modern interoperability standards have the potential to enable meaningful cross-center benchmarking and quality improvement at scale.

Research/Grant Support: This work is supported by the UPMC ICU Service Center. No external funding received.

Abstract 36

A MODULAR SANDBOX FOR VISION LANGUAGE MODEL-BASED CARDIOPULMONARY RESUSCITATION PERFORMANCE ANALYSIS FOR MULTI-VIEW VIDEO FEEDS

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Introduction: High-quality cardiopulmonary resuscitation (CPR) is the strongest determinant of survival after cardiac arrest, yet adherence to American Heart Association (AHA) guidelines remains poor. Only 22% of chest compressions delivered by trained personnel simultaneously meet recommended depth and rate targets. Existing feedback devices address isolated metrics but cannot assess visual elements such as hand placement or compression quality. Vision language models (VLMs), which integrate computer vision with natural language reasoning, offer a promising approach to bridge this gap. However, no standardized platform exists to systematically evaluate and compare VLM-based pipelines for CPR performance.

Hypothesis: A modular environment with pose estimation models, VLMs, and 3D object tracking can enable rapid development of AI pipelines for video-based CPR assessment.

Methods: We developed a modular software sandbox that ingests synchronized multi-view video from four GoPro cameras (one egocentric, three exocentric), capturing simulated CPR scenarios. The platform provides a drag-and-drop, node-based canvas where users compose analysis pipelines by connecting multiple CV modules: (1) Frame extraction: each multi-view video's frames are extracted uniformly at configurable frame rates using OpenCV. (2) 2D Pose Analysis: YOLO11n-pose and MoveNet are used to track rescuer body keypoints (3) SAM 3D-Body is used for 3D body reconstruction of the rescuer and patient. Each person is modeled using meshes and represented as a Momentum Human Rig (MHR) from monocular video. (4) VLM Coaching uses AHA metrics with VLMs to generate natural-language feedback.

Results: Using the sandbox, we designed a pipeline utilizing 2D pose estimation pipeline which estimated compression rates of 25, 31, 37, and 30 versus ground-truth counts of 26, 34, 34, and 25 (mean absolute error: 3.25) across four CPR recordings. Across multiple clips, we found that SAM 3D-Body consistently tracked hand placement relative to the patients' lower third of sternum. It also consistently measured and corrected elbow angles when the arms were too bent, and relative compression depth through wrist tracking. Through the sandbox, we found Gemini-2.5 as the best-performing foundational VLM for understanding CPR recording context.

Conclusions: Our modular sandbox demonstrates that VLM-based pipelines can extract meaningful CPR performance metrics from multi-view video.

Significance: The Sandbox platform establishes an intuitive platform for developing and evaluating AI-driven CPR analysis, advancing the development of real-time visual coaching systems that could improve resuscitation quality.

Abstract 37

SYSTEMIC IMMUNE RESPONSIVE GENE 1 (IRG1) KNOCKOUT INFLUENCES INFLAMMATORY CYTOKINE EXPRESSION AND FEAR CONDITIONING RESPONSE AFTER CONTROLLED CORTICAL IMPACT IN MICE

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Introduction: The immune-responsive gene 1 (IRG1) / itaconate pathway has emerged as a pivotal regulator of neuroinflammation. Itaconate is a Krebs cycle-derived immunometabolite produced primarily by myeloid cells including microglia, macrophages, and granulocytes. Microglial-specific *Irg1* knockout exacerbates neuroinflammation and neurological deficits in the controlled cortical impact (CCI) model of traumatic brain injury (TBI) — implicating IRG1-mediated itaconate signaling as a key regulator of microglial function after TBI. We investigated whether global knockout of IRG1, impacting infiltrating myeloid cells as well as microglia impacts outcomes after CCI.

Hypothesis: We hypothesized that global knockout of IRG1 would attenuate inflammatory cytokine expression and improve neurologic outcome after TBI

Methods: CCI was performed in adult male (C57BL/6NJ-Irg1) global knock-out and wild-type (WT) mice (5m/s, 1.2mm depth). Cytokine analysis (n=5/group) was performed on pericontusional tissue at 24h and 7d after injury with the Meso Scale Discovery multiplex and normalized to total protein. Behavioral analysis was performed using 6m/s 2mm injury level and included Morris Water Maze, Sucrose splash test, and Fear Conditioning. Student's t-test or ANOVA was performed as appropriate and $p<0.05$ determined significance.

Results: At 24 hours post-injury, WT mice demonstrated robust elevations in multiple pro-inflammatory cytokines after CCI, whereas IRG1 KO mice showed a trend towards attenuated cytokine levels. At 7 days post-CCI, IRG1 KO mice had reduced expression of several inflammatory mediators including interleukin-6 and tumor necrosis factor alpha. Fear conditioning performance revealed that IRG1 KO mice were overall less fearful than WT mice, including: longer latency to freeze, less time frozen, and less freezing episodes in extinction testing.

Conclusions: Our study reveals vulnerability in associative learning and reduced cytokine expression in pericontusional tissue after injury in a global IRG1 knockout mouse.

Significance: These findings indicate that IRG1 deficiency may have cell-type specific effects after TBI.

Research/Grant Support: Funding: 5T32HD040686 (AMD), R01 NS127372 (DS)

Abstract 38

INTERHOSPITAL TRANSFER PATTERNS AS A MEASURE OF HOSPITAL RESILIENCY UNDER STRAIN

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Introduction: The ability to rapidly transfer patients between hospitals may be an important determinant of hospital resilience during periods of strain. However, tools to characterize the strength, structure, and stability of interhospital transfer networks—and individual hospitals' access to them—remain limited. We used network analysis to map interhospital transfer patterns across five U.S. states and describe these networks using novel measures that may better capture nuances of network structure than traditional metrics. Our objective was to explore approaches to measuring hospital transfer networks in the context of hospital resilience and the capacity to withstand system strain.

Hypothesis: Novel measures of interhospital transfer networks provide a more robust description of network strength and stability when compared to the more traditional measure of out degree.

Methods: We performed a retrospective cohort study using 2016–2019 Healthcare Cost and Utilization Project all-payer claims data from adult acute care hospitals in Florida, Iowa, Maryland, Nebraska, and Wisconsin. All adult emergency department and inpatient encounters were included. Interhospital transfers were identified by linking unique patient identifiers across encounters at two hospitals occurring on the same or following day. Network analysis was used to map hospital connections created by patient transfers. For each hospital, we calculated three measures of network structure: out-degree (traditional descriptor), transfer instability index (TII), and inverse Herfindahl-Hirschman Index (iHHI). We examined relationships among these measures and their associations with hospital characteristics from the 2016–2019 American Hospital Association Annual Surveys. STATA 19 was used for data analysis.

Results: We identified 894,195 interhospital transfers between 575 hospitals over the study time period. Mean hospital out-degree was 12.25 (SD 7.74), mean TII was 5.32 (SD 3.33), and mean iHHI was 3.71 (SD 2.18). All measures increased with hospital size and were higher among urban, for-profit, and system–affiliated hospitals. TII and iHHI were strongly correlated (Pearson r = 0.96) and showed less variability across time and hospital characteristics than out-degree. iHHI demonstrated the lowest temporal variability. Mean percent absolute difference (maximum vs minimum) was 22.7% for iHHI, 34.9% for out-degree, and 4.3% for TII. Mean year-over-year percent difference was 14.9%, 21.8%, and 15.8%, respectively.

Conclusions: Hospitals vary substantially in the size and structure of their transfer networks. Compared with out-degree, TII and iHHI better capture subtle differences in network structure. iHHI showed the greatest temporal stability, suggesting it may best reflect a hospital's intrinsic ability to transfer patients.

Significance: This is the first use of iHHI and TII as descriptors of transfer network strength and stability in the context of hospital resiliency. Future work should utilize these more powerful measures when describing transfer networks.

Research/Grant Support: Supported by US National Institutes of Health and National Heart, Lung, and Blood Institute (grant number R35HL144804)

Abstract 39

PEDIATRIC RISK OF ILLNESS MORTALITY EVALUATION (PRIME) AND FEDERATED PRIME (F-PRIME) PERFORMANCE AT A QUATERNARY CHILDREN'S HOSPITAL

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Introduction: There remains a need for generalizable population-level risk adjustment models within intensive care and an urgent need to update current pediatric models, which use data from more than a decade ago. Real world data sources, such as the electronic health record (EHR), offer the ability to incorporate more information into risk adjustment models. Federated approaches offer the potential for privacy-preserving multi-site collaboration.

Hypothesis: Curated EHR data can be used to develop high performing standardized mortality ratios for critically ill children.

Methods: This is a retrospective cohort study of admissions to a quaternary PICU from Oct. 2015-July 2024. EHR data though 2022 were curated from the first 24 hours of PICU admission. Patients were assigned randomly to training (70%) or test (30%) datasets. A ridge logistic regression model was trained on a hospital mortality outcome, tuned using 10-fold crossvalidation. A federated model was trained by splitting the training dataset into three nodes, training individual ridge models, and aggregating model characteristics. The model was validated on temporal holdout data from 2023 and 2024. Model performance was assessed by examining area under the receiver operating curve (AUROC), area under the precision recall curve (AUPRC), standardized mortality ratios (SMR), calibration plots, Brier scores, and the Hosmer-Lemeshow test; performance was compared with the DeLong test. Data are presented with counts (%), medians (IQR), and 95% confidence intervals.

Results: There were 21950 encounters with 398 (1.8%) deaths. Primary admission reasons were respiratory (7901, 36.0%) and injury/toxic ingestion (3004, 13.7%). PRIME demonstrated excellent discrimination with an AUROC of 0.91 [0.87-0.95] and an AUPRC of 0.52 [0.38-0.63] in the validation data. Visualized calibration was good, the Hosmer-Lemeshow statistic had *P*=0.51, the SMR was 1.00, and Brier score was 0.011. F-PRIME performed similarly to the centralized model. Both PRIME and F-PRIME significantly outperformed the electronic PRISM Score (ePRISM; *P*=0.03).

Conclusions: In a diverse cohort of critically ill children, PRIME and F-PRIME demonstrated excellent performance and outperformed existing risk adjustment models.

Significance: Interoperable EHR data can be leveraged to efficiently facilitate risk adjustment and improve upon current models. Given that F-PRIME preserves the performance of the centralized model, it provides a framework for a multi-site model that could be continuously updated without sharing patient-level data.

Research/Grant Support: None

Abstract 40

ASSOCIATION OF FUNCTIONAL STATUS AFTER CRTIICAL ILLNESS AND CHILD OPPORTUNITY INDEX

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Introduction: Critically ill children often experience new functional impairments across multiple health domains, a phenomenon known as post-intensive care syndrome in pediatrics (PICS-p). We aimed to identify if Child Opportunity Index (COI), a composite measure of neighborhood resources, is associated with functional status post-PICU discharge.

Hypothesis: Patients with a lower COI will have a worse functional status scale (FSS) post-PICU discharge.

Methods: We analyzed medical record data from 100 patients enrolled in the Critical Illness Recovery for ChiLdrEn (CIRCLE) program at the UPMC Children's Hospital of Pittsburgh between September 2021-December 2023. We abstracted FSS at baseline, hospital discharge, and 1-3 months post-discharge. New functional impairment was defined as a change of > 1 point from baseline to follow-up for each FSS subscale: Communication, Feeding, Mental, Motor, Respiration, and Sensory. State-normed COI groups were categorized as low (very low to low) and high (moderate to very high). Rates of new functional impairment by COI group were assessed using chi-square tests with Bonferroni correction for multiple comparisons.

Results: 42 (42%) patients were characterized as being in the low COI group while 58 (58%) were in the high COI group. The two groups had different rates of mechanical ventilation (66.7% in the low COI group vs 72.4% in the high COI group) and race (57.1% identified as White in the low COI group vs 87.9% in the high COI group). Overall, 49 (55.7%) had a new impairment in FSS, similar between the low COI (54.3%) and high COI (56.5%) groups. The subscale with the highest rates of new impairment was motor (39.8%), followed by feeding (15.9%), and communication (11.4%), though these were not different by COI group. New mental health impairment occurred in 20% of the low COI group versus 0% in the high COI group (p=0.015).

Conclusions: We found increased post-PICU mental health impairments in children from low versus high COI groups.

Significance: COI may not be significantly associated with overall functional status after PICU discharge, though there may be a relationship between COI and mental health status after critical illness. This could be due to lack of access to services, or the cumulative effect of social determinants of health. Interventions involving mental health screening and treatment should be targeted towards patients from lower COI areas to mitigate this disparity.

Research/Grant Support: UPMC Children's Hospital of Pittsburgh Foundation

Abstract 41
DOES DEXMEDETOMIDINE INFLUENCE OPIOID REQUIREMENTS AMONG CRITICALL ILL CHILDREN?

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Objective: We aimed to evaluate whether early dexmedetomidine administration in the first 24 hours of PICU admission was associated with lower opioid exposures among critically ill children requiring mechanical ventilation.

Design: An observational cohort study of critically ill children receiving mechanical ventilation in a quaternary PICU over an 11-year period. Multiple linear regression with and without propensity score matching were used to evaluate the association between dexmedetomidine administration and mean opioid 48-hour exposure among children who did versus did not receive dexmedetomidine in the first 24 hours of admission.

Results: Among 26,954 PICU encounters, 662 (2.5%) met inclusion criteria, of which 122 (18%) received dexmedetomidine within 24 hours of admission. Age and race did not differ between groups. Compared to children who did not receive dexmedetomidine, children who received dexmedetomidine had lower illness severity, and were more likely to be female and have a primary respiratory diagnosis. The prevalences of early hypotension and bradycardia were similar between groups. In the multiple linear regression model, early dexmedetomidine administration was not significantly associated with lower 48-hour opioid exposure. Younger age and greater early opioid exposure were associated with greater 48-hour opioid exposure. Propensity score development achieved optimal covariate balance. Across univariate and multivariate models incorporating propensity score matching, early dexmedetomidine was not significantly associated with decreased 48-hour opioid exposure. Early opioid exposure and lorazepam exposure were significantly associated with greater 48-hour opioid exposure, whereas ketamine use was associated with significantly lower opioid exposure.

Conclusions: Early dexmedetomidine initiation was not associated with reduced 48-hour opioid exposure in this study. Lorazepam exposure was associated with greater opioid exposure and ketamine exposure was associated with lower opioid exposure. More studies are needed to identify optimal sedative-analgesic medication regimens for critically ill children who require mechanical ventilation.

Research/Grant Support: Clinical Scientist Training Program Scholar Award (OMO);5K23HD099331-02 (CMH); 5T32HD040686-20 (JHP), 5K23NS104133 (AKA), 5T32HD040686-19 (JR); TL1TR001858(KC); The American Foundation for Pharmaceutical Education

Abstract 42

NASA-TLX FOR EARLY SELF-IDENTIFICATION OF COGNITIVE OVERLOAD IN CRITICAL CARE

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Introduction: Cognitive overload is common in the ICU. The NASA Task Load Index (NASA-TLX) is a validated measure of task load across six domains. Physician Task Load (PTL), the sum of four NASA-TLX domains, correlates with cognitive overload and burnout.

Hypothesis: We hypothesized that the NASA-TLX may be feasible as a tool for CCM fellows to recognize cognitive overload and identify those who may benefit from near-peer coaching.

Methods: This was a prospective mixed-methods feasibility pilot study across 6 academic blocks (July-Dec. '25). In the first week of each block, first-year CCM fellows were asked to complete the NASA-TLX daily, with weighting performed on day 1 of the block. We calculated fellows' weekly mean TLX, PTL, and burnout cluster (BC) scores. Those scoring above pre-set risk thresholds (PTL>120; BC>60) were referred for near-peer coaching. Monthly semi-structured debriefs evaluated feasibility, explored cognitive load experiences, and examined perceived framework utility. Qualitative data underwent analysis using a grounded theory approach. Primary outcomes were participation and threshold exceedance rates; secondary outcomes were implementation barriers and themes in participant experiences.

Results: 16 of 19 first-year fellows (84%) participated. Weekly participation ranged from 21-69%. Fellows completed the survey 2(1-3) times per week. Median TLX score was 139.2(98.8-181.0), with PTL 96(76-124) and BC 35(22-61). 1 fellow screened in for near-peer coaching. 3 primary themes emerged from the debriefs. Framing workload via NASA-TLX domains helped fellows identify sources of cognitive overload. That awareness helped them modify behaviors without external intervention. Barriers included added task load of survey completion and ambiguity of the scoring system. The framework's educational impact emerged independent of score magnitude or risk threshold screening.

Conclusions: The NASA-TLX framework helped CCM fellows to identify and mitigate factors contributing to cognitive load, but only screened in 1 fellow for coaching. Limitations include effort of daily survey completion and subjective scales. Further research may focus on developing task load management skills through a cognitive load theory lens in adult physician learners.

Significance: This study suggests the potential of an educational approach rooted in cognitive load theory for helping adult learners in medical education develop and optimize task load management skills. Further research is necessary to develop a more optimal tool for self-assessment.

Research/Grant Support: None

Abstract 43

INTERACTIVE SIMULATION OF TEMPORARY VENOUS PACEMAKER TROUBLESHOOTING IMPROVES CRITICAL CARE FELLOWS' TEMPORARY PACING SKILLS AND CONFIDENCE

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Introduction: Placement and management of temporary venous pacemakers (TVPs) is a technically difficult, but necessary skill for critical care medicine (CCM) fellows. Although well-established simulation modalities exist to teach TVP placement, including high and low-fidelity task-trainers, no literature currently exists on modalities to simulate management of TVP complications and emergencies. InterSim® III is a novel software that simulates different unstable arrhythmias amenable to pacing.

Hypothesis: Using interactive simulated pacemaker software (InterSim® III) will improve CCM fellows' knowledge of and confidence with TVP management and troubleshooting.

Methods: First-year CCM fellows participated in a 1.5-hour session, with a lecture followed by simulated TVP placement, and five pre-programmed simulated cases of TVP management and troubleshooting. For initial TVP placement, learners utilized the PacerMan® simulation system; learners utilized the InterSim® III software system for the cases. Pre- and post-intervention, learners completed five parallel pairs of expert-reviewed, validated questions based on the learning objectives, and subjective confidence questions.

Results: 13 first-year CCM fellows participated. 12 completed the pre-test; 11 completed the post-test. Fellows' scores on the knowledge questions improved ($p<0.01$). Fellows' confidence improved in TVP placement ($p<0.01$), recognizing TVP complications ($p<0.01$), choosing initial pacing settings ($p<0.01$), and troubleshooting TVP problems ($p<0.01$). Fellows found the simulation to be relevant to their clinical practice and at an appropriate level of difficulty.

Conclusions: Realistic TVP troubleshooting with an interactive simulation platform improved CCM fellows' knowledge and confidence. This simulation modality may benefit other trainees for whom TVP management is a necessary skill. Further research is needed to assess skill and knowledge retention several months after the simulation.

Significance: This interactive simulation-based approach to TVP troubleshooting may be applicable to trainees in specialties including emergency medicine, cardiology, and cardiac anesthesia.

Research/Grant Support: Beckwith Society Front Line Innovation Grant, 2023

Abstract 44

IMPROVING NURSING CONFIDENCE: A SIMULATION-BASED CURRICULUM IN HIGH-RISK LOW FREQUENCY EVENTS IN THE CARDIOTHORACIC ICU

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Introduction: High-risk low-frequency events (HRLFEs) in the Cardiothoracic ICU (CTICU) demand immediate, coordinated response despite occurring rarely. Over three years, CTICU nursing leadership and physicians observed a consistent pattern: when these events arose, time to event identification was prolonged, nursing responses were delayed, and communication pathways were unclear. High nursing turnover continuously reduced the unit's experiential base with these critical scenarios. Four HRLFEs were prioritized based on this needs assessment: loss of airway, temporary pacing emergencies, veno-venous ECMO (VV-ECMO) initiation, and cardiac arrest after cardiac surgery. A mandatory simulation- and skills-based curriculum was developed to address these gaps.

Hypothesis: A flipped-classroom, simulation- and skills-based curriculum will improve CTICU nurses' knowledge of and confidence in management of four key HRLFEs.

Methods: All CTICU nurses participated in this required educational initiative. Using a flipped-classroom model, participants completed four asynchronous online training modules prior to the in-person session. The in-person component consisted of four 30-minute hands-on skill stations emphasizing key nursing skills relevant to each HRLFE. The sessions culminated in four 15-minute high-fidelity simulation scenarios, each followed by a structured group debriefing addressing potential challenges related to knowledge, technical skills, and team communication. Participants also completed pre- and post-tests to assess learning outcomes.

Results: 81 CTICU nurses participated; 79 completed both assessments. Self-rated confidence improved significantly for all four HRLFEs (Wilcoxon signed-rank test, $p<0.0001$). Knowledge scores showed a ceiling effect at baseline (pre-test mean 92%; post-test 91%; $W=591$, $p=0.167$), with 93.6% agreement that the simulation helped consolidate their prior knowledge.

Conclusions: A flipped-classroom, simulation- and skills-based curriculum significantly improved CTICU nurse confidence in HRLFE management. The absence of knowledge score improvement reflects a ceiling effect from high baseline scores; a 6-month retention test is planned. Behavioral impact on unit response will be assessed prospectively.

Significance: This suggests the potential for similar flipped-classroom simulation-based curricula to be used for developing confidence in management of other HRLFEs, as well as other key ICU nursing skills, in future continuing education for nursing.

Research/Grant Support: None

Abstract 45

EPIDEMIOLOGY, MORBIDITY, AND MORTALITY OF PEDIATRIC PULMONARY EMBOLISM: A RETROSPECTIVE MULTICENTER ANALYSIS

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Introduction: Pulmonary embolism (PE) in children is increasingly recognized and associated with significant morbidity and mortality. However, multicenter data describing outcomes of pediatric PE remain limited. We sought to characterize the epidemiology, morbidity, mortality, and temporal trends of pediatric PE using a large national administrative database.

Hypothesis: We hypothesized that pediatric PE is associated with substantial morbidity and mortality among hospitalized children, and that epidemiology has changed over time.

Methods: We performed a retrospective cohort study using the Pediatric Health Information System (PHIS) database. Patients <18 years discharged between January 1, 2005 and December 31, 2024 with a diagnosis of PE during an inpatient or observation encounter were identified. Patients were required to have received anticoagulation during hospitalization. Patients with chronic or septic PE and encounters that occurred within six months of a prior PE hospitalization were excluded. Demographics, hospital characteristics, comorbidities, and outcomes were extracted. Outcomes included mortality, ICU admission, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), thrombolysis, and hospital length of stay. Temporal trends were evaluated using a segmented binomial regression model.

Results: The cohort included 7,359 children with PE. Incidence of pediatric PE per 100,000 admissions increased by 4.2% per year since 2013 ($p<0.001$). Mean age was 12 years old and median age was 15 years old. PE was associated with substantial morbidity. Overall mortality was 8.4% but there was a bimodal age distribution with 48% of all mortality in children < 1 years old and 28% of mortality in children age 12-18 years old. ICU-level care was required in 59% of patients, 25% required mechanical ventilation, and 7.1% required ECMO support. Thrombolytic therapy was used in 7.9% of cases, and the median hospital length of stay was 8 days. Most patients had significant comorbidities, including complex chronic conditions (66%), infection (49%), cardiovascular disease (37%), and technology dependence (25%).

Conclusions: Pediatric PE is associated with substantial critical illness, including frequent ICU admission, advanced organ support, and mortality, and its incidence has increased over time.

Significance: Pediatric PE represents a significant source of critical illness in hospitalized children. Improved prevention, early recognition, and standardized management strategies may reduce morbidity and mortality in this population.

Research/Grant Support: N/A

Abstract 46

PLASMA METABOLOMIC PROFILING IN PEDIATRIC CARDIAC ARREST: A PROPENSITY-MATCHED CRITICAL CARE COHORT STUDY

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Introduction: Pediatric cardiac arrest (CA) carries substantial morbidity and mortality, yet the underlying metabolic perturbations that distinguish it from other forms of critical illness remain poorly characterized. We aimed to perform a metabolomics analysis to identify plasma metabolites and pathway-level dysregulation reflecting ischemia-reperfusion injury, mitochondrial dysfunction, and end-organ stress in the post-CA state in a cohort of critically ill children with sepsis, and to assess the association of these metabolites with mortality in children with CA.

Hypothesis: We hypothesize that pediatric CA is associated with a distinct and reproducible plasma metabolic signature with dysregulation of key metabolic pathways that differs from other forms of critical illness, independent of baseline illness severity and prior health status.

Methods: We identified a subset of patients with CA from the Phenotyping Sepsis-Induced Multiple Organ Failure Study (PHENOMS) cohort admitted to a pediatric or cardiac intensive care unit, and performed comprehensive metabolomic profiling across a priori defined biological pathways. Critically ill non-CA comparator patients from PHENOMS cohort were used. Three pre-specified analyses were performed: (1) within-CA comparison of in-hospital survivors vs non-survivors; (2) CA vs all comparator patients; and (3) CA vs 1:1 propensity score-matched controls from comparator cohort using nearest-neighbor matching on age, sex, cumulative organ failure days, and previously healthy status. Post-matching covariate balance was assessed using standardized mean differences (SMD). All tests were two-sided; $p<0.05$ was considered statistically significant.

Results: The CA cohort (n=19) was predominantly male (68.4% vs 53.7%), older (median age 10.4 vs 5.5 years), and more previously healthy (68.4% vs 44.6%) than the comparator cohort (n=354). In-hospital mortality was higher in CA patients than comparators (36.8% vs 9.6%; $p<0.001$). All 19 CA patients were successfully matched 1:1 to controls on age, sex, and organ failure days, with adequate post-matching balance across covariates (SMDs <0.25). Across 85 metabolites tested spanning 11 pathways, the most consistent finding was marked depletion of sphingolipid metabolites, including ceramide, N-palmitoyl-sphingosine, and N-stearoyl-sphingosine, all significantly lower in CA versus both the unmatched comparator cohort (all $p\leq0.001$) and propensity-matched controls ($p=0.003$, 0.014, and 0.005, respectively). Indoxyl sulfate was elevated in CA in both unmatched ($p=0.010$) and matched ($p=0.007$) analyses. After propensity-score adjustment, TCA cycle intermediates succinate ($p=0.026$) and fumarate ($p=0.045$) were elevated in the CA cohort. Among CA patients, gluconate was the only metabolite to be markedly higher in non-survivors than survivors (median 14.26 vs 0.40; $p=0.007$).

Conclusions: Among children with sepsis and organ failure, having CA is associated with a distinct plasma metabolomic signature versus children with sepsis and organ failure, including sphingolipid depletion, elevated indoxyl sulfate, and TCA cycle intermediate accumulation, that persists after adjustment for illness severity, versus no CA. This suggests pathophysiology specific to the post-CA state, beyond that of critical illness alone.

Significance: This pilot study identified novel pediatric CA-specific metabolic signatures that may inform the pathobiology of post-CA syndrome, highlighting candidate biomarkers and therapeutic targets for future investigation. Validation in a larger cohort is warranted.

DEPARTMENT OF EMERGENCY MEDICINE

Oral Abstract O3

LEVERAGING PRE-IMPLANT ECG FEATURES AND EXPLAINABLE MACHINE LEARNING TO PREDICT POST-ICD ADVERSE EVENTS IN HEART FAILURE

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Introduction: Implantable cardioverter-defibrillators (ICDs) are crucial for preventing sudden cardiac death in patients with heart failure with reduced ejection fraction (HFrEF, i.e., <35%), yet outcomes after implantation continue to be heterogenous. Left ventricular EF (LVEF) remains the cornerstone of guideline-based ICD implantation but is an imprecise indicator of future arrhythmia and mortality. The electrocardiogram (ECG) can elucidate latent information about cardiac function, especially through advanced calculated features (e.g., morphologic, repolarization-dispersion, etc.). The purpose of this study was to evaluate whether these calculated features can identify subtle electrical vulnerabilities predictive of future adverse events.

Hypothesis: We hypothesized that calculated ECG features can elucidate latent risk signatures associated with future adverse events.

Methods: This was a retrospective study of consecutive adult patients with HFrEF selected for an ICD and ECG performed within 30 days of implantation. Our primary outcome was adverse events, defined as death or ICD shock within 5 years of procedure. ECGs were preprocessed and analyzed using a validated signal processing pipeline to calculate >400 features, including depolarization/repolarization, interval/temporal, vectorcardiographic, spectral/variability. Feature selection was performed by first removing highly correlated features and then applying SelectKBest method. Random forest (RF) classifier was trained after splitting data into 88/12 training/testing sets using stratified sampling. Hyperparameters were optimized using grid search with cross-validation. Model performance was assessed using the area under the receiver operating characteristic curve (AUC), average precision (AP). Model explainability was assessed with SHAP analysis. We used Python's RandomForestClassifier Scikit-learn library v 1.7.2.

Results: The sample consisted of 4,180 participants (age 66 ± 13 years, 69% male, 36% adverse events). Median time to adverse event was 804 days. After feature selection, forty ECG features, along with age and sex, were fed into the RF model, resulting in testing AUC=.70, AP=.55. SHAP analysis revealed that 8/20 top model contributors were atrial depolarization metrics.

Conclusions: Calculated ECG features identified patterns associated with increased risk of adverse events following ICD implantation. These findings suggest that the features capture clinically relevant risk beyond that reflected by LVEF. Future studies should validate these findings in external cohorts and assess performance in populations with higher shock prevalence to refine identification of patients most likely to benefit from ICD therapy.

Significance: Risk following ICD implantation is multidimensional, and calculated ECG features highlight underrecognized aspects of electrical vulnerability beyond traditional markers like LVEF.

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Abstract 47

MEAN ARTERIAL PRESSURE TARGETS AFTER OUT-OF-HOSPITAL CARDIAC ARREST: A TARGET TRIAL EMULATION

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Introduction: Clinical trials comparing mean arterial pressure (MAP) targets in comatose survivors of out-of-hospital cardiac arrest (OHCA) have been neutral, yet observational data suggest higher MAP may ensure cerebral perfusion. Clinical trials may lack generalizability, which can be addressed using rigorous analysis of real-world data, and are prone to post-randomization confounders, which requires careful interpretation.

Hypothesis: We used target trial emulation to test whether MAP $\geq$65 mmHg vs MAP $\geq$80 mmHg increased 14-day OHCA mortality, while accounting for daily changes in patient treatment.

Methods: We emulated a target trial with adult OHCA survivors treated at a single center from 2010 to 2018. We included participants who followed verbal commands, did not undergo brain imaging, or died before hospital admission. We excluded participants who arrived at our center >12 hours after collapse; were pregnant; had a neurologic, traumatic, or hemorrhagic etiology of arrest; had a high risk of progression to brain death based on initial imaging; or required mechanical circulatory support or had severe cardiopulmonary failure prior to ICU admission. To adjust for time-varying confounders, including vasopressor and sedation, neurological exam, and laboratory parameters, we estimated a marginal structural model using inverse probability weighting with stabilized weights on enrollment then daily for 14 days.

Results: We included 407 participants (age 57$\pm$16 years, 40% shockable rhythm, 56% 14-day mortality). Mortality was 51.4% vs 46.8% in the MAP $\geq$65 mmHg vs $\geq$80 mmHg groups (risk ratio 0.91 (95% confidence interval 0.78 to 1.01)).

Conclusions: In this single-center target trial emulation, MAP $\geq$80 mmHg did not significantly reduce 14-day mortality compared to MAP$\geq$65 mmHg. However, the direction and magnitude of the effect suggest the potential for a small-to-moderate benefit that was not observed in large clinical trials.

Significance: These findings support a role for alternative methods of knowledge generation to supplement traditional clinical trials.

Research/Grant Support: None

Abstract 48

STRENGTHENING ED DISPOSITION PLANNING WITH PREDICTIVE EARLY WARNING SCORES

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Background: Early identification of patients in the pediatric emergency department requiring ICU level care is challenging for patients with borderline intensive care needs. The Pediatric Early Warning Systems (PEWS) is an established tool in inpatient settings to identify patients at risk for deterioration, but evidence of their use in the pediatric emergency department (ED) is quite limited despite studies showing beneficial prognostic capability. We evaluated our inpatient PEWS (CHP VIEW), a virtual intelligent early warning model to explore its capability to predict ICU risk 6 hours post admission at the time of ED disposition.

Hypothesis: Higher CHP VIEW scores at the time of emergency department disposition are significantly associated with an increased requirement for ICU-level care within 6 hours of inpatient admission

Methods Retrospective cohort analysis of 15,458 ED admissions from January 2024 to January 2025, evaluating ICU admission defined as both direct ICU admission and unplanned floor-to-ICU transfer. The CHP VIEW scores were analyzed as a continuous predictor and an optimal ED threshold model using Youden's J statistic was derived to predict potential binary outcome measures. The Model's performance was assessed using receiver operating characteristic (ROC) analysis, confusion matrix–based operating characteristics, and likelihood ratio metrics. Comparative analyses were performed between the CHP VIEW and Emergency Severity Index (ESI) and combined model using logistic regression. Incremental predictive value was assessed using nested model comparison with likelihood ratio testing. Stratified analyses evaluated ICU capture within each triage acuity level.

Results: The CHP VIEW scores demonstrated moderate discrimination for ICU admission (AUC ≈ 0.73), comparable to ESI (AUC ≈ 0.73; p = 0.85). At the Youden-derived threshold, the model achieved sensitivity ≈ 0.64, specificity ≈ 0.73, and PPV ≈ 0.23, NPV ≈ 0.94 with balanced operating characteristics similar to an ESI ≤2 classification. Logistic regression demonstrated that a combined ESI and CHP VIEW model provided significant incremental predictive value beyond ESI alone (ΔDeviance = 252.7, $p < 2\times10^{-16}$) and beyond CHP VIEW alone (ΔDeviance = 1171.3, $p < 2\times10^{-16}$), indicating complementary information. Stratified analyses showed that the Threshold model captured approximately 75% of ICU cases in ESI 1, 69% in ESI 2, and 51% in ESI 3 patients, including meaningful detection of early floor-to-ICU deterioration among moderate-acuity patients. Likelihood based risk demonstrated that among moderate acuity patients, a positive model result increased ICU probability by nearly double (ESI 2: 21% ->38%, ESI 3: 4.5% ->10%), while a negative result nearly halved the risks (ESI 2 -> 11%, ESI 3: -> 2.3%)

Conclusions: CHP VIEW demonstrates moderate ability to predict near term ICU need from ED disposition and provides added predictive value when combined with ESI.

Significance: The CHP VIEW enhances risk stratification within triage categories, particularly among moderate-acuity patients, and may serve as a valuable adjunct in identifying patients at risk for ICU level care.

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DEPARTMENT OF NEUROLOGICAL SURGERY

Oral Abstract O4

MULTI-OMICS IDENTIFY UNIQUE PROTEIN SIGNATURE OF REPEATED TBI IN PLASMA AND CEREBROSPINAL FLUID

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Introduction: Traumatic brain injury (TBI) is a heterogeneous condition and involves multiple pathophysiological pathways that compound over time. Military personnel and first responders are subject to increased exposure to repeated brain trauma, and experience distinct etiology compared to civilians. High-dimensional protein and metabolic assays are well-suited for identifying biological processes given the broad range of injury and recovery mechanisms. This study harnesses proteomics and metabolomics to identify biological signatures unique to repetitive chronic TBI in military personnel and first responders.

Hypothesis: We hypothesized that a multi-omic approach could distinguish a cohort of subjects with repeated (r)TBI from controls, as well as from a cohort of severe (s)TBI patients (positive control).

Methods: Under IRB approved protocols, veterans and first-responders with a history of rTBI and self-reported cognitive complaints (n=22, 40±8.5 years old, 19% female, 5.8±3.3 TBI incidents, 10.6±6.7 years post-injury), cognitively-intact controls (n=8, 38±6.1 years old, 13% female) and sTBI patients admitted to the ICU (n=9, initial Glasgow Coma Scale score 3-8, 46±21 years old, 21% female, 4 days post-injury) were enrolled. Cerebrospinal fluid (CSF) and plasma from a single time-point was analyzed using proteomics (Alamar, Seer) and metabolomics (Metabolon). Demographic and injury history information was also recorded.

Results: K-means clustering of plasma proteins identified a module enriched with neural (BDNF [Brain-Derived Neurotrophic Factor], APOE [Apolipoprotein E], and NPTX1 [Neuronal Pentraxin 1]) and immune (interleukin-6 receptor, chemokine CCL17 and CCL13) markers that showed relatively higher expression in rTBI compared to controls. In CSF, principal component analysis separated all three groups by proteome. Sparse partial least squares discriminant analysis predicted rTBI versus control (AUC=0.896). Gene set enrichment analysis in CSF indicated that rTBI is associated with reduced enrichment of synaptic and axonal pathways versus control (adjusted $p<0.05$). No differences in plasma and CSF metabolites were observed between rTBI and controls, although many pathways were significantly altered in sTBI.

Conclusions: Additional analysis is underway to associate protein changes with specific cognitive outcomes and neuroimaging. Altogether, these data identify unique protein signatures of rTBI in both plasma and CSF distinct from controls and sTBI.

Significance: Targeted validation of key biomarkers may lead to improved diagnosis, monitoring and intervention strategies for individuals with rTBI. This also emphasizes the unique pathophysiology of chronic rTBI and high-dimensional biomarker analyses have the potential to elucidate secondary injury processes across the spectrum of TBI.

Research/Grant Support: Dept. of Defense W81XWH-18-1-0739 (DOO), NIH T32HD040686 (SES)

Abstract 49

NOVEL 4DOXYWAVELET FMRI IDENTIFIES BRAIN CIRCUITRY DRIVING RECURRENT SEIZURE RESPONSES IN KAINIC ACID TEMPORAL LOBE EPILEPSY RAT MODEL

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Introduction: Epilepsy affects 45000 children and 300000 adults in the United States. The most common form of acquired epilepsy is temporal lobe epilepsy (TLE), which is typically initiated by insults, such as status epilepticus (SE). Currently, *there is no method to identify patients who will develop epilepsy after SE.* Mitochondrial dysfunction is increasingly recognized as an inciting factor for epilepsy. However, there is a current methodological gap: no methods exist to monitor mitochondrial dysfunction non-invasively and longitudinally.

Hypothesis: We hypothesize that longitudinal monitoring of mitochondrial brain function during acute phases post an SE-event can predict the development of downstream epileptogenesis and describe key brain circuitry underlying recurrent seizure responses.

Methods: We have successfully developed a novel *in vivo* 4D Oxy-wavelet MRI capable of probing *in vivo* mitochondrial dysfunction in intact live brains in a spatially specific manner, leveraging a novel hybrid low-rank k-t space-sampling scheme. Sprague-Dawley rats were subjected to multiple low-doses of kainic acid (KA) to elicit Racine scale 3/4/5 SE then monitored by 4D Oxy-wavelet MRI longitudinally (Days 3, 7, 10, 14 and 21).

Results: We identified a sexual dimorphic KA injury profile with temporally variable remodeling and insult responses in male and female rats. Eigenvalue decomposition and clustering delineates oxywavelet mitochondrial responses by injury severity. We observed global and local submodule network alterations in severely injured, recurrent seizure animals (n=6) compared to their non-recurrent seizure counterparts (n=11). Recurrent seizure animals demonstrate a reduction in small-worldness and a reduction in stable temporal submodules. Discriminability analysis showed that mitochondrial dysfunction during the acute phase most critically predicts recurrent seizure response and identifies a primary epileptic hub, a propagation network, and subcortical network modulation. Global modularity dynamics suggest recurrent seizure response is characterized by a reduction in submodule dynamics, indicating pathologic brain network locking.

Conclusions: Our study showed that 4D Oxy-wavelet MRI combined with graph theory and discriminability analysis elucidates dynamic brain network re-wiring at both the global and nodal scale, with a reduction in dynamic module variability characterizing the underlying recurrent seizure response.

Significance: The 4D-OxyWavelet fMRI platform enables in vivo, spatially resolved, simultaneous assessment of anatomical structure and mitochondrial function applicable to diverse organ systems and species, including fetal and adult stages. As the first non-invasive imaging technology to study mitochondrial function longitudinally it holds promise for broad applications in neuroscience, cardiology, and beyond.

Research/Grant Support: NIH: NS121706, EB023507 (PI: Yijen Wu, Ph. D); DoD: W81XWH-22-1-0221, W81XWH1810070 (PI: Yijen Wu, Ph. D); DoD: W81XWH1810070, W81XWH-22-1-0221 (PI: Yijen Wu, Ph. D)

Abstract 50

STEREOTACTIC RADIOSURGERY FOR OLIGODENDROGLIOMAS

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Introduction: Oligodendrogliomas are infiltrative primary brain tumors that mainly occur in the cerebral hemispheres, particularly the frontal and temporal lobes. The treatment of oligodendrogliomas raises many challenges because although there are prognostic factors such as age and tumor location, there is no universal treatment. Forms of treatment include radiation therapy, chemotherapy, and resection. This study will focus on Gamma Knife radiosurgery as a form of treatment for oligodendrogliomas. Gamma Knife stereotactic radiosurgery (SRS) is a form of treatment that uses highly focused beams of gamma radiation in order to target specific areas. Each patient has a Leksell stereotactic headframe applied with local anesthesia, then receives intravenous conscious sedation if they are older than 13 or receives general anesthesia if they are younger than 13. Magnetic resonance imaging (MRI) or enhanced computed tomography (CT) are used to localize a target, then a Gamma Knife unit is used.

Hypothesis: There will be greater overall survival (OS) and progression-free survival (PFS) for this cohort of patients in comparison to cohorts of other studies that do not use stereotactic radiosurgery as a form of treatment. Grade II tumors will have better OS and PFS than grade III tumors.

Methods: This is a retrospective study that will evaluate patients who were diagnosed with oligodendrogliomas and treated with Gamma Knife SRS at University of Pittsburgh Medical Center hospitals. Data will be retrospectively collected via electronic medical records in Epic and Leksell Gamma Plan. Data that will be collected includes age at diagnosis, age at SRS, pre- and post-SRS treatments, tumor progression, death status, time from SRS to death, SRS parameters (i.e. margin dose, isodose, max dose). Data analysis will use RStudio to perform Fisher's exact test, calculate the OS, and calculate the PFS.

Results: 29 patients (90.60%) initially presented with symptoms; 18 of 32 patients (56.3%) demonstrated stable or improved neurological function at last clinical follow-up, whereas 13 of the 32 patients (40.63%) demonstrated tumor stability or shrinkage.

Conclusions: It was determined that there was no statistically significant difference in outcomes between grade II and grade III oligodendrogliomas. SRS ultimately serves as a multimodal treatment method for longitudinal disease management as opposed to an explicit solution, as seen in the engagement in additional treatment in most of the patients in the cohort.

Significance: Data is limited regarding Gamma-Knife SRS as a treatment for oligodendrogliomas

Research/Grant Support: Not applicable

Abstract 51

BLOOD BRAIN BARRIER SIGNALING BIOMARKERS DEMONSTRATE TIME-ASSOCIATED NEUROPROTECTIVE OR DETRIMENTAL OUTCOME EFFECTS FOLLOWING TBI

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Introduction: Disruption of the blood brain barrier (BBB) is a secondary injury process leading to neurological deficit and disability after traumatic brain injury (TBI). Matrix metalloproteinase 9 (MMP-9), tissue inhibitors of metalloproteinase-1 (TIMP-1), vascular endothelial growth factor (VEGF), interleukin (IL-)1β, and tumor necrosis factor alpha (TNF-α) play a role in BBB permeability after TBI and their potential as prognostic biomarkers have yet to be elucidated. The dynamics of these biomarkers in TBI patients across time, injury severity categorized with the Glasgow Coma Scale (GCS), and outcome measures categorized by the Glasgow Outcome Score-Extended (GOS-E).

Hypothesis: We hypothesize that BBB permeability biomarkers will be elevated in subjects with more severe GCS scores and unfavorable GOS-E measurements.

Methods: Under an approved IRB protocol, mild (GCS = 13-15), moderate (GCS = 9-12), and severe (GCS ≤ 8) TBI subjects were enrolled. Serum was collected 1, 3, 5 days, 2- and 12-weeks post-injury and outcome assessments were completed at 2- and 12-weeks. Outcome measurements were dichotomized into favorable (GOS-E ≥ 5) and unfavorable (GOS-E ≤ 4) groups for analysis. Biomarkers were measured using the Meso Scale Discovery platform. Mixed effects models were used to analyze the significance of time, injury severity, and outcome measurements for each biomarker using a normalized log10 transformed data set.

Results: Significant time effects were observed for all biomarkers when grouped by GCS category or 2-/12-week GOS-E ($p<0.05$). When grouped by 2-week GOS-E, significant interaction was found in MMP-9 ($p=0.0070$) and VEGF ($p=0.0021$), indicating different biomarker trajectories between groups and increased biomarker concentration in the unfavorable group. Significant outcome interaction was found in TIMP-1 ($p=0.0048$), indicating a higher biomarker concentration in the unfavorable group. When grouped by 12-week GOS-E, significant interaction was found in MMP-9 ($p=0.0102$) and TIMP-1 ($p=0.0091$), indicating a different biomarker trajectory between groups and increased biomarker concentration in the favorable group. Significant outcome interaction was found in MMP-9 ($p=0.0263$) and IL-1β ($p=0.0244$), noting a higher concentration of MMP-9 and a lower concentration of IL-1β in the favorable group.

Conclusions: This initial analysis shows significant time interactions for all biomarkers measured. A specific time-effect was observed for MMP-9 and TIMP-1. Higher concentrations of biomarkers were indicative of an unfavorable outcome assessment at 2 weeks while the opposite was observed at 12 weeks, with higher concentrations indicating a favorable outcome assessment.

Significance: These findings suggest both neuroprotective and detrimental effects occur through the recovery period following TBI. As these findings are elucidated further, clinical experts may use BBB secondary injury mechanisms as a measurement to TBI recovery, noting the neuroprotective mechanisms these biomarkers may have.

Research/Grant Support: The Walter L. Copeland Fund of the Pittsburgh Foundation Funding for Cranial Research

Abstract 52

MACHINE LEARNING FACTOR ANALYSIS REVEALS INJURY-INDUCED MULTI-COMPARTMENT INFLAMMATORY HETEROGENEITY AND ITS THERAPEUTIC ATTENUATION AFTER CONTROLLED CORTICAL IMPACT

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Introduction: Traumatic brain injury (TBI) produces variable inflammatory responses, yet whether this heterogeneity extends across biological compartments and is therapeutically modifiable remains understudied. Understanding multi-compartment inflammatory variation is critical for improving preclinical therapeutic screening.

Hypothesis: Celastrol attenuates TBI-induced multi-compartment inflammation across brain, CSF, and serum.

Methods: Forty-eight male Sprague-Dawley rats underwent controlled cortical impact (CCI; 4 m/s, 2.7 mm depth) or sham surgery and received celastrol or vehicle (DMSO) via intraperitoneal injection immediately and 24 hours post-injury (n = 12/group). Ipsilateral hippocampal lysate, CSF, and serum were collected at 48 hours; nine cytokines were quantified by multiplex electrochemiluminescence immunoassay. Multi-Compartment Factor Analysis (MCFA), an unsupervised Bayesian approach adapted from Multi-Omics Factor Analysis, decomposed cytokine covariance into latent inflammatory axes. Group separation was tested by permutational multivariate analysis of variance (PERMANOVA) and inter-animal heterogeneity by permutational analysis of multivariate dispersion (PERMDISP; 9,999 permutations).

Results: MCFA identified three factors capturing 74.5% of total variance: a hippocampus-dominant axis (89.5% hippocampal variance), a CSF-dominant axis (59.0%), and a serum-dominated axis (74.9%). PERMANOVA confirmed group separation (pseudo-$F=5.90$, $p<0.001$); the hippocampal axis distinguished injury from sham ($p=0.002$) and the serum axis distinguished celastrol from vehicle ($p<0.01$). Critically, PERMDISP revealed CCI vehicle animals exhibited roughly twice the inter-animal heterogeneity across factor space (mean centroid distance=2.66) compared to shams (1.31), while celastrol attenuated this dispersion to sham-like levels (1.07; $p=0.001$). Serum loadings on the hippocampal factor identified a peripheral cytokine signature tracking central inflammation.

Conclusions: TBI induces measurable, animal-specific multi-compartment inflammatory heterogeneity beyond mean cytokine shifts, and this heterogeneity can be therapeutically attenuated by celastrol, as quantified through machine learning factor analysis.

Significance: These findings verify that celastrol attenuates multi-compartment inflammatory heterogeneity after TBI, establishing a robust foundation for a higher-powered study utilizing direct-brain delivery methods to minimize systemic toxicity. Future work will determine whether reductions in inflammatory heterogeneity translate to measurable behavioral and functional improvements, linking multi-compartment inflammatory profiles to the outcomes most relevant for therapeutic development.

Research/Grant Support: Physician Scientist Training Program Fellowship, R01NS091062

Abstract 53

CENTROMEDIAN-RESPONSIVE NEUROSTIMULATION (CM-RNS) VERSUS MEDICAL MANAGEMENT ALONE FOR TREATMENT OF GENETIC GENERALIZED EPILEPSY: A COST-EFFECTIVENESS ANALYSIS

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Introduction: Centromedian Responsive Neurostimulation (CM-RNS) is increasingly used in the treatment of Generalized Genetic Epilepsy (GGE) with demonstrated seizure improvement. Yet the cost-effectiveness compared to medical management is unknown. We compare the cost-effectiveness of CM-RNS to standard-of-care medical management for GGE treatment.

Hypothesis: CM-RNS is cost-effective compared to medical management for GGE treatment

Methods: We developed and analyzed a Markov decision model to evaluate the cost-effectiveness of CM-RNS compared with medical management from the U.S. health care perspective, using a 16-year time horizon. We used medical literature estimates to quantify seizure frequency and model the impact of CM-RNS on quality-adjusted life-years (QALYs). We included CM-RNS implantation costs, programming, replacement, battery changes, device-related adverse effects, and mortality rates. All costs are expressed in United States dollars; costs and QALYs were discounted at 3% per year. We conducted deterministic sensitivity analysis for key variables and probabilistic sensitivity analysis to test the model.

Results: The incremental cost-effectiveness ratio (ICER) for CM-RNS compared with medical management is $59,509 per QALY gained in the base case. Scenarios using alternative quality-of-life utilities yielded ICERs of $75,043 and $80,761 per QALY gained. All ICERs demonstrate CM-RNS as cost-effective relative to medical management, with ICERs below the benchmark WTP of $100,000/QALY gained. The variation in the cost of uncontrolled seizures and the utility of uncontrolled seizures had the greatest impact on the ICER. However, no parameter variation changed the strategy's favorability at the willingness-to-pay (WTP) threshold of $125,000 per QALY gained or higher, supporting the cost-effectiveness of RNS compared to medical management. Probabilistic sensitivity analyses favored CM-RNS in approximately 90% of simulations at a WTP of $100,000/QALY gained.

Conclusion: Based on this analysis, CM-RNS therapy appears to be a cost-effective therapeutic option for patients with drug-resistant Genetic Generalized Epilepsy compared with medical management, with ICERs below $100,000/QALY gained.

Significance: These findings suggest that CM-RNS may be a treatment modality for GGE. Given the limited treatment options, it encourages the development of necessary economic policies that promote the use of CM-RNS and its insurance coverage in GGE treatment.

Research/Grant Support: none

Abstract 54

COMPUTATIONAL SCHEMA TO DECODE EPENDYMAL-DRIVEN CSF FLOW PATTERN IN BRAIN-INJURY MOUSE MODELS OF CILIARY DYSFUNCTION AND POST-TRAUMATIC HYDROCEPHALUS

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Background: Ependymal cilia, powered by ATP, create coordinated beating patterns that drive directional cerebrospinal fluid (CSF) circulation through the brain ventricles, ensuring proper nutrient distribution, waste clearance, and neuronal signaling. Abnormal ependymal cilia can lead to hydrocephalus, a condition characterized by excessive CSF and ventriculomegaly (enlarged ventricles). Emerging evidence shows that abnormal CSF flow patterns are important. However, the cilia-driven CSF patterning that drives hydrocephalus is poorly understood. Hydrocephalus can develop due to the aftereffects of a traumatic brain injury (TBI), called post-traumatic hydrocephalus (PTH). TBI mice develop PTH after cranial impacts and display the same abnormal CSF flow.

Hypothesis: The goal of this project is to establish a robust computational pipeline to analyze ependymal cilia-driven CSF flow patterns using the TBI mice model to correlate with hydrocephalus development.

Methods: We established an ependymal near-wall ciliary flow assay to quantify fluorescent bead velocity as a measure for ependymal ciliary function. Fresh ependymal tissues were harvested from the lateral ventricles of TBI mice at varying injury depths and wild type mice and maintained in physiological buffer. Fluorescent beads were added to the "cilia carpet" to quantify the velocity using fluorescent video microscopy. The motion vectors and dynamics of the flowing beads through the ependymal tissues were quantified and computed by our in-house method using Particle Image Velocimetry (PIV) with the MQD algorithm. After calculation of vector motion fields, each bead from the previous step was assigned to a set of vectors and the motion of that bead was tracked. Vector metrics were characterized by quantifying the ciliary dynamics.

Results: We acquired ~450 flow videos from each mouse lateral ventricle. Each video covers ~1-3% of the ventricle. We stitched together all image time series for a given ventricle to create an overall ventricle flow map for each animal. For each image time series, we segmented fluorescent beads from the background. Dice score-based comparison of automated segmentations and ground truth manual segmentations of bead flow showed validation of automated pipeline. Quantitative flow analysis demonstrated that hydrocephalus mice presented with a reduction in overall flow velocity and reduced angular velocity.

Conclusion and Significance: Our study showed that ciliary dysfunction in TBI mice resulted in abnormal CSF flow which correlates to abnormal CSF flow patterns leading to hydrocephalus. These findings can be useful for characterizing hydrocephalus, and can have provide a framework for future studies.

Abstract 55

LONGITUDINAL FUNCTIONAL TRAJECTORY AND SURGICAL OUTCOMES AFTER INTRACRANIAL MENINGIOMA RESECTION: IMPLICATIONS FOR SURGICAL DECISION-MAKING IN OLDER PATIENTS

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Introduction: Intracranial meningiomas are increasingly encountered in older patients. While surgical resection remains the primary treatment for symptomatic tumors, longitudinal functional outcomes across age groups are not well characterized. This study evaluates age-related differences in tumor characteristics, surgical outcomes, and postoperative functional trajectory.

Hypothesis: Older patients undergoing meningioma resection experience different trajectories of postoperative functional decline and recovery compared to younger patients.

Methods: A retrospective cohort study of 396 consecutive patients who underwent intracranial meningioma resection at a single academic center between 01/2023 and 09/2025 was conducted. Patients were stratified by age (<65 vs ≥65 years) and further analyzed across five age subgroups. Functional status was assessed using the Karnofsky Performance Status (KPS) scale preoperatively, at discharge, and at last follow-up. Logistic regression was used to identify predictors of prolonged length of stay (LOS >5 days) and poor functional outcome (KPS <80).

Results: Older patients (≥65 years, n=181) had higher comorbidity burden, more aggressive tumor characteristics, longer median LOS (6 vs 4 days, p=0.005), and higher meningioma-related mortality (6.6% vs 1.9%, p=0.013). KPS at discharge and last follow-up were lower in older patients (p<0.001 and p=0.019, respectively), though many older patients maintained functional independence (KPS ≥80) at discharge and follow-up (78.5% and 76.8%, respectively). Among patients with postoperative decline, recovery rates were comparable between age groups. On multivariable analysis, independent predictors of prolonged LOS included preoperative KPS (OR 0.97, p=0.019), diabetes (OR 2.82, p=0.004), posterior fossa location (OR 2.04, p=0.009), tumor diameter (OR 1.36, p<0.001), postoperative edema (OR 2.80, p=0.008), and neurosurgical complications (OR 2.86, p=0.004). Independent predictors of poor functional outcome at discharge included older age (OR 1.05, p=0.006), preoperative KPS (OR 0.90, p<0.001), posterior fossa location (OR 3.38, p=0.004), neurosurgical complications (OR 4.35, p=0.002), and recurrent meningioma (OR 3.06, p=0.017). Subgroup analysis revealed a marked inflection in functional decline in patients aged ≥75 years.

Conclusions: Older patients demonstrated greater initial postoperative functional decline but maintained preserved recovery capacity comparable to younger patients. Functional outcomes may be more strongly influenced by baseline functional status, tumor characteristics, and perioperative factors than by age alone.

Significance: These findings support individualized surgical decision-making in older patients with meningiomas, emphasizing consideration of functional reserve and modifiable risk factors rather than chronological age alone. Recognition of an age-related threshold around 75 years may further refine risk stratification and preoperative counseling.

Research/Grant Support: None

Abstract 56

MULTI-SCALE HIGH-DEFINITION FIBER TRACTOGRAPHY REVEALS PERSISTENT CORPUS CALLOSUM NETWORK DISRUPTIONS IN PRE-CLINICAL AND CLINICAL MILD TBI

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Introduction: Repeated mild traumatic brain injury (rmTBI) frequently results in persistent cognitive impairment despite normal clinical imaging, suggesting that subtle disruptions in structural brain networks underlie long-term deficits. However, a major gap remains in identifying a translatable framework that can detect these disruptions across preclinical models and TBI patients.

Hypothesis: We hypothesized that the mechanism involves multi-scale disruptions in structural connectivity from local hippocampal circuits to global inter-hemispheric networks and that these disruptions can be captured using a unified HDFT-based framework across both preclinical and clinical datasets.

Methods: Male Sprague Dawley rats (8-10 weeks) received dual mild lateral fluid percussion injuries (1.25 atm) or sham surgeries 24 hours apart (n=18/group). Motor function was assessed acutely post-injury, followed by spatial learning and memory testing at 8 weeks. At the terminal timepoint (9 weeks post-injury), serum neurofilament light chain (NFL) was quantified. Brains were collected for as *ex vivo* high-definition fiber tractography (HDFT; n=6/group) with graph theoretical connectomics to quantify structural connectivity across intra-hippocampal, inter-hippocampal, and whole-brain networks as well as, histological assessment of myelin integrity (MBP), microglial activation (IBA1), astrocytosis (GFAP), and synaptic density (synaptophysin). We applied an identical processing framework to longitudinal *in vivo* imaging in mTBI patients, with repeat scans assessing within-subject structural connectivity up to 1-year post-injury.

Results: Ex vivo HDFT with graph theoretical analysis revealed that, contrary to our hypothesis, intra-hippocampal trisynaptic circuit connectivity was preserved; however, significant disruptions were observed at the inter-hippocampal and whole-brain levels (unpaired t-tests, $p<0.05$), with prominent alterations centered in the corpus callosum. These network-level disruptions were supported by hallmark pathological features of rmTBI, including reduced corpus callosum volume, histological evidence of demyelination (MBP) and gliosis (IBA1, GFAP), and alterations in synaptic density (synaptophysin). Serum NFL remained significantly elevated at terminal timepoints, indicating persistent axonal injury. Longitudinal translation to clinical datasets demonstrated dynamic remodeling of structural connectivity, including a compensatory increase in corpus callosum fiber density within the right hemisphere at 1-year post-injury.

Conclusion: Multi-scale structural network disruptions following rmTBI preferentially affect inter-hemispheric and whole-brain connectivity while sparing local hippocampal circuits. These disruptions are centered in the corpus callosum and are supported by persistent axonal injury and neuroinflammation. Clinical tractography revealed asymmetric remodeling of corpus callosum connectivity, with increased fiber density in the right hemisphere, mirroring the preclinical model and identifying a conserved signature of injury-induced network reorganization across species.

Significance: These findings establish a unified translational framework linking preclinical and clinical TBI, enabling longitudinal tracking of network-level pathology. Future work will integrate peripheral biomarkers with connectomics to link systemic injury signals to network disruption.

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Abstract 57

TRANSCRIPTOMIC AND MULTISYSTEM ALTERATIONS FOLLOWING TRAUMATIC BRAIN INJURY IN SICKLE CELL DISEASE MICE

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Introduction: Hemoglobinopathies, including sickle cell disease (SCD), affect over 300 million individuals worldwide and are characterized by chronic inflammation and vascular dysfunction. These baseline abnormalities may potentiate systemic injury following traumatic brain injury (TBI).

Hypothesis: We hypothesized that SCD amplifies TBI-induced transcriptomic changes, resulting in enhanced multisystem dysregulation compared to wild-type (WT) controls.

Methods: Berkeley SCD and C57BL/6J WT mice (12–18 weeks; n=2–6/group) underwent controlled cortical impact (CCI; 6 m/s, 1.6 mm depth) or sham procedures. Whole blood was collected 72 hours post-injury for bulk RNA sequencing. Differential gene expression and ranked gene set enrichment analyses were performed using R (v4.5.1) with Mus musculus KEGG pathway annotations. Interaction effects were evaluated using the contrast: ([SCD-CCI – SCD Sham] – [WT-CCI – WT Sham]).

Results: Compared to WT mice, SCD mice demonstrated significant enrichment of pathways related to neutrophil extracellular trap formation, platelet activation, neurodegeneration, cardiac muscle contraction, non-alcoholic fatty liver disease, renal acid secretion, and vasopressin-mediated water reabsorption (FDR<0.05). Pathways related to cell adhesion molecules, cytokine–receptor interactions, and hematopoietic lineage were significantly downregulated (FDR<0.05). Notable upregulated genes included H3 clustered histone 10 (Log2FC 5.8), prothrombin (Log2FC 5.7), P2Y12 receptor (Log2FC 0.9), alpha-synuclein (Log2FC 1.7), and alpha-synuclein interacting protein (Log2FC 3.0). Downregulated genes included peptidyl arginine deiminase 4 (Log2FC -0.5), P-selectin (Log2FC -0.9), and VCAM-1 (Log2FC -1.3).

Conclusions: TBI induces distinct transcriptomic alterations in SCD mice, reflecting widespread dysregulation across immune, vascular, neurologic, and end-organ pathways compared to WT controls.

Significance: These findings highlight the role of hemoglobinopathy in modulating systemic responses to TBI and suggest potential mechanistic targets for mitigating secondary injury in this high-risk population. Ongoing histologic and imaging studies aim to further define organ-specific sequelae.

Research/Grant Support: CHP RAC Award and Walter L Copeland Fund of The Pittsburgh Foundation (PI: Dr. Shaun Carlson, PhD)

Abstract 58

INFLAMMATORY BIOMARKERS IN SWEAT PATCHES OF COLLEGIATE FOOTBALL PLAYERS PRE- AND POST-SEASON

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Introduction: With 37.9% of D1 football players diagnosed with a traumatic brain injury (TBI) during their career, the concussion remains a significant concern within the sports community. Biomarkers are an attractive medium for the objective quantification of trauma severity. While biomarkers are typically analyzed through blood, sweat serves as a potential non-invasive source for the detection of biomarkers. Our previous pilot study indicated a significant relationship between the concentration of TBI protein biomarkers in football players between pre- and post-season time points. This study expands on those results and explores this further with the examination of an inflammatory biomarker array.

Hypothesis: We hypothesized that inflammatory biomarkers would be detectable in the sweat of college football players, and their concentrations would be greater at post-season because of contact-induced neuroinflammation.

Methods: Participants were enrolled during the 2023 football season from an NCAA Division III college enrolled under an IRB approved protocol (N = 17 preseason, N =17 postseason). At both time points, a non-invasive sweat patch was applied for approximately 24 hours, and physical activity assessments were conducted with collection of demographic data and injury history. Sweat patches were stored in a -80°C freezer until batch analyses. Sweat was extracted using a previously published protocol, before biomarker concentrations were measured via a multi-plex protein assay detecting IFN-γ, IL-10, IL-12P70, IL-17, IL-1β, IL-2, IL-4, IL-6, and TNF-α. A t-test or Mann-Whitney test was performed to analyze each biomarker depending on if it followed a normal or non-normal distribution, respectively.

Results: No concussions and minimal symptoms were reported at post-season. No significant differences were present in biomarker concentrations between players with and without a TBI history. T-test statistical analysis showed that the concentration of IL-2 ($p=0.0158$) significantly decreased from pre- to post-season. Changes in other biomarkers were nonsignificant.

Conclusions: This study demonstrates the possible detection of neuroinflammatory biomarkers in sweat of healthy collegiate football players, and the minimal changes observed between pre- and post-season concentrations indicate that the sport's contact does not significantly increase inflammation within healthy athletes.

Significance: These results can inform future study in sweat biomarker analysis and the development of less invasive collection techniques. Furthermore, the lack of significant change in inflammation has implications for further research into the impact of participation in contact sports.

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DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION

Oral Abstract O5

CHARACTERIZATION OF PHYSICAL ACTIVITY IN CHILDREN WITH COMPLICATED MILD VS MODERATE TO SEVERE TBI

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Introduction: Traumatic brain injury (TBI) is the leading cause of morbidity and mortality in children and can cause lasting neurobehavioral impairments. Physical activity has been shown to improve neurobehavior in other pediatric populations and has therapeutic potential to promote neurobehavioral recovery in children with TBI. However, physical activity has not yet been evaluated in children with TBI in the months after injury. The objective of this study is to quantify and compare physical activity in children with complicated mild TBI (cmTBI) and moderate to severe TBI (msTBI) using wearable activity monitors.

Hypotheses: Physical activity will increase in duration for children with TBI from acute hospital discharge to one-month post-injury. Children with msTBI will have lower levels of activity initially after injury than children with cmTBI.

Methods: We recruited children (6-18 years old) admitted to UPMC Children's Hospital of Pittsburgh with complicated mild TBI (n = 5) and moderate to severe TBI (n=7). Participants wore two Axivity AX6 accelerometers (on the nondominant wrist and on the opposite ankle) for two nine-day periods: upon acute hospital discharge and at one month post injury. Duration of inactivity and light, moderate, and vigorous physical activity were analyzed using pre-established cut points for physical activity intensity in children with acquired brain injury. Differences between physical activity levels by TBI severity (cmTBI vs msTBI) were assessed using the Wilcoxon signed-rank test.

Results: Duration of daily inactivity decreased from acute discharge to one-month post-injury (acute: 429.6 [369.1, 559.5] min, 1M: 362.8 [347.9, 374.9] min; acute: 340.7 [283, 501.7] min, 1M: 264.4 [233.7, 289.3] min) for participants with cmTBI and msTBI, respectively. Duration of daily light (acute: 98.4 [94.8, 98.7] min, 1M: 136.6 [125.6, 145.3] min; acute: 115.6 [106.3, 119.8] min, 1M: 119.3 [115.4, 141] min), moderate (acute: 55.8 [36.4, 60.7] min, 1M: 56.3 [55.9, 61.4] min; acute: 62.1 [50.3, 65.7] min, 1M: 68.1 [65.8, 68.9] min), and vigorous (acute: 356.5 [169.7, 363.3] min, 1M: 447.2 [414, 448.9] min; acute: 282.0 [226.3, 369.6] min, 1M: 426.9 [386.4, 451.4] min) physical activity increased over time for both cmTBI and msTBI, respectively. At one-month post-injury, children with msTBI had significantly lower duration of physical inactivity than children with cmTBI (msTBI: 264.4 [233.7, 289.3] min, cmTBI: 362.8 [347.9, 374.9] min, $p = 0.036$). There were no other significant differences between groups ($p > 0.05$).

Conclusions: These surprising results suggest that children with cmTBI are more inactive at 1-month post injury but should be evaluated further with a larger sample. The higher levels of physical inactivity in children with cmTBI could suggest caregiver overprotection after injury or less engagement in rehabilitation for children with less severe injuries. Median inactivity decreased over time for both cmTBI and msTBI, while median durations of light, moderate and vigorous physical activity increased over time for both msTBI and cmTBI.

Significance: This study is the first to characterize physical activity in the subacute stage of pediatric TBI recovery using wearable sensors outside of the hospital setting. Determining the duration and intensity of physical activity in children with TBI will allow for the development of guidelines and interventions for rehabilitation in clinical settings.

Research/Grant Support: Brain Injury Association of America Early Career Seed Grant and UPMC Rehabilitation Institute Pilot Grant

Abstract 59

HYPERTENSION AMPLIFIES NEUROBEHAVIORAL DYSFUNCTION AND NEUROPATHOLOGY AFTER TRAUMATIC BRAIN INJURY: A LIFESPAN TRANSLATIONAL STUDY

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Introduction: The prevalence of traumatic brain injury (TBI) necessitates post-injury cognitive and emotional assessments, especially considering overlapping comorbidities. An estimated 50% of adults have hypertension, which can precipitate cardiovascular disease, strokes, and premature death. We investigated, for the first time, how hypertension affects adult rats after pediatric TBI (pTBI) or adult TBI (aTBI).

Hypothesis: We hypothesized that comorbid hypertension worsens post-TBI cognitive performance, with adult rats subjected to injury under a pre-existing hypertensive state putatively exhibiting the worst outcomes.

Methods: Male Spontaneously Hypertensive (SHR) and normotensive Wistar rats received a moderate controlled cortical impact or sham injury at 17 days or four months old. The 3-Choice serial reaction time test (3-CSRT; sustained attention), T-maze attentional set-shifting (behavioral flexibility), open field testing (OFT; anxiety), and the shock-probe defensive burying test (SPDB; active and passive coping) assessed neurobehavior. Histology and serum analyses assessed ventricular volumes, astrocytic markers (GFAP and aquaporin-4; AQP4), and inflammatory biomarkers.

Results: In the pTBI cohort, adult TBI rats required longer 3-CSRT training, with TBI in normotensive rats resulting in lower accuracy and higher omissions. SHR-pTBI rats showed significantly greater distractibility ($p<0.05$). In the aTBI cohort, all TBI rats showed accuracy and omissions deficits on 3-CSRT, with SHR-aTBI rats demonstrating the greatest deficits and more impulsivity, seen as a higher number of premature responding ($p<0.05$). SHR-pTBI rats showed impaired rule learning on the T-maze and set-shifting deficits when required to turn left, suggesting hemispatial neglect ($p<0.05$), and greater active avoidance in SPDB ($p<0.05$), indicating anxiety. SHR-aTBI rats displayed attentional deficits (specifically in accuracy and impulsivity) beyond either condition alone, and they approached and buried the probe less in SPDB ($p<0.05$). In the pTBI cohort, hypertension enlarged lateral ventricles, while TBI enlarged ipsilateral ventricles ($p<0.05$). In aTBI rats, injury enlarged ventricles in the ipsilateral hemisphere for both injured groups, with the hypertensive injured animals displaying a significant increase versus both normotensive injured and uninjured rats ($p<0.05$). SHR-pTBI rats showed disrupted colocalization of GFAP and aquaporin-4 in the dorsal hippocampus. Inflammatory marker KC-GRO was elevated in SHR-pTBI rats at 4 months post-injury, while aTBI rats showed significant IL-6 elevations, further exacerbated by hypertension ($p<0.05$).

Conclusions: These findings support the hypotheses and underscore assessing preclinical studies of comorbidities in TBI to enhance translatability and therapy development.

Significance: Hypertension may act both as a *state-dependent amplifier* of injury severity when present at the time of traumatic brain injury, and as a *second-hit modifier* that unmasks latent neurobehavioral vulnerability following early-life brain injury, together defining a lifespan trajectory of compounded risk.

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Abstract 60

TREAT THE AGITATION, KEEP THE GAINS: A PRECLINICAL EVALUATION OF BREXPIPRAZOLE AFTER TBI

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Introduction: Managing agitation following traumatic brain injury (TBI) commonly involves the use of antipsychotic drugs (APDs), despite evidence that dopamine D_2 receptor antagonists, like haloperidol, disrupt recovery. Identifying APDs that do not hinder recovery is therefore critical for TBI patients. Brexpiprazole (REXULTI®), a third-generation atypical APD, exhibits partial agonist activity at D_2 and 5-HT_{1A} receptors, a pharmacological profile associated with improved outcomes after experimental TBI.

Based on these properties, we **hypothesized** that brexpiprazole would not adversely affect recovery after TBI and may support improved outcomes.

Methods: Isoflurane anesthetized adult male rats underwent either a controlled cortical impact (2.8 mm depth at 4m/s) or sham injury and randomized to receive brexpiprazole (0.5, 1.0, or 2.0 mg/kg; i.p.) or vehicle beginning 24 h post-injury for 21 days. Motor function (beam-walk time and beam-walk score) was assessed on days 1-5 and cognitive performance (acquisition of spatial learning and memory) was assessed on days 14-19. The behavioral data were analyzed by repeated measures ANOVAs and Newman-Keuls post-hoc tests. Cortical lesion volume will be quantified on day 21 by ANOVA.

Results: No differences were observed between brexpiprazole and vehicle-treated sham groups and hence they were pooled for analysis. Shams outperformed TBI groups on all behavioral measures ($p<0.05$). No significant differences were detected between brexpiprazole and vehicle-treated TBI groups on motor outcomes ($p>0.05$). However, rats receiving 0.5 mg/kg brexpiprazole demonstrated improved acquisition of spatial learning compared to vehicle controls and the two higher dose brexpiprazole groups ($p<0.05$). Cortical lesion analyses are ongoing.

Conclusions: Brexpiprazole did not impair recovery following TBI, supporting the hypothesis and its safety in this context. Moreover, the lower dose improved spatial learning, suggesting a potential dose-dependent cognitive benefit.

Significance: While motor outcomes were unaffected, brexpiprazole's pharmacological profile warrants further investigation for its potential to manage agitation while preserving and possibly enhancing other behaviors affected by TBI.

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Abstract 61

PRIOR TRAUMATIC BRAIN INJURY AS A CONTRIBUTOR TO ALLOSTATIC BURDEN AND PSYCHOLOGICAL HEALTH OUTCOMES

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Introduction: Traumatic brain injury (TBI) represents a significant public health burden, with an estimated 1.5-2 million occurring annually in the United States. Recovery from TBI is difficult and influenced by biological, physiological, and psychosocial factors. Allostatic burden (AlloB), the cumulative impact of chronic stress, is increasingly recognized as a determinant of coping, resilience, and psychological health (PH). Prior TBI is a known risk factor for adverse outcomes following subsequent TBI, yet its relationship with AlloB remains understudied despite its potential to contribute through prolonged neurobiological dysregulation.

Hypothesis: We hypothesized that individuals with history of TBI would demonstrate elevated AlloB and worse PH outcomes compared to those presenting with a first TBI.

Methods: Data from an observational cohort with moderate-to-severe (ms) TBI were collected at baseline and up to 6 months post-injury and averaged. AlloB was measured with the Perceived Stress Scale (PSS)-10, UCLA Loneliness Scale (ULS)-8, Duke-UNC Functional Social Support Questionnaire (FSSQ), and Connor-Davidson Resilience Scale (CD-RISC). PH was measured by the Patient Health Questionnaire (PHQ)-9, Generalized Anxiety Disorder (GAD)-7, Neurobehavioral Symptom Inventory (NSI), and PTSD Checklist for DSM-5 (PCL-5). The Life Experiences Checklist (LEC)-5, Adverse Childhood Experiences (ACEs) checklist, Percent Back to Normal (PBTN) and Behavioral Assessment Screening Tool (BAST) were also assessed as AlloB-adjacent measures. Lifetime TBI status was classified using the self-report Ohio State University TBI Identification Form. Prior TBI and no prior TBI groups were compared using Mann-Whitney U tests.

Results: The study cohort (n=35) was predominantly male (68.6%) and white (91.0%), with a mean age of 45.7 years and an average 13.3 years of education. From months 1 through 6, the prior TBI group (n=9) median was higher than the no prior TBI group (n=26) for the PSS-10, ULS-8, GAD-7, NSI, PCL-5, LEC-5, and ACEs, indicating more perceived stress, loneliness, anxiety, neurobehavioral symptoms, PTSD symptom, stressful life events, and adverse childhood experiences. Median scores were lower for the prior TBI group on the PHQ-9, FSSQ, CD-RISC, and PBTN, indicating less self-reported depression, social support, resilience, and feelings of being back to normal. The ULS-8, FSSQ, LEC-5, and ACEs were all significant between groups ($p<0.04$), and the PCL-5 and GAD-7 were marginally significant ($p<0.1$).

Conclusions: Individuals with a history of TBI demonstrated greater AlloB and poorer PH outcomes compared to those experiencing a first TBI, with significant differences in loneliness, social support, stressful life events, and adverse childhood experiences, suggesting that prior TBI history is an important clinical consideration and potential contributor to AlloB after msTBI.

Significance: Understanding how prior TBI and AlloB interact may help identify who is at higher risk for poor recovery outcomes and establish TBI's role as an allostatic disrupting event.

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