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100. Patient Satisfaction with Telehealth in Neurosurgery Outpatient Clinic during COVID-19 Pandemic

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Introduction: In response to the COVID-19 pandemic, neurosurgical outpatient practices have rapidly adopted telemedicine services to meet the needs of patients. To date, patient satisfaction with telemedicine in the neurosurgery, outpatient setting has not been evaluated with a validated survey.
Methods: Patients that completed telemedicine (phone or video) visits (new, return, or postoperative visits) in the outpatient neurosurgery clinic from June 1, 2020 to August 15, 2020 were queried with a portion of the Press Ganey® (PG) survey. Survey questions related to satisfaction with the care provider. For each question, satisfaction was defined as a score of 4 or greater on 5 point scale. Demographic data was also collected. ANOVA F-test® was used to compare the continuous variables while Chi-square test or Fisher's exact test was used to compare categorical variables among the three groups.
Results: The response rate was 19% of the 934 participants who were eligible to participate via email. The 179 respondents included 97 new consults, 20 postoperative visits, and 62 return visits. Mean age was 63 years (range 16-91 years). The female to male ratio was 49.7%-50.3%. For all Press Ganey® questions relating to the care providers, respondents reported aggregate satisfaction rates greater than 92%. There were no significant differences among the three groups (new consults, postoperative visits, return visits) in terms of their demographics or degree of satisfaction.
Conclusion: Implementation of telehealth in an academic neurosurgery program is viable. Our findings demonstrate high levels of patient satisfaction with clinical providers during telehealth visits. Additional study is needed to understand factors driving patient satisfaction with telehealth.

Best International Abstract Award
101. Automated Planning of Navigated Lumbosacral Pedicle Screws Using a Convolutional Neural Network

Moritz Scherer, MD (Heidelberg, Germany); Scherer Moritz, MD; Lisa Kausch; Andreas Unterberg, MD

Introduction: Use of navigation for spinal instrumentation has gained traction in recent years but preoperative trajectory-planning is a time-consuming task. We sought to develop and validate an automated planning tool for lumbosacral pedicle screws using a convolutional neural network (CNN).
Methods: We used planning data from random 155 CT-navigated instrumentations and extracted screw parameters from 1052 pre-planned pedicle screws covering L2-S1 levels, which served as training data for a CNN. A vertebra instance-based approach employing a state-of-the-art U-Net framework was developed and trained followed by internal 5-fold cross-validation. The retrieved net was evaluated on an external test-set of 30 cases not involved in training. Automatic screw parameters were compared to corresponding pre-planned screws in the test-set by mean absolute difference (MAD) of screw head and tip points, length and diameter, respectively. Clinical acceptability of algorithm-generated screws was evaluated by experts using the Gertzbein-Robbins (GR) classification.
Results: Automated planning was feasible for all targeted 198 screws. Compared to pre-planned screws, MAD was 4.3±2.1mm for screw head, 4.2±2.4mm for tip points, 4.6±3.1mm for length and 0.4±0.3mm for diameter. In ANOVA followed by Dunn's multiple comparison, MAD for head and tip points was significantly greater at L5 and S1 compared to other segments (p<0.001), reflecting increasing degrees of freedom in caudal screw placement. No difference between segments was found for screw length and diameter. Upon expert rating, screws were predominantly classified grade A (189, 95%) with only 9 grade B screws (5%) according to GR indicating that screws showed either no, or only minor (<2mm) cortical breach. All planned screws were classified clinically acceptable.
Conclusion: We derived a fully automated planning tool for lumbosacral pedicle screws using CNN. Validation showed sufficient accuracy to facilitate screw planning with high potential to increase time-efficiency in navigated spinal instrumentation when integrated into commercial navigation systems.

102. A Cre-Lox Based Mouse Model for Conditional Somatic KRASG12D Expression to Induce De-Novo Cerebral Arteriovenous Malformations

Keyan Peterson; Stephanie Coffman, MD; Anthony Anzalone, MS; Nathan McMullen; Nicholas Contillo; Zhidan Xiang, PhD; Stacey Wolfe, MD (Madison, NC)

Introduction: Recent evidence supports a high prevalence of somatic mosaicism in the KRAS gene within the vascular endothelium of sporadic cerebral arteriovenous malformations (AVMs). Establishing a clinically-relevant animal model is necessary to determine whether KRAS mutations are causal in AVM pathogenesis, and to facilitate testing of novel therapeutic agents targeting this pathway to treat these lesions.

Methods: A newly discovered AAV2 serotype labeled AAV2-BR1 was used for its tropism for cerebral endothelial cells. AAV2-BR1 was packed with improved Cre-recombinase (AAV2-BR1-CAG-iCRE-GFP) and injected into heterozygote LSL-KRAS G12D mice, resulting in the expression of active KRAS G12D solely within endothelial cells of the brain. The AAV dose was optimized via stepwise titration of various doses (4.5 x 10 10 – 1.8 x 10 11 vp). Mice were then injected with the optimized AAV dose (4.5 x 10 10 vp) after 8 weeks perfused by liquid latex. Brains were harvested and submerged in a parenchyma-transparentizing solution to enhance detection of altered vascular morphology. KRAS G12D and downstream pERK protein was measured to detecting mutant signaling activity within cerebral endothelial cells.

Results: Injection of AAV2-BR1-CAG-iCRE-GFP into LSL-KRAS G12D   mice (n=8) successfully induced KRAS G12D   expression, resulting in increased pERK signaling activity within CD31+ endothelial cells of the brain. Latex perfusion demonstrated local vascular remodeling with vascular dysregulation and nidal formation in > 60% of experimental specimens and 0% of control specimens after 8 weeks.

Conclusion: This experiment suggests that endothelial KRAS mutations may be causal in the pathogenesis of sporadic AVMs. Future studies will explore the timing and duration of mutation induction on the development of AVMs, providing insight into the natural history of lesion development, and will allow us to study translational therapeutic targets including MEK and BRAF inhibitors with and without radiosurgery.

103: Immunology of Cerebrovascular Injury: Innate Drivers of Damage and Repair

Panagiotis Mastorakos, MD PhD (Bethesda, MD); Dorian McGavern

Introduction: Secondary injury following vascular injury results in detrimental functional and structural sequelae as it affects the extent of acute damage and impedes repair. While it is established that the innate immune response contributes to this process the contribution of microglia and as infiltrating myelomonocytic cells is not well understood. Here we identified the mechanisms by which innate immune responses mediate damage and repair after cerebrovascular injury and proposed therapeutic targets to minimize the effects of secondary injury.

Methods: We developed a new model of isolated vascular injury using a combination of ultrasound and intravenously injected microbubbles. We studied the dynamics of injury response using two-photon laser scanning microscopy and probed the system using various inhibitors and transgenic animals. We used multiparameter flowcytometry and qPCR to map the immune landscape and evaluated the effect of diapedesis inhibition on edema formation and survival. We also evaluated angiogenesis and neurogenesis using immunohistochemistry, qPCR and bulk RNA sequencing.

Results: We discovered that injurious and reparative responses diverged based on time and cellular origin. Resident microglia initially rapidly surrounded, stabilized damaged vessels and sealed the blood brain barrier. Simultaneously we observed an influx of monocytes and neutrophils that caused severe edema. A single combination dose of anti-adhesion molecules within 6 hours prevented fatal cerebral herniation. Long term follow-up demonstrated that proinflammatory monocytes and angiogenic microglia orchestrated repair and prolonged inhibition of innate immunity prevented angiogenesis, lead to fibrotic healing.

Conclusion: These data demonstrate how temporally distinct myeloid cell responses can contain, exacerbate, and repair cerebrovascular injury. Except for the early extravasation of peripheral cells, the myeloid response to cerebrovascular injury is beneficial. Our findings serve as the bedrock for the design of anti-adhesion immunotherapy strategies to treat cerebrovascular injuries and discourage approaches of indiscriminate and continuous immunosuppression.

104. Charles Jacques Bouchard

Sarfraz Akmal (Piscataway, NJ); Elizabeth Ginalis, MD; Fareed Jumah, MD; Anil Nanda

Introduction: Charles Jacques Bouchard was a 19th century pathologist known for his discovery of the Charcot-Bouchard aneurysm. Little is written on Dr. Bouchard, especially in the English language. The objective was to review any existing literature written about Dr. Bouchard for a historical vignette on his contribution to medicine and neurosurgery.
Methods: The authors performed a basic literature search on PubMed and Google scholar, in both the English and French language. All articles written on the life of Charles Jacques Bouchard were included.
Results: In 1866 while working as a resident under Dr. Jean-Martin Charcot, Bouchard wrote his thesis titled "A Study of Some Points in the Pathology of Cerebral Hemorrhage" in which he described Charcot-Bouchard aneurysms and argued that they were a major cause of cerebral hemorrhage. Although Bouchard did not identify the root cause of the aneurysms at the time, he did hypothesize they were a result of a chronic disease process that presented in old age; we now know them to be a result of chronic hypertension. The concept of an acute pathology like cerebral hemorrhage being the result of a chronic process was a novel idea during Bouchard's time, and his discovery significantly shifted the understanding of cerebral hemorrhage. Bouchard's later career was focused on infectious disease. Bouchard's career was also mired with controversy with his former mentor Dr. Jean Martin Charcot.
Conclusion: Charles Jacques Bouchard was a model physician-scientist throughout his entire career. His most prominent finding was the Charcot-Bouchard aneurysm, a revolutionary finding that changed the discourse on the pathogenesis of cerebral hemorrhage. Bouchard's academic career and bench to bedside philosophy is one modern physicians and neurosurgeons can strive for.

105. Comparison of Prognostic Scoring Systems for Durability of Pain Relief after Microvascular Decompression for Trigeminal Neuralgia

Abdullah Hamid Ishaque (Edmonton, Canada); Hayden Danyluk; Blaise Wheatley, MD, PhD; Robert Broad, MD; Tejas Sankar, MD

Introduction: Though many patients with trigeminal neuralgia (TN) respond well to microvascular decompression (MVD), a significant minority experience pain relapse despite technically successful surgery. Two recently published pre-operative scoring systems (S1 and S2) use a combination of pain-type, degree of neurovascular compression, and response to medication as predictor variables in determining the risk of post-operative pain recurrence over the long-term. In a validation study, we compared the performance of these two scoring systems in predicting pain-free survival after MVD for first-time treatment of TN in an independent, single-centre cohort.
Methods: We retrospectively included patients undergoing first-time MVD at our institution from 2007-2019. Each patient was assigned pre-operative S1 and S2 scores according to: 1) S1—TN type (I or II), vessel score, and compression score; and 2) S2—TN type, response to medication, and degree of neurovascular compression. Radiological features were graded using high-resolution T2-MRI. Outcome data were obtained from charts and telephone follow-up. Primary endpoint was long-term pain status. Univariate and multivariate cox proportional-hazards regression models were used to investigate which scoring schemes and individual characteristics predict pain-free status following MVD. Kaplan-Meier survival analyses were conducted to investigate differences in mean survival times.
Results: Sixty-eight patients were included (TN1=58, TN2=10) with average symptom duration of 64.6±61.0 months. Fourteen patients had pain recurrence within one year. In univariate analysis, S1 and S2 scores both predicted pain-free survival (P <0.05). In multivariate analysis, only S2 contributed to pain-free survival, with increasing S2 scores associated with longer pain-free survival (P <0.05). Compression score independently predicted pain-free survival: increased trigeminal nerve compression predicted longer pain-free survival times (P <0.05).
Conclusion: Pre-operative S2 scores were better at predicting pain-free survival than S1 scores in patients undergoing MVD for TN. Patients with severe compression of the trigeminal nerve on preoperative MRI also had the longest pain-free outcome.

106. Kilohertz-Frequency Neuromodulation for Fiber-Selective Blockade of Acute Disc Herniation-induced Radiculopathy in a Rat Model

Ken Porche, MD (Gainesville, FL); Savannah Dewberry, BS; Alexander Dru, MD; Kyle Allen, PhD

Introduction: Pain management strategies for symptomatic intervertebral herniated discs often result in long-term opioid use/dependence, dosage increases, and diminished benefit. Therapies for acute non-compressive herniations remains paramount. Previous studies demonstrated that kilohertz-level frequency sciatic neuromodulation produced selective nerve blockade in a rat model of cuff-induced peripheral neuropathy. Our group describes a pre-clinical study of sciatic neuromodulation, eliminating allodynic responses in an acute non-compressive disc herniation rat model.

Methods: Lewis rats (n=24) were randomized to 3 groups: 1) right L5 dorsal root ganglia exposed to nucleus pulposus (NP-affected) with a circumferential neurostimulator implanted around the sciatic nerve (NP+KHFAC), 2) NP-affected with a sham stimulator (NP+Sham), and 3) a double sham (Sham-Sham). Surgeries and testing were performed in a double-blinded fashion. Rats received baseline von-Frey testing, with objective responses recorded as paw-licks with 50% withdrawal threshold (50%WD). At 5, 7, 9, and 14 days postoperatively, the animals underwent von-Frey testing of both paws pre-stimulation, during stimulation (50 kHz/1Amp), and post-stimulation. Repeated measures ANOVA and post-hoc Tukey testing were used. Data are reported as right paw 50%WD averages±standard error.

Results: 7 rats were lost due to head-cap malfunctions and surgical complications. Of the remaining rats, 6 were in NP+KHFAC, 6 in NP+Sham, and 5 in Sham-Sham. Pre-stimulation, NP+KHFAC was similar to NP-Sham (13.2±2.6 vs 16.8±2.6, p=.364) and lower than Sham-Sham (23.0±2.7, p=.021). During stimulation, NP+KHFAC was similar to Sham-Sham (26.7±2.4 vs 25.8±2.5, p=.789) and higher than NP-Sham (17.5±2.4, p=.022). Post-stimulation scores rapidly returned to pre-stimulation values (NP+KHFAC=15.5±2.6, NP-Sham=19.2±2.6, Sham-Sham=24.2±2.7).

Conclusion: Sciatic neuromodulation at kilohertz-level frequency produces selective nerve block in an acute disc herniation rat model where tactile allodynic responses to von Frey testing normalize in a rapidly reversible fashion.

107. Integrative Genomic Analysis Implicates Specific Brain Regions and Developmental Time Points in Craniosynostosis

Emre Kiziltug; Riki Kawaguchi; Shreyas Panchagnula; Kristopher Kahle (New Haven, CT)

Introduction: Craniosynostosis (CS) is the premature fusion of one or more of the calvarial sutures, resulting in deformities in craniofacial appearance. It presents with a great degree of clinical heterogeneity including various neurocognitive impairments, suggesting a complex interplay of genetic and environmental causes. Given the neurodevelopmental symptoms associated with CS patients, we hypothesize that the genes involved in the pathophysiology of the disease may play a key role in the functional development of the brain.

Methods: Using a bulk-mRNAseq expression data set encompassing sixteen human brain regions across human development, we applied weighted gene co-expression network analysis to construct transcriptional networks and identified twenty gene modules. We also explored a single-cell RNA-seq expression dataset from the meninges of E14 Col1a1-GFP GFP/+ mice and applied spatial autocorrelation analysis to identify sixteen additional gene co-expression modules.

Results: We identified time-point, brain regions and cell types in which these converge and disrupt the developmental process. Twenty gene modules were discovered in bulk expression analysis and four modules were enriched in genes associated with CS. Furthermore, one of the four modules was highly associated with developmental disorders and autism. Moreover, the spatiotemporal correlation analysis revealed that the genes of the CS-enriched modules converge in early fetal development and are highly expressed in the caudal ganglionic eminence, prefrontal cortex, cerebellar cortex, orbital cortex, hippocampus and the mediodorsal nucleus of the thalamus. Sixteen additional gene modules were discovered in a subsequent single cell expression analysis, and two of these modules that were enriched with CS-associated genes were highly expressed in pia and dura mater.

Conclusion: These data support the role of CS-genes in early neuronal and bone development and an association between CS-genes and neurodevelopmental disorders. This approach ultimately identifies spatiotemporal and cell-type specific mutations to be further studied to clarify CS pathophysiology.

108. Mutations in TFAP2B and Previously Unimplicated Genes of the BMP, Wnt, & Hedgehog pathways in Syndromic Craniosynostosis

Charuta G. Furey, MD (Phoenix, AZ); Andrew Timberlake, MD, PhD; Sheng Jin, PhD; Joelle Hartke, MD; Gabriella Paisan, MD; Baltazar Zavala, MD, PhD; Michael Lawton, MD; Nader Sanai, MD; Kristopher Kahle, MD, PhD; John Persing, MD; Richard Lifton, MD, PhD

Introduction: Craniosynostosis, with an estimated prevalence of 1 in 2,300 live births, is one of the most common birth defects, resulting from premature fusion of cranial sutures. Syndromic craniosynostosis cases, featuring additional extracranial anomalies, account for approximately 15% of cases.

Methods: We recruited and exome sequenced DNA isolated from 384 patients with non-syndromic midline craniosynostosis, comprised of 291 patient-parent trios and 93 singleton non-syndromic cases, and 12 patients with syndromic craniosynostosis, comprised of 12 patient-parent trios in whom previous genetic evaluations were unrevealing 1,2 . Exome-sequencing data from these 909 individuals was then analyzed to identify rare de novo and transmitted mutations contributing to non-syndromic and syndrome craniosynostosis.

Results: Exome sequencing of families with non-syndromic midline craniosynostosis revealed 10% of patients have damaging, de novo mutations or rare, inherited damaging mutations in negative regulators of developmental bone formation cascades, including the Wnt, BMP, and Ras/ERK signaling pathways ($p = 2.4 \times 10^{-11}$). In syndromic cases, we found damaging de novo or transmitted loss of function (LOF) mutations in 8 genes that are highly intolerant to LOF mutation ($P = 4.0 \times 10^{-8}$). Four probands had rare damaging mutations in TFAP2B, a transcription factor that orchestrates neural crest cell migration and differentiation ($P = 8.2 \times 10^{-12}$). Three probands had rare damaging mutations in GLI2, SOX11, or GPC4, which function in the Hedgehog, BMP, and Wnt signaling pathways; other genes in these pathways have previously been implicated in syndromic CS. Similarly, damaging de novo mutations were identified in genes encoding the chromatin modifier KAT6A and CTNNA1.

Conclusion: These findings reveal novel disease-causing mutations in regulators of developmental signaling cascades essential for bone formation and osteoblast differentiation, elucidating a genetic cause for 10% of non-syndromic cases and establishing TFAP2B as a novel syndromic craniosynostosis gene. Such results provide insight into the pathophysiology of craniosynostosis as well as new opportunities for improved genetic counseling and prognostic assessment of risk of recurrence and adverse neurodevelopmental outcomes for treatment planning.

109. Reading in the Brain: Distributed Network Dynamics for Written Language

Kiefer Forseth (Houston, TX); Elliot Murphy, PhD; Latane Bullock, BS; Nitin Tandon, MD

Introduction: People decode linguistic information from both orthographic representations at high speed and fidelity. In contrast to speech production and perception, the ability to read is a relatively recent evolutionary development. We use large-scale human electrophysiology to delineate the cortical network architecture for reading sentences and to investigate effective connectivity between network nodes in separable functional states.

Methods: Intracranial electrodes (n=13298, 71 patients), including both surface grid and stereotactic depth electrodes, were implanted for the evaluation of refractory epilepsy. These directly recorded the full spectrum of neural oscillations with coverage encompassing the entirety of language dominant cortex. Patients were asked to quickly and accurately articulate the name of common objects described by short written sentences. We mapped the distributed reading network by integrating high-gamma (60-120 Hz) power and low-frequency (2-15 Hz) phase responses with a surface-based mixed-effects multilevel analysis. We then derived the cortical dynamics of this network using an autoregressive hidden Markov model (ARHMM).

Results: Causal interactions between network nodes, quantified with pairwise partial direct coherence, revealed the progression of functional network motifs engaged during reading and leading into articulation. Presentation of each word triggered the engagement of the orthographic decoding state, recruiting a local network that extended from early visual cortex to the visual word form area anteriorly. This was immediately followed by states corresponding to the distinct lexical (fast) and phonological (slow) routes of reading with nodes in ventral temporal, posterolateral temporal, inferior parietal, and inferior frontal cortex. After the final word, the reading network engaged a broadly distributed lexical semantic network anchored in mid-fusiform gyrus and pars triangularis that subsequently activated an articulatory state localized to perisylvian cortex.

Conclusion: Research on the neurophysiological basis of reading will contribute to rehabilitative solutions and neuro-prosthetic designs to help the substantial population with dyslexia (5-17% of adults).

110. Cell Type- and Projection-specific Optogenetic Modulation in a Mouse Model of Cognitive Behavior

Xiaonan (Richard) Sun, MD, PhD (Manhasset, NY); Simon Musall; Steven Gluf; Anne Churchland

Introduction: A major challenge in neuromodulation relates to the targeting of specific neural populations, which may be critical in the treatment of neuropsychiatric disorders. While neurons may be defined by gene expression or projection patterns, these properties in cognitive behaviors are poorly understood. To address this, we combined rodent psychophysics with genetic and viral tools to investigate the roles of various glutamatergic pyramidal neuron (PyN) subclasses. In this work, we developed a mouse model of human decision-making and used optogenetic silencing to explore the causality of discrete cortical circuits on decision-making behavior.
Method: Head-fixed, water-restricted, mice implanted with cortical optical fibers were trained to perform an auditory discrimination task in soundproof booths with video monitoring. We expressed a soma-targeted anion-conducting channelrhodopsin (stGtACR) using transgenic and intersectional viral (AAV and CAV-2) strategies for silencing specific cell types in prefrontal and parietal cortices. The behavior task and LED photostimulation were controlled using a low-latency state machine.
Result: We developed a two-alternative forced choice auditory decision task where two (left- and right-sided) randomly-generated sequences of sound pulses are simultaneously presented. Mice are trained to report the side with the higher rate by licking the corresponding water spout. We tested the effects of silencing four neural subpopulations: all PyNs, cortico-cortical, cortico-striatal, and cortico-fugal neurons. Among the PyN subtypes, the highest degree of impairment in decision performance was found with prefrontal cortico-striatal silencing, which also resulted in the largest deficits in sensory evidence accumulation, as determined by psychophysical reverse correlation.
Conclusion: Through silencing PyN subtypes in task-performing mice, we gained mechanistic insights into the roles of long-range cortical projections in decision-making. We demonstrate strong functional differences across PyN subclasses, most notably the impact of cortico-striatal neurons in decision formation. Our ongoing work focuses on the comparison of neural dynamics across cell types at cellular-resolution using two-photon imaging. Results from this work may provide valuable biological and methodological implications in the targeted treatment of neuropsychiatric disorders.

111. Neurosurgeons as Innovators: Effect of Physician Inventor Presence on United States Neurosurgical Device Patent Success

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Introduction: Physicians contribute significantly to medical device innovation. The rapidly evolving nature of neurosurgery affords opportunities for neurosurgeons to substantially influence the development of future devices and operative techniques. The objective of this study was to determine the effect of physician involvement on neurosurgical device patent creation on patent success and impact.
Methods: Google Patents was queried between years 2005-2015 for surgical devices using search terms related to cranial and spinal surgery. Inventor names within the resulting list of patents were cross-referenced with the Centers for Medicare and Medicaid Services (CMS) National Provider Identifier (NPI) database to identify physicians and their specialty (i.e. neurosurgery/orthopedics). Primary endpoints for comparison between patent applications with and without physician innovators included: whether a patent was ultimately granted, number of citations, and time between application and granting (if applicable).
Results: Neurosurgeons were involved in 12.6% of patents, and orthopedic surgeons on 28.5%. The highest rates of patent success (61.4%, p=0.009) were associated with devices having both neurosurgeon and orthopedic surgeon inventors. Applications with solely an orthopedic surgeon had higher rates of success than those with solely a neurosurgeon (57.2% vs. 54.4%, p<.00001). The highest approval rate was associated with patents involving 3 physicians (68.6%); however, the number of physicians was not significantly correlated with citations received (p=0.18).
Conclusion: Physician presence on neurosurgical device patents, and a greater number of physician inventors, is associated with higher likelihood of patent acceptance. Further study elucidating the effect of physician involvement on device innovation may have significant future policy implications regarding medical device innovation.

112. Can We Improve and Use the CMS Hierarchical Condition Category Risk Adjustment Model For Spine Surgery?

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Introduction: The Centers for Medicare and Medicaid Services (CMS) Hierarchical Condition Category (HCC) coding is a risk-adjustment model that allows for the estimation of risk—and cost—associated with health care provision. Current models may not include key factors that fully delineate the risk following spine surgery.

Methods: The National Inpatient Sample (2005-2011) was queried for spinal fusion patients. This data was merged with county-level socioeconomic variables (e.g., poverty rates, unemployment rates, life expectancy, and housing vacancy) obtained from the Brookings Institute. We constructed pairs of logistic regression models to predict outcomes (death, non-routine discharge, length of stay (LOS; top quartile), total charges (top decile), and complication)—one model using CMS HCC score alone and another model augmenting CMS HCC scores with age, sex, comorbidity, race, insurance type, income quartile, unemployment rate, poverty rate, and life expectancy. Models were compared using receiver operating characteristic curves. Variable importance was assessed in conjunction with Wald testing.

Results: Overall, 653,815 spinal fusion discharges were analyzed. Expanded models outperformed CMS HCC score alone for mortality (AUC:0.816 vs. 0.741), non-routine discharge (AUC:0.738 vs. 0.571), LOS (AUC:0.650 vs. 0.580), total charges (AUC:0.684 vs. 0.594), and complication occurrence (AUC:0.708 vs. 0.646). For the expanded models, variable importance analyses demonstrated that the CMS HCC score was of chief importance for models of mortality, LOS, and complication occurrence. For models of non-routine discharge and total charges, age and unemployment rate were the most important variables, respectively.

Conclusion: With the addition of key demographic and socioeconomic characteristics, CMS HCC risk-adjustment models can be substantially improved when modeling perioperative outcomes following spinal fusion. This may have important implications for payers, hospitals, and policymakers.

113. Predicting Adjacent Segment Disease with Deep Learning on Pre-Operative Cervical MRI for Patients Undergoing Single-Level Anterior Cervical Discectomy and Fusion

Caroline Goedmakers (Boston, MA); Asad Lak, MD; Akiro Duey; Alexander Senko, PhD; Omar Arnaout, MD; Michael Groff, MD; Timothy Smith; Carmen Vleggeert-Lankamp; Hassan Zaidi, MD; Aakanksha Rana, PhD; Alessandro Boaro, MD

Introduction: Patients that undergo anterior cervical discectomy and fusion (ACDF) are at risk of developing adjacent segment disease (ASD). Predicting which patients will develop ASD remains challenging for clinicians and is mostly based upon clinical judgment and experience. The aim of this study was to use a deep learning approach to develop an algorithm capable of predicting ASD using the pre-operative cervical MRI of patients undergoing single-level ACDF.

Methods: Retrospective chart review was performed for 1243 patients undergoing single-level ACDF between January 1st, 2000 and May 1st, 2019 in two tertiary care centers. 340 patients met all inclusion and exclusion criteria. A Convolutional Neural Network (CNN) based prediction model with 48 convolutional layers was designed and trained using preoperative T2-sagittal cervical MRI images. The dataset was split into 208 train images, 48 validation images, and 93 test images with no absolute overlap. In order to validate model performance, a clinical expert provided ASD predictions for the 93 test images as well.

Results: Of the 93 patients in the test set, 15 (16%) patients developed ASD, and 78 (84%) did not develop ASD. The model was able to predict ASD on the 93 test images with an accuracy of 0.95, sensitivity (80%), and specificity (97%). The clinical expert provided predictions with lower accuracy (0.64), sensitivity (47%), and specificity (67%) when compared to the algorithm.

Discussion: Preoperative ASD risk assessment for patients undergoing ACDF surgery has not been done before using Deep Learning but is essential in determining optimal surgical strategy. The model demonstrates good discriminative capacity for preoperative identification of patients that are likely to develop ASD after ACDF, solely based on the preoperative MRI. Future re-evaluation and external validation are required to further support the utility of this model in practice.

114. Optimized Biodegradable Tissue-Engineered Grafts for Spinal Fusion Using a Biomimetic Platelet-Derived Growth Factor Delivery System with Osteoinductive Bone Particles and Adipose-Derived Stem Cells

Alexander Perdomo-Pantoja, MD (Baltimore, MD) ; Alexandra Rindone, BS; Christina Holmes, PhD; Warren Grayson, PhD; Timothy Witham, MD

Introduction: A newly designed, biodegradable polycaprolactone-decellularized bone (PCL-DCB) hybrid is a promising graft material for spinal fusion due to its ability to degrade as new bone tissue grows into the graft while also providing mechanical stability during the early stages of bone healing. In this study, we optimized this graft using a novel biomimetic platelet-derived growth factor-BB (PDGF) delivery system using heparin-conjugated, decellularized bone particles (HC-DCB) that allows the controlled release of PDGF-BB in adipose-derived stem cell (ADSC)-loaded PCL-DCB grafts in our rat model.

Methods: ADSCs were isolated from syngeneic Lewis rats and cultured in vitro. The cultured-expanded ADSCs were seeded onto PCL-DCB scaffolds along with HC-DCB particles and PDGF for subsequent transplantation. Dorsolateral spinal fusion surgery at L4-L5 was performed on rats divided into 5 experimental groups: [1] PCL only; [2] PCL-DCB + HC-DCB particles; [3] PCL-DCB + HC-DCB particles + PDGF; [4] PCL-DCB + HC-DCB particles + 2.5x10 6 ADSCP2/side; and, [5] PCL-DCB + HC-DCB particles + 2.5x10 6 ADSCP2/side + PDGF. Fusion was evaluated eight weeks post-surgery via microCT imaging, histology and immunohistochemistry.

Results: In the microCT scans, we found fusion masses in all the PCL-DCB groups [2,3,4,5] while no bone formation was observed when the PCL scaffold was implanted alone without DCB particles. When we compared fusion bone volumes among the bone-forming PCL-DCB groups, we found a higher bone volume in the PDGF group without additional stem cell transplantation ($p<0.05$). In the histology, we found more ossified tissue in the interface between graft and transverse processes in treated groups [3,4,5], again more in the PDGF group; also showing expression of RUNX2, CD31, and Osteocalcin in these groups.

Conclusion: We demonstrated that biodegradable PCL-DCB grafts enable spinal fusion when combined with osteoinductive HC-DCB particles. PDGF-BB enhanced bone formation when added to these grafts using this delivery system.

115. Clinical Anatomy of Human C7 Nerve Donors for Surgical Transfer in Patients with Spastic Arm Paralysis

Sara E Ratican (Hillsborough, CA); Michael Song, DPhil; Yanqun Qiu, MD; Jiang Su, MD; Wending Xu, MD; Jennifer Hong, MD

Introduction: Recently, contralateral C7 (CC7) nerve transfer has been used to successfully restore hand function in patients with spastic hemiplegia from chronic central nervous system injuries. This involves grafting the contralateral C7 nerve from the patient's non-paralyzed arm to the paralyzed arm to restore function. Despite its clinical significance, very little is known about the natural morphology of human C7 root anatomy and its variations. To date, there is no literature on the standard intraoperative measurements employed in these procedures, including variations in C7 size, length or branch count prior to transfer. This study describes anatomical features of the C7 nerve in previously successful CC7 transfer operations.

Methods: A photo database from 21 patients, 2 females and 19 males undergoing CC7 surgery was searched for photographs with standard ruler measuring donor C7 root length after section and prior to transfer. Photographs were analyzed by two observers for C7 root morphology, length, diameter and number of branches.

Results: The mean values of the nerve diameter, nerve length, and branch length following surgery were 5.0725mm, 53.5238mm, and 18.3496mm with standard deviations of 0.9462mm, 7.9957mm, and 6.2669mm, respectively. These results were all normally distributed. Right sided brain injuries yielded significantly longer branches, but otherwise the patients' medical history did not influence intraoperative anatomy.

Conclusion: CC7 nerve transfer completed in 21 patients yielded normally distributed anatomical outcomes largely unaffected by the patients' characteristics or medical history. This is promising for procedural precision and predictable outcomes minimally affected by individual variations. Our findings - derived from passively collected data - establish anatomical guidelines for optimizing surgical outcome whilst catering for patient diversity.

116. Reoperative Brachial Plexus Neurolysis after Previous Supraclavicular Decompression for Neurogenic Thoracic Outlet Syndrome

Momodou L Jammeh (St Louis, MO) ; Momodou Jammeh, MD; Alexander Yang, MD, PhD; Ahmmad Abuirqeba, BA; John Ohman, MD; Robert Thompson, MD

Purpose: To assess clinical outcomes for reoperative brachial plexus neurolysis in patients with recurrent symptoms after a previous supraclavicular (SC) decompression for neurogenic thoracic outlet syndrome (NTOS).
Methods: Between 2009 and 2019, 85 patients that had previously undergone anatomically-complete SC decompression presented with recurrent neurogenic NTOS for which reoperative SC brachial plexus neurolysis was performed. Data from a prospectively maintained database were analyzed retrospectively.
Results: The mean patient age at reoperation was 36.9 ± 1.3 years (range 15-64), 75% were female and the mean interval after previous operation was 2.4 ± 0.2. The mean Disability of the Arm, Shoulder and Hand (QuickDASH) score prior to reoperation was 65.2 ± 2.6, reflecting substantial preoperative disability. Operative findings consisted of dense fibrous scare tissue encasing the brachial plexus, with complete neurolysis used to mobilize all 5 nerve roots and 3 trunks. Compared to the previous primary operations, reoperations had a shorter mean operative time (161 ± 5 vs 198 ± 4 minutes, $p <0.01$) and hospital stay (3.6 ± 0.1 vs 4.4 ± 0.2 days, $p <0.01$), but there were no differences in the frequency of prolonged hospitalization (4.7% vs 7.1%), early reoperation (1.2% vs 3.5%) or 30-day readmission (7.1% vs 8.2%). During 2.4 ± 0.2 years follow-up, the mean improvement in the QuickDASH scores was 23.3 ± 2.6 (34.2 ± 3.6%, $p <0.01$) and the patient-rated outcomes were considered excellent in 24%, good in 42%, fair in 26% and poor in 8%.
Conclusion: For carefully selected patients that have developed recurrent NTOS after a previous anatomically-complete thoracic outlet decompression, reoperative SC brachial plexus neurolysis is technically challenging but safe and effective toward improving symptoms and function. Diminishing the development of perineural scar tissue would decrease the need for reoperative interventions but this remains an elusive goal.

117. Neurotrauma from Crowd Control Weapons

Erika Kaske (Minneapolis, MN); Samuel Cramer, MD, PhD; Isabela Pena Pino, MD; Truong Do, MD; Bryan Ladd, MD; Dylan Sturtevant, BS; Aliya Ahmadi, BA; Birra Taha, MD; David Freeman, MD, PhD; David Darrow, MD, MPH

Introduction: George Floyd's death in Minneapolis, MN, catalyzed what is estimated to be one of the largest international protests in history, prompting the deployment of widespread crowd control measures. Less-lethal control measures, including kinetic impact projectiles and chemical irritants, can lead to significant morbidity and mortality depending on the implementation. Clinical outcomes prompted our systematic characterization of trauma during the protests.
Methods: We screened emergency department, urgent care, and primary care records from two large Minnesota hospital systems during the time period associated with the George Floyd protests. Charts with ICD10 codes S00-T59 or charts noting "riot," "rubber bullet," "tear gas," "protest," or "projectile" were reviewed. Injury Severity Score (ISS) and distribution of projectile injuries by anatomic region served as primary outcome measures.
Results: We screened 6626 encounters and identified 89 patients who sustained injuries due to projectiles (51%), chemical irritants (36%), or both types of weapons (13%). The majority of patients (53%) self-identified as non-Hispanic White, and ISS did not vary with race, ethnicity, or age. While exposure to tear gas resulted in minor injuries (ISS = 1.36, SD = 1.65), projectiles (i.e. rubber bullets, beanbags, and tear gas canisters) resulted in mild, moderate, and severe injuries (ISS = 6.18, SD = 5.16). Traumatic brain injury was diagnosed in 18% of patients. Additionally, a disproportionate number of projectile injuries were to the head or face (40.4%), and the number of hits to the head or face ($p < 0·0001$) conferred higher injury severity.
Conclusion: Less-lethal crowd control measures can cause severe injuries requiring neurosurgical intervention. Current guidelines state that projectiles should not be aimed at the head or face, however, we report a significant number of serious head injuries. As protests are ongoing, neurosurgeons should be aware of the potential surgical trauma burden of these weapons.

118. Avoiding Antibiotic Drain Prophylaxis Decreases C difficile Without Increasing SSI: 5 Year Retrospective.

Alexandria Marino, MD (Charlottesville, VA); Alexandria Marino; Evan Robinson; Jakob Durden; Amy Mathers; Mark Shaffrey

Introduction: Post-procedural infection is a serious complication in neurosurgery, leading to re-operations, morbidity, and increased readmission rates and increased cost. To prevent SSI, some practitioners administer post-procedural drain prophylaxis (PPDP) while surgical or external ventricular drains (EVDs) are in place. This practice is best studied in spine surgery, and in this context PPDP has not been shown to reduce rates of SSI. In addition, extended antibiotic administration can increase rates of Clostridioides difficile (C difficile) infection, which can lead to severe complications including fulminant colitis and death. However, rates of C difficile have not been examined with respect to drain prophylaxis across a wide neurosurgical cohort.
Methods: The University of Virginia department of neurosurgery discontinued the administration of PPDP for EVDs as well as all post-operative cranial and spine drains in May 2017. Rates of C difficile infection, surgical site infection requiring re-operation, and meningitis in the setting of EVDs were examined in a 5 year period spanning this practice change.
Results: The patient cohort included 7577 unique patients that underwent 8040 surgical procedures and 413 EVD insertions. Rates of C difficile infections significantly decreased from 0.57% to 0.11% (p <0.001, X 2 test of independence) after the discontinuation of PPDP, with a relative risk reduction of 80.7%. This was not accompanied by a significant change in rates of SSI requiring re-operation or EVD-associated meningitis.
Conclusion: Elimination of extended PPDP in the presence of surgical drains was associated with a decrease in the rate of C difficile infection without a change in the rates of SSI or EVD-associated meningitis. This is the first examination of the association of PPDP with post-procedural infection and C difficile in a diverse neurosurgical cohort. These results support the specialty-wide discontinuation of the use of PPDP.

119. Glioma Network Resilience Predicts Early Postoperative Language Recovery

Alexander Aabedi (San Francisco, CA); Anne Findlay; Leighton Hinkley; Saritha Krishna; Sofia Kakaizada; Jasleen Kaur; Jacob Young; Srikantan Nagarajan; Shawn Hervey-Jumper

Introduction: Despite the use of multimodal intraoperative brain mapping prior to glioma cytoreduction, for reasons that have yet to be elucidated, some patients still experience a paradoxical worsening of language function in the postoperative setting. Because gliomas induce a variety of local and global network alterations, particularly in regions encompassing language pathways, it may be possible to identify patients at risk of postoperative impairment by measuring their overall network resilience prior to surgery.
Methods: 36 patients with dominant-hemisphere gliomas scheduled for maximal safe resection with intraoperative language mapping underwent pre- and postoperative language testing via the validated Quick Aphasia Battery (QAB). Each patient additionally underwent 256-channel resting-state magnetoencephalography (MEG). Unweighted graphs based on thresholded alpha-band imaginary coherence values were extracted after reconstruction of each voxel time-series in source space. The global assortativity coefficient was then calculated for each patient as a proxy of their overall resilience to network insults (i.e., from tumor cytoreduction).
Results: Postoperative language function declined across all seven domains of the QAB including word and sentence comprehension, word finding, grammatical construction, motor speech, repetition, and reading (p $<<<$ 0.001, Wilcoxon signed-rank). Patients with high network resilience on preoperative MEG (i.e., diffuse distribution of network hubs) were more likely to retain postoperative language function, while those with low network resilience (i.e., only a few focal high-traffic hubs) were more likely to have worsened function (R-squared = 0.23, p = 0.00001).
Conclusion: Patients at risk of worsened postoperative language function despite multimodal intraoperative brain mapping can be identified via their network alterations in response to glioma. Such patients may benefit from more targeted operative planning and postoperative rehabilitation.

120. A Rapid Genotyping Panel for Detection of Primary Central Nervous System Lymphoma

Mihir Gupta, MD (San Diego, CA); Evan Burns; Nicholas Georgantas; Julia Thierauf; Javier Romero; Priscilla Brastianos; Kensuke Tateishi; Jochen Lennerz, MD; Jorg Dietrich; Daniel Cahill; Bob Carter; Ganesh Shankar

Introduction: Primary central nervous system lymphoma (PCNSL) remains challenging to diagnose due to nonspecific clinical and radiologic features and the low yield of cerebrospinal fluid (CSF) studies. While histologic diagnosis by brain biopsy remains the gold standard, procuring intracranial specimens is associated with periprocedural risk, which is higher in difficult to access lesions. We sought to characterize the workflow in the diagnosis of suspected PCNSL, and design a diagnostic targeted genotyping platform for CNS neoplasms.

Methods: We characterized the clinical evaluation of suspected PCNSL (N=1007 patients) and designed a rapid multiplexed genotyping assay for MYD88, TERT promoter, IDH1/2, H3F3A, and BRAF mutations to facilitate the diagnosis of PCNSL from CSF and detect other neoplasms in the differential diagnosis.

Results: Among 159 patients with confirmed PCNSL, the median time to secure a diagnosis of PCNSL was 10 days, with a range of 0-617 days. Permanent histopathology confirmed PCNSL in 142/152 biopsies (93.4%), whereas CSF analyses were diagnostic in only 15/113 samplings (13.3%). Among 86 archived clinical specimens, our targeted genotyping assay accurately detected hematologic malignancies with 57.6% sensitivity and 100% specificity (95% CI: 44.1-70.4% and 87.2–100%, respectively). MYD88 and TERT promoter mutations were prospectively identified in DNA extracts of CSF obtained from patients with PCNSL and glioblastoma, respectively, within 80 minutes. Across 132 specimens, hallmark mutations indicating the presence of malignancy were detected with 65.8% sensitivity and 100% specificity (95% CI: 56.2-74.5% and 83.9-100%, respectively).

Conclusion: Establishing a diagnosis of PCNSL is challenging with current clinical workflows given the low specificity of liquid-based diagnostics and overlap with radiographic mimics such as glioma. This targeted genotyping approach offers a rapid, scalable adjunct to reduce diagnostic and treatment delays in PCNSL.

International Travel Scholarship

200. Cost-Effectiveness Analytic Comparison of Follow-up Strategies after Pipeline Embolization Device Treatment of Intracranial Aneurysms

Mohamed Salem, M.D (Alexandria, Egypt, Arab Rep.).; Mohamed Salem, MD, MPH; Mira Salih, MD; Felix Nwajei, MD, PhD; Santiago Gomez-Paz, MD; Ajith Thomas, MD; Christopher Ogilvy, MD; Justin Moore, MD, PhD

Introduction: Flow diversion via Pipeline Embolization Device (PED) is one of the established modalities for the treatment of unruptured intracranial aneurysms that require a robust follow-up regimen. However, to date, there is no consensus regarding the optimal imaging modality and timing intervals for such a strategy. This study aims to compare multiple commonly implemented follow-up strategies after flow diversion with pipeline embolization device utilizing Monte Care Simulation.

Methods: A decision-analytical study using Markov modeling was performed to compare five commonly used multistep follow-up strategies utilizing different combinations of Diagnostic cerebral angiogram (DSA) and magnetic resonance angiography (MRA): 1) DSA 6, MRA 12, 24 months. 2) DSA 6, 12, 24 months. 3) MRA 6, 12, 24 months. 4) DSA 6, 12, MRA 24 months. 5) DSA 12, MRA 24 months. Input parameters were mainly collected from large cohort studies and current meta-analysis; and 1-way, 2-way, and probabilistic sensitivity analyses were conducted to assess the model robustness.

Results: Strategy 5 incorporating DSA at 12 months and MRA at 24 months was the most cost-effective strategy in >99% of the 10,000 iterations in the probabilistic sensitivity analysis (PSA) at a willingness-to-pay threshold of $100,000/QALY. The result remains robust in one way and two-way sensitivity analysis.

Conclusion: Given the current literature, delayed imaging follow-up at one year with DSA, and two years with MRA after PED treatment are more cost-effective than early follow up after PED at 6 months.

300. Decompression Versus Fusion for Lumbar Spondylolisthesis: Are There Differences in Reoperations? Results from the Lumbar Quality Outcomes Database

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Introduction: Index treatment of lumbar spondylolisthesis with decompression versus fusion may have differences in reoperation timing and causes.
Methods: We reviewed 608 patients from the lumbar Quality Outcomes Database (QOD) who had undergone elective single-segment surgery for grade 1 spondylolisthesis. We recorded reoperations related to the index surgery, assessed at 30-day, 1-year, 2-year, and 3-year time points.
Results: 468 (77.0%) patients underwent fusion and 140 (23.0%) underwent decompression alone. The overall reoperation rate was 6.9% (42 patients with 44 reoperations). There were a similar proportion of reoperations for decompression and fusion cohorts (9.3% vs. 6.2%, p=0.21). There were significantly more reoperations within 30 days for the fusion cohort (p=0.02), whereas there were significantly more reoperations from 30 days to 1 year for the decompression cohort (p=0.01). There were no significant differences at other time points (p>0.05). For the decompression cohort, 7 (53.8%) of the reoperations required a revision decompression, of which 6 were at the same level as the index surgery. The remaining revision decompression surgery was at an adjacent level. The remaining 6 (46.2%) reoperations for the decompression-only cohort required a transition to fusion (1 at the same level, 5 including adjacent levels). For the fusion cohort, 13 (41.9%) reoperations required a revision fusion [8 for adjacent segment disease, 5 for pseudarthrosis]. There was one (3.2%) reoperation requiring a decompression at an adjacent level. Other reoperations in the fusion cohort (n=17, 54.8%) were for miscellaneous reasons including surgical site infection (n=8), implant revision/removal (n=6), hematoma evacuation (n=1), wound revision for suture granuloma (n=1), and spinal cord stimulator placement (n=1).
Conclusion: The fusion cohort had a higher reoperation rate within 30 days postoperatively, whereas the decompression cohort had a higher rate between 30 days and 1 year. The reasons for reoperation vary with surgical approach.

301. Contrast Enhancement and Microbleeds in the Wall of Unruptured Intracranial Aneurysms

Jorge A. Roa, MD (New York, NY); Timothy Morris, BS; Ryan Sabotin, BS; Alberto Varon, MD; Ashrita Raghuram; Mario Zanaty, MD; Daizo Ishii, MD; Edgar Samaniego, MD, MS; David Hasan, MD

Introduction: Contrast enhancement of the wall of unruptured intracranial aneurysms (UIAs) on high-resolution vessel wall imaging (HR-VWI) may be a biomarker of inflammation and instability. MR-quantitative susceptibility mapping (QSM) can identify microbleeds (MBs) in the wall of unstable UIAs preceding subarachnoid hemorrhage. We aim to objectively assess the correlation between HR-VWI and QSM findings.
Methods: Patients with UIAs prospectively underwent QSM and HR-VWI on a 3T Siemens MRI at diagnosis. UIAs were deemed unstable when MBs were identified in the wall after QSM analysis. The contrast enhancement ratio between maximal signal intensity values measured in the aneurysmal wall and the pituitary stalk (CR stalk) on T1 post-contrast images was calculated. Multiple t tests were computed to assess the correlation between several morphological variables (size, neck, aspect ratio, size ratio), PHASES score, CR stalk and presence of MBs. A ROC curve was plotted to determine the best CR stalk cutoff to distinguish unstable from unstable IAs.
Results: 123 patients harboring 178 UIAs underwent HR-VWI. 97 UIAs (54%) were excluded: 54 due to QSM artifacts, 19 due to fusiform morphology, 9 due to size (<2 mm), 8 due to location in the cavernous segment of the internal carotid artery and 7 due to poor HR-VWI quality. 81 unruptured IAs were analyzed: 66 stable (MBs absent) and 15 unstable (MBs present). Unstable UIAs with MBs were larger (8.4±5.5 mm vs 5.5±2.3 mm, P=0.007), showed higher CR stalk (0.6±0.2 vs 0.5±0.1, P=0.05) and scored higher on PHASES (6.9±3.5 vs 4.8±2.6, P=0.02). We found a trend for unstable UIAs to demonstrate higher aspect ratio (2.1±1.3 vs 1.9±0.9, P=0.56) and higher size ratio (3.3±1.6 vs 2.6±1.2, P=0.11), although such differences were statistically non-significant. ROC curve analysis demonstrated that the best CR stalk cut-off to discriminate between UIAs with and without MBs was ≥ 0.55 (82% sensitivity, 67% specificity).
Conclusion: There is a strong positive association between aneurysmal wall enhancement and MBs. CR stalk ≥ 0.55 may be used as a biomarker of aneurysmal instability in clinical practice.

302. Alliance A071601: Phase II Trial of BRAF/MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas

Priscilla Kaliopi Brastianos, MD (Boston, MA); Erin Twohy; Susan Geyer, PhD; Elizabeth Gerstner, MD; Timothy Kaufmann, MD; Daniel Cahill, MD, PhD; Priya Kumthekar, MD; Helen Shih, MD; Paul Brown, MD; Sandro Santagata, MD, PhD; Frederick Barker II, MD; Evanthia Galanis, MD

Introduction: Craniopharyngiomas, a rare suprasellar tumor, often cause significant clinical sequelae. Surgery and radiation, the only effective treatments, can cause significant morbidity. 95% of PCP harbor BRAF- V600E mutations (Brastianos et al. Nature Genetics 2014). We evaluated BRAF/MEK inhibition efficacy in patients (pts) with previously-untreated PCP.
Methods: Eligible pts without prior radiation whose PCP harbored BRAF mutations received oral vemurafenib/cobimetinib in 28-day cycles. Centrally-reviewed volumetric response rate (RR) was the primary endpoint, with partial response defined as > 20% volumetric decrease. This single arm, Simon two-stage phase 2 trial had 89% power to detect a true RR of at least 30% (vs. null RR 5%; alpha=0.04). In this design, 3 or more confirmed responses in 16 evaluable pts would be considered promising activity.
Results: Of 16 pts evaluated, 56% were female; median age was 49.5 years. Median follow-up was 22mo (95% CI: 16-26.5) and median treatment cycles was 8. Three patients progressed after therapy was discontinued; none have died. 14/15 pts with centrally-reviewed volumetric data had responses (93%; 95%CI: 68% to 99.8%). Of 16 patients evaluable based on local review, 15 had responses (93.75%; 95%CI: 70% to 99.8%). Median tumor volume reduction was -83% (range: -52% to -99%). The one nonresponder stopped therapy after 2 days of treatment for toxicity. Median progression-free survival was not reached. Grade 3 toxicities at least possibly related to treatment occurred in 12 pts (rash in 6). Two grade 4 toxicities occurred: hyperglycemia (n=1) and increased CPK (n=1). Three pts discontinued treatment for adverse events.
Conclusions: Vemurafenib/cobimetinib provided volumetric response in all pts who received 1 or more therapy cycles. BRAF/MEK inhibitors are an active treatment for previously untreated PCP and warrant further evaluation. A second arm of this study is enrolling pts with progressive PCP after prior radiotherapy. Support: U10CA180821, U10CA180882; U24CA196171, U10CA180868 (NRG); Genentech; https://acknowledgments.alliancefound.org

303. Development and External Validation of a Deep Neural Network Analysis of CT Scans to Predict Outcomes in Severe Traumatic Brain Injury Patients: a TRACK-TBI Study

Matthew W. Pease, MD (Pittsburgh, PA); Matthew Pease, MD; Dooman Arefan, PhD; Esther Yuh; Jason Barber, MS; Nancy Tempkin; Jane Sharpless; Julia Billigen; Andrew Legaretta; Kerri Hochberger; Shandong Wu; David Okonkwo

Introduction: Traumatic Brain Injury (TBI) is the leading cause of death and disability in young adults worldwide. Physicians and other validated models predict long-term outcomes with only moderate success. Multi-institutional models, such as IMPACT, are designed to guide clinical trial design and are not intended to guide clinical decision-making. Machine Learning (ML) models can identify abnormalities in radiographic images with a high degree of accuracy. We applied ML models to CT scans and clinical information from severe TBI for prognostication.
Methods: We developed our model using 537 severe TBI patients from a prospectively collected database at a single institution from 2002-2018 with a CT scan prior to neurosurgical intervention. We applied transfer learning and a 3D convolutional neural network (CNN) to build a model using CT scans alone for mortality prediction. The cohort was chronologically split into 70%, 10%, and 20% for training, validation, and independent testing. We also developed an ML-based combined model using clinical variables augmented with CT scans. We externally validated our imaging and combined models with 223 severe TBI patients from 15 institutions in TRACK-TBI.
Results: The CNN model using CT scans predicted mortality in the independent test cohort with an AUC of 0.86 (95% CI: 0.77-0.92; accuracy of 83%). For the combined model, the AUC increased to 0.91 (95% CI: 0.84-0.96; accuracy 88%). The IMPACT model had a lower AUC 0.63 (p<0.001). When tuning our model to a specificity of 1 (i.e. never recommending withdrawing care on a patient who would survive), the sensitivity was 0.51 (95% CI: 0.31-0.66). In the TRACK-TBI external validation, the AUC was 0.81 for the CT image model and 0.75 for the combined model.
Conclusion: A deep learning CNN model of head CT scans can predict mortality outcomes following severe TBI in a prospective multi-institutional database.

Southeastern Brain Tumor Foundation (SBTF) Award
304. Characterization of the Minimal Residual Disease in Human Glioblastoma

Maleeha A Qazi (Toronto, Canada); Sabra Salim; Neil Savage; Kevin Brown, PhD; Nicholas Mikolajewicz; Hong Han, PhD; Amanda Khoo; Thomas Kislinger, PhD; Sidhartha Goyal, PhD; Jason Moffat, PhD; Sheila Singh, MD, PhD

Introduction: Despite aggressive standard-of-care (SoC) chemoradiotherapy, glioblastoma (GBM) remains incurable and inevitably relapses. Recent data has identified differential genomic and expression patterns between primary and recurrent GBM, suggesting that recurrence is a distinct biological entity. We hypothesized that profiling and characterizing the minimal residual disease post-SoC, a stage that remains elusive to our current diagnostic technologies, may offer an early window into identifying clonal composition and therapeutic targets in GBM recurrence.

Methods: Patient-derived GBM cells were barcoded using in-house cellular DNA barcode library and intracranially engrafted in immunocompromised mice. Using MRI, tumour volumes were monitored over the course of mouse-adapted SoC chemoradiotherapy and allowed for the identification of MRD timepoint. Clonal composition of GBM was assessed at multiple timepoints during the disease and treatment course by multi-plex barcode sequencing. Transcriptomic profiling of MRD cellular population was assessed using single-cell RNA-sequencing and validated using bulk RNA-sequencing and whole-cell proteomics.

Results: We developed a therapy-adapted xenograft model of GBM recurrence that can be used to study disease course at multiple timepoints throughout treatment course and disease progression. We successfully barcoded patient-derived GBM cells at single cells resolution to interrogate the temporal fate of distinct barcoded GBM subpopulations through SoC. We identified variable patterns of pre-existing and therapy-driven GBM subpopulations seeding different GBM tumour relapse that correlated with patient survival. Through single-cell RNA-sequencing, we profiled the transcriptomic composition of GBM cells post-SoC at MRD and identified the impact of cell-state transitions in post-SoC in disease outcomes. We also identified transcription and antigen-presentation signalling pathways as key mediators of survival outcomes in GBM patients.

Conclusion: Profiling the dynamic nature of heterogeneous GBM subpopulations through disease progression and SoC treatment may lead to the identification of novel targets in clonally evolving subpopulations of GBM for personalized treatment strategies.

Journal of Neuro-Oncology Award
305. Cytolytic Score Correlates with an Immunosuppressive Tumor Microenvironment and Reduced Survival in Medulloblastoma

Jia-Shu Chen (Providence, RI); Alexander Haddad, BS; Taemin Oh, MD; Elaina Wang, BS; Sudheesha Perera, BS; Manish Aghi, MD, PhD

Introduction: There is limited knowledge of the medulloblastoma immune microenvironment and the prognostic significance of infiltrating immune cells. Cytolytic activity score (CAS) is an index of anticancer immunity that has highlighted mechanisms of tumor-intrinsic resistance in many cancers. The objective of this study was to use CAS to stratify medulloblastoma tumors according to degree of CD8+ T-cell activity in the microenvironment then identify immune cell populations and molecules that may explain survival trends or serve as immunotherapeutic targets.

Methods: Clinical and RNA-sequencing data for 112 patients with medulloblastoma was obtained from the Gabriella Miller Kids First Data Portal. The geometric mean of GZMA and PRF1 expression was used to calculate CAS. CIBERSORT was utilized to estimate abundance of immune cell-types. Spearman correlation was used to characterize relationships between CAS and expression of other genes. Pearson's chi-squared and Wilcoxon rank-sum test was used to compare categorical and continuous variables, respectively.

Results: 27 of 112 patients (24.1%) had high CAS. High CAS was significantly associated with increased mortality (40.7% vs. 16.5%, $p = 0.008$) and faster time to death (HR=2.258, 95% CI= [1.023, 4.983], $p = 0.044$). The high CAS group had significantly greater infiltration of CD8+ T-cells ($p = 0.002$), CD4+ T-cells ($p < 0.001$), activated natural killer cells ($p = 0.008$), M2 macrophages ($p < 0.001$), and neutrophils ($p = 0.010$). Furthermore, CAS was significantly and positively correlated with immunosuppressive genes like PD1 ($R_S = 0.70$, $p < 0.001$), CTLA4 ($R_S = 0.55$, $p < 0.001$), TIM3 ($R_S = 0.44$, $p < 0.001$), and IDO1 ($R_S = 0.44$, $p < 0.001$). Finally, the high CAS subgroup also had higher levels of pre-cytolytic activity, with greater expression levels in antigen processing (IFI30, TAP1, B2M), T-cell activation (IFN-gamma, TNF), and T-cell homing (CXCL10, CCL3).

Conclusion: CAS possesses a strong positive correlation with worse prognosis, higher expression of immunosuppressive genes, and greater infiltration of pro-tumoral immune cells (M2 macrophages, neutrophils) in patients with medulloblastoma. However, high CAS microenvironments also have greater levels of anti-tumoral immune cells and pre-cytolytic activity gene expression. Thus, high CAS patients may benefit from multi-faceted immunotherapies, given their already elevated tumor CD8+ T-cell levels.

Mizuho Minimally Invasive Brain Tumor Surgery Award

306. Deep Neural Networks Can Perform Automated Instrument Detection in Endoscopic Skull Base Surgery

Guillaume Georges Kugener (Newton, MA); Dhiraj Pangal, BS; Tyler Cardinal, BS; Casey Collet, BS; Elizabeth Lechtholz-Zey, BS; Arman Roshannai; Yichao Zhu, MS; Daniel Donoho, MD; Gabriel Zada, MD

Introduction: Expert analysis of surgeon instrument movement can accurately assess surgeon performance across a variety of tasks. In other fields, when experts are scarce, machine vision techniques have been used to evaluate performance. However, it is unknown whether instrument movement during neurosurgical tasks can be reliably detected. We describe the first neuroendoscopic video dataset and compare two deep learning approaches to detect neurosurgical instruments.

Methods: Fifty surgeons of varying training levels participated in an endoscopic endonasal surgical task in a perfused cadaveric specimen. Intraoperative video from a neurosurgical endoscope was extracted. We annotated the spatial location of 8 tools (suction, grasper, cottonoid, muscle, string, scalpel, drill, and a composite of all other tools) using bounding boxes. We then trained two object detection neural networks (YOLOv3, RetinaNet) to detect tool identity and location. The mean average precision (mAP) (area under the precision vs. recall curve) was used to evaluate the model.

Results: Our dataset contains 98 video recordings, (23,091 frames; 385 min). There were 16,208 instances of suction, 10,984 of grasper, 2,695 of muscle, 6,882 of cottonoid, 8,964 of string, and 167 of other tools. The mAP for YOLOv3 and RetinaNet on our test dataset (7 trials; 1,916 frames, 4,093 tools) was 0.676 and 0.731, respectively. We achieved the following mAP for YOLOv3 and RetinaNet, respectively: suction 0.83, 0.91 (n=1459); grasper 0.81, 0.87 (n=952); cottonoid 0.35, 0.52 (n=665); string 0.55, 0.45 (n=840), muscle 0.33, 0.06 (n=177).

Conclusion: We introduce the first tool-annotated, intraoperative neurosurgical dataset and demonstrate its realism, computational accessibility, and clinical relevance. Two state-of-the-art object detection networks successfully detected common surgical instruments within an endoscopic field. This demonstrates the feasibility of automated instrument detection and establishes the cornerstone for future development of automated methods of surgeon skill assessment based upon surgical videos.

307. Spectro-temporal Encoding of Speech Responses in Glioma-Infiltrated Cortex

Alexander Aabedi (San Francisco, CA); Benjamin Lipkin; Jacob Young; Saritha Krishna; Sofia Kakaizada; Jasleen Kaur; Mitchel Berger; David Brang; Shawn Hervey-Jumper

Introduction: Emerging evidence suggests that gliomas interact with neurons (and therefore neural micro-circuitry) through both paracrine signaling and electrochemical synapses. Macroscopically, glioma-infiltrated tissue demonstrates resting state excitability. However, established models have failed to establish whether glioma-infiltrated cortex can encode cognitively relevant information, such as event-related responses to task-based stimuli. Addressing this significant gap in the literature carries important implications for our understanding of glioma-brain circuit dynamics and the role of glioma cytoreduction on cognition.

Methods: Patients with cortically-projecting IDH-mutant gliomas underwent electrocorticography of the inferior frontal gyrus (IFG) while naming pictures (172 trials) and reading text (103 trials). Glioma-infiltrated electrodes were identified via stereotactic comparison with regions of FLAIR signal abnormality on preoperative imaging. After pre-processing and manual electrode inspection, spectra in the high-gamma range (70–150 Hz) were computed via complex Morlet wavelet convolution. Principal components analysis (PCA) was conducted across the spectra. Cluster-based corrections (corrected threshold: $p<0.001$) using 1,000 permutations of the temporal responses followed initial parametric tests of significance (uncorrected threshold: $p<0.0001$).

Results: PCA revealed two ensembles of time-locked spiking activity across glioma-infiltrated electrodes (n=72) during picture-naming and text-reading. Electrodes with positive loadings for the first ensemble (51% of total variance) exhibited statistically significant high-gamma activity (HGA) during the speech event (average lag time = 14 ms). Electrodes with positive loadings for the second ensemble (28% of total variance) had maximal HGA after stimulus onset, but before the speech event. No significant differences were found between spectra from glioma-infiltrated electrodes and electrodes overlying normal-appearing tissue.

Conclusion: Cortical regions infiltrated with IDH-mutant glioma are capable of encoding cognitively and behaviorally relevant information (i.e., pre-articulatory and articulatory processes). These results have important implications for surgical planning approaches across glioma subtype and cognitive recovery following glioma resection.

Ronald L. Bittner Award on Brain Tumor Research
308. B-cell-based Vaccine, an Effective Immunotherapy for Preclinical Models of Glioblastoma

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Introduction: Glioblastomas (GBMs) create a strong immunosuppressive environment, contributing to their poor prognosis. Immunotherapies have shown limited therapeutic benefit in GBM. B-cells, an under-investigated entity within GBM research, have the potential to kill tumors by both cellular and humoral immunity. We identified a subset of B-cells expressing 4-1BBL which are activated in a way that suggests prior antigen exposure, likely from the GBM. 4-1BBL + B-cells provide a cellular platform for our B-cell-based vaccine (B Vax) for GBM treatment.
Methods: B Vax is generated by isolating 41BBL + B-cells from GBM tumor bearing mice or peripheral blood from GBM patients, and subsequently activating them with BAFF, CD40, and IFN . Antibody repertoire was assessed in vivo from serum of MuMT B-cell knockout mice treated with B Vax or by ex vivo - stimulation of human B Vax.
Results: In a CT2A murine model, we have shown a survival benefit of (1) B Vax in combination with radiation therapy and temozolomide, and (2) B Vax compared to DC Vax. B Vax has shown cellular immunity by activating CD8 T-cells in GBM patient samples, subsequently leading to tumor cell death, as measured by cytotoxicity assays. After intravenous administration, about 50% of murine-derived B Vax upregulate CD138, a marker of plasmablast formation. Murine B Vax - and B Naive -derived serum immunoglobulin generated in vivo showed that the majority of murine B Vax -derived Ab were IgG isotype, while B Naive mainly produced IgM isotype. B Vax IgG treated mice showed improved survival suggesting anti-tumor cytotoxicity through humoral immunity. Human B Vax activated ex vivo demonstrates a plasmablast phenotype and the Ab repertoire supports the previous findings seen in our murine model.
Conclusion: B Vax provides an effective alternative immunotherapeutic option for GBM patients which has shown a survival benefit in preclinical models through both cellular and humoral immunity. These findings have been supported using GBM patient-derived samples.

309. Defining the Anatomic Substrates of Gerstmann Syndrome Using Connectivity-Based Meta-Analysis

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Introduction: The Gerstmann syndrome is a constellation of neurological deficits that include agraphia, acalculia, left right discrimination and finger agnosia. Although this syndrome has always been linked to damage to the left inferior parietal lobe, the available evidence lacks structural specificity. Since the deficits involved have been shown to involve more complex brain networks, the syndrome needs to be investigated in further detail with the aim of establishing the exact anatomical location in the cerebrum which leads to the neurological deficits in order to prevent neurosurgeons from causing this deficit.
Methods: Using task-based fMRI and PET studies, an activation likelihood activation (ALE) was generated for each cognitive domain. Machine-learning was used to match activated regions of the ALE to the corresponding parcellation from the cortical parcellation scheme, previously published under the Human Connectome Project. DSI based tractography was performed to determine the structural connectivity between the relevant cortical regions.
Results: A frontoparietal network was found to be involved in the four cognitive domains. There were three parcellations in the left hemisphere where the ALEs of the four networks were found to be overlapping. These were the areas AIP, MIP, and 7PC in the lateral parietal lobe.
Conclusion: We present a tractographic model of the four neural networks involved in the Gerstmann syndrome. We identified the Gerstmann core, which is essentially the cortical region in the lateral parietal lobe where the four networks overlap, leading to the clinical manifestations of the syndrome. Future neurosurgical procedures may use these results to avoid the neurological deficits by sparing the cortical regions identified.

310. Serial Connectome Mapping of Domain-General Higher-Order Cognition in Cortical Neurosurgery

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Introduction: The Multiple Demand (MD) system is the brain's spatially-distributed architecture for executing domain-general cognitive processes. This system contains a "Core" frontoparietal network that interfaces with a "Penumbra" of sub-networks to orchestrate goal-directed behaviour. To date, the MD system has largely been underappreciated in neurosurgery. By longitudinally mapping the networks governing cognition, we may predict and rehabilitate cognitive trajectories in neurosurgical care. In this study, we sought to establish the relevance of the MD system in health and then its response to low-grade glioma (LGG) surgery and long-term recovery.
Methods: With MRI and cognitive data from n=629 individuals across the lifespan, we first validated the structural, functional, and topological relevance of the MD system to higher-order cognition. Next, in n=17 patients undergoing LGG surgery, we longitudinally acquired connectome and cognitive data: pre-surgery, post-surgery Day 1, Month 3, & 12. We assessed how glioma infiltration, surgery, and rehabilitation affected MD system trajectories at the single-subject level. Deploying transcriptomic and graph theoretical analyses, we tested if perioperative connectome modularity can accurately distinguish long-term cognitive trajectories.
Results: Controlling for age and sex, the MD system's structural and functional architecture was positively associated with higher-order cognition (Catell's fluid intelligence). Pre-operative glioma infiltration into the MD system was negatively associated with the number of long-term cognitive deficits (OCS-Bridge cognitive battery), suggesting its functional reorganisation. Mixed-effects modelling demonstrated the resilience of the MD system to infiltration and resection, while the early post-operative period was critical for effective neurorehabilitation. Graph analyses revealed perioperative modularity can distinguish patients with long-term cognitive deficits at one-year follow-up. Transcriptomic analyses of inter-module MD hubs revealed genes enriched for mitochondrial metabolism and synaptic plasticity.
Conclusion: This is the first serial functional mapping of LGG patient trajectories for domain-general cognition. We demonstrate how connectomics can predict long-term rehabilitation trajectories and identify neurobiologically-grounded personalised targets for 'interventional neurorehabilitation'.

311. Predictive Modeling of Early Post-Operative Seizures after Craniotomy for Tumor Resection

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Introduction: Studies of prophylactic perioperative antiepileptic drug (AEDs) use after brain tumor resection are limited by low post-operative seizure incidence in non-risk stratified patient populations. Predictive modeling of post-craniotomy seizures may identify high-risk populations most likely to benefit from seizure prophylaxis.
Methods: The IBM Watson Health MarketScan Claims Database was canvassed for adult patients receiving craniotomy for resection of a primary parenchymal mass, meningioma, or metastasis (2007-2015). Patients were censored at the end of continuous post-discharge follow-up or first outpatient AED prescription. The primary endpoint was a coded post-discharge seizure. Exclusion criteria included AED use or seizure in the 6-months before surgery. Three machine learning (ML) approaches were evaluated and the best-performing strategy (logistic regression with Elastic Net regularization) was used to train and validate a classifier integrating patient-, hospitalization-, and tumor-specific features to predict early post-discharge seizure risk (within 90-days). Predicted risk was stratified into equally sized tertiles ("low-risk", "medium-risk", "high-risk").
Results: Across 5,470 patients, 983 (18.0%) had a post-discharge coded seizure. Strongest predictors of early post-discharge seizures included supratentorial location (OR=4.64, 95%CI=3.11-6.93), discharge to additional care (OR=3.39, 95%CI=2.48-4.63), tumor malignancy (OR=1.78, 95%CI=1.11-2.86), and hospitalization duration (OR=1.05, 95%CI=1.03-1.07). Our best-performing binary classification approach for predicting early-onset seizures demonstrated robust discrimination (AUC=0.766) and high accuracy (Brier Score=0.097, null-model=0.107). Held-out validation cases predicted by our model as "high-risk" more frequently developed seizures within 90-days of discharge (24.1% ["high-risk"] vs 3.8% ["low-risk"], p<0.001). No held-out patients predicted as "low-risk" developed status epilepticus (SE), while 1.69% of predicted "high-risk" patients developed SE.
Conclusion: In seizure- and AED-naïve patients receiving craniotomy for tumor resection, we constructed an ML classifier to estimate overall and short-term seizure risk without seizure prophylaxis. This risk-stratification instrument may help identify patients at highest seizure risk most likely to benefit from AED prophylaxis.

312. Risk of Tract Recurrence with Stereotactic Biopsy of Brain Metastases: An 18-year Cancer Center Experience

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Introduction: Stereotactic biopsy is increasingly performed on brain metastases (BrM) as improving cancer outcomes drive aggressive multimodality treatment including laser interstitial thermal therapy (LITT). However, the risk of tract recurrence (TR) is poorly defined in an era defined by focused-irradiation paradigms. As such, we evaluated the BrM-biopsy TR rate.
Methods: A single-center retrospective review identified stereotactic BrM biopsies performed from 2002-2020. Surgical indications, tumor type, radiographic characteristics, stereotactic planning, dosimetry, pre- and post-operative CNS-directed and systemic treatments, and clinical courses were collected. Recurrence was evaluated using RANO-BM criteria.
Results: Four-hundred and ninety-eight patients underwent stereotactic intracranial biopsy for any diagnosis, including 80% for gliomas or CNS lymphoma. Twenty-four of these (4.8%) were for pathologically-confirmed viable BrM, of which 88% (21/24) underwent postoperative stereotactic radiotherapy in plans not specifically targeting biopsy tracts (15/21, 71%; SBRT), or whole-brain irradiation (6/21, 29%). Of 11 patients with >/=3 months radiographic follow-up (median 11.9; range 4.5-30.6), five (45%) developed discontinuous TR at a median 6.4 months (range 2.3-17.1) post-biopsy. Prior to TR, 2 of these previously-irradiated BrM underwent LITT intraoperatively immediately post-biopsy. The remaining biopsy-associated TR were untreated pre-biopsy, and underwent SBRT+/-LITT post-biopsy (n=3 and 1, respectively). Biopsy tracts were not included in any post-operative radiation treatment plans. TR were treated with resection, re-irradiation, or observation/systemic therapy.
Conclusion: We identify a nontrivial, higher-than-previously-described rate of BrM-biopsy TR. As BrM are commonly treated with SBRT limited to enhancing tumor margins, consideration should be made, in cases lacking CNS-active systemic treatments, to include biopsy tracts where feasible

313. IDH Mutated Gliomas Promote Epileptogenesis via D-2-Hydroxyglutarate Dependent mTOR Hyperactivation

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Introduction: Epileptic seizures in patients with low-grade, isocitrate dehydrogenase (IDH) mutated gliomas reach 90%, a major source of morbidity for these patients. While there are multiple factors that contribute to tumor related epileptogenesis, IDH mutations play an independent role in this process, but the pathogenesis remains poorly understood. We demonstrate that IDH-mutated tumors promote epileptogenesis through D-2-hydroxyglutarate (D-2-HG) dependent mTOR hyperactivation and metabolic reprogramming.
Methods: We utilized an in vitro rat cortical neuronal model on microelectrode arrays to investigate the role of D-2-HG on neuronal excitability. Various mTOR and lysine demethylase (KDM) modulators were applied to better elucidate the epileptogenic mechanism. mTOR signaling was evaluated through western blot analysis and multiplex immunofluorescence of downstream mTOR signaling markers. Metabolic function were analyzed via Seahorse glycolytic/mitochondrial assays and metabolomic analysis. Human epileptic and nonepileptic cortex were identified by subdural electrodes in patients with IDH-mutated gliomas (n=5) and were then evaluated for mTOR regulation and metabolomic analysis.
Results: We revealed D-2-HG increased normalized bursting rate compared to control (p<0.0001). Furthermore, we detected mTOR hyperactivation upon D-2-HG treatment, independent of bursting activity, which correlated with upregulation of mTOR signaling in human epileptic tissue. Inhibition of mTOR with rapamycin corrected bursting levels to control levels. We established mTOR hyperactivation and neuronal hyperexcitability could occur through KDM inhibition, which we demonstrated with D-2-HG along with succinate and a small molecule KDM inhibitor, PFI-90. Significantly, we found that epileptic cortex and D-2-HG-treated neurons compared to peritumoral nonepileptic cortex and control, respectively, have distinct metabolism independent of bursting activity (p<0.0001).
Conclusion: We demonstrate IDH-mutated gliomas promote epileptogenesis through a D-2-HG dependent mTOR hyperactivation via KDM inhibition, a putative mechanism and potential therapeutic targets. Furthermore, we argue mTOR hyperactivation may cause epileptogenesis through metabolic reprogramming, a heretofore unrecognized aspect of pathologic mTOR signaling in neurological diseases.

314. Causal Manipulation of Anterior Cingulate Neurons in Mice and Human Selectively Affects Approach during Reward-Threat Conflict

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Introduction: Conflicting motivational stimuli, such as a perceived threat during reward presentation, require responses that balance immediate needs of the organism with long-term survival. Neuronal processing of such conflict has been correlated with dorsal anterior cingulate cortex (dACC) activity in both humans and lower animals; however, the causal role of the dACC in conflict processing has yet to be determined. Using mouse and human behavioral models, coupled with invasive neuronal manipulation paradigms, we sought to better understand the role of dACC in conflict processing.

Methods: Water-restricted mice trained to gather a cue-based water reward were intermittently exposed to an innately threatening auditory or visual stimulus while freely exploring an open arena. Optogenetic manipulation of cell-type and projection-specific neurons in the dACC was performed to enable causal interrogation of the specified circuits during conflict processing. One human subject, harboring implanted stereoelectroencephalography electrodes for refractory central pain syndrome, received high frequency stimulation of dACC during an analogous reward/threat conflict task (Clarke Task).

Results: Optogenetic activation of dACC neurons projecting to midbrain periaqueductal grey (PAG) during conflict trials dampened defensive behavior responses in mice, promoting reward attainment despite the presence of threat. Optogenetic inhibition of the same neuronal population had the opposite effect. In our human subject, high frequency (130Hz) stimulation of the dACC during task-based reward seeking significantly increased pursuit of liquid reward despite increased potential for a painful stimulus exposure.

Conclusion: Behavioral response to conflicting stimuli has been demonstrated to require activity of neurons of the dACC across multiple species. We found for the first time in and mice and a human that causal manipulation of dACC during threat/reward conflict selectively affects approach behavior. These results shed light on higher cognitive processes and can guide development of targeted neuromodulatory therapies for neuropsychiatric diseases affecting conflict processing, such as Tourette Syndrome or Obsessive-Compulsive Disorder.

315. Predictive Analysis of patients with medically-refractory Obsessive-Compulsive Disorder who receive Gamma Knife Ventral Capsulotomy reveals early and sustained trajectory of improvement in functional capacity

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Introduction: Gamma Knife Ventral Capsulotomy (GKVC) is a procedure that targets the ventral, anterior internal capsule and has proven effective for treating some with severe, medical-refractory Obsessive-Compulsive Disorder (OCD). Our team has shown that predictive trajectory analysis can model expected change in compulsion and obsession severity after GKVC. In addition, patients with severe OCD experience major impairment in overall functional capacity, but the expected change in global function after GKVC is unknown.

Methods: We examined a prospective cohort of OCD patients treated with GKVC (n=55). We assessed global function using the well-established Global Assessment of Function score (GAS), a measure of psychological, social, and occupational functioning. GAS assessments were administered prospectively 6, 12, 24, 36, 48, and 60 months postoperatively for each patient. We developed parametric and piecewise linear models to fit the prospective data and determined the best fit model for GAS scores using a sample-size adjusted Bayesian Information Criterion.

Results: For the GAS, a parametric model with two classes and a zero class best fit the data. In the model, 90% of patients in this study belong to the class exhibiting the greatest overall improvement. Individuals in this class can expect to achieve notable improvement in the first postoperative year (21.4%) with continued improvement (55.5% by year 5). A small class of patients (7%) will show transient improvement in GAS (38.8% by year 1) with a subsequent worsening of GAS below baseline (100% by year 5). The remaining 3% fall into the zero class and can expect no change in GAS after GKVC.

Conclusion: Predictive analyses suggest that significant improvement in overall global function can be expected in nearly all OCD patients by the first year after GKVC with the overwhelming majority experiencing continued improvement. The degree of average improvement seen in the majority class translates to an overall improvement in severity on the GAS from major impairment to moderate difficulty in social, occupational, or school functioning.

316. Basis Profile Curve Identification to Understand Electrical Stimulation Effects in Human Brain Networks

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Introduction: Brain networks can be explored by delivering brief pulses of electrical current in one area while measuring responses in other areas.
Objectives: If we focus on a single brain site and observe the average effect of stimulating each of many other brain sites, visually-apparent motifs in the temporal response shape emerge from adjacent stimulation sites. There are no existing approaches to identify and quantify the spatiotemporal structure of these motifs.
Methods: Individual stimulation trials are correlated with one another, then a correlation-significance matrix quantifying similarity between stimulation sites is decomposed with non-negative matrix factorization, in which the inner dimension is iteratively reduced. The dimensionality reduction identifies stimulation sites that produce a common elicited temporal response, and linear kernel PCA is applied to obtain the robust profile of this response cluster.
Results: We describe and illustrate a data-driven approach to determine characteristic spatiotemporal structure in these response shapes, summarized by a set of unique "basis profile curves" (BPCs). Each BPC may be mapped back to underlying anatomy in a natural way, quantifying projection strength from each stimulation site using simple metrics. Our technique is demonstrated for an array of implanted brain surface electrodes in a human patient, and our code is shared at https://purl.stanford.edu/rc201dv0636.
Conclusions: This framework enables straightforward interpretation of single-pulse brain stimulation data, and can be applied generically to explore the diverse milieu of interactions that comprise the connectome.

317. Evaluation of Cerebrovascular Reserve using Acetazolamide-Challenged Perfusion MRI in Pediatric Moyamoya Disease and Syndrome

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Introduction: In pediatric Moyamoya disease, cerebrovascular reserve (CVR) is an important indicator for post-operative clinical outcomes and prognosis. We investigated changes in CVR following surgical revascularization using acetazolamide-challenged perfusion MRI in children with Moyamoya disease and syndrome.
Methods: We retrospectively identified Moyamoya patients < 18 years old undergoing direct or indirect bypass between 2012 and 2019 at our institution. Arterial spin labeling MRI perfusion with acetazolamide challenge was performed before and after surgical revascularization. Cerebral blood flow (CBF) measurements were collected in the ipsilateral anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories. CVR in each territory was defined as the difference between post-acetazolamide and pre-acetazolamide CBF. Pre-operative and post-operative CVRs were compared using the paired Wilcoxon signed-rank test with Bonferroni correction (a priori adjusted alpha = 0.017).
Results: Seventeen male and 15 female patients undergoing 29 direct and 16 indirect bypasses were included in our analysis. Of these, fourteen patients had Moyamoya syndrome. Median age at surgery was 9.7 years (IQR: 7.6-15.7). Median time from surgery was 8 days (IQR: 2-37) for pre-operative imaging and 228 days (IQR: 179-286) for post-operative imaging. Changes in ipsilateral MCA CVR between pre- and post-operative imaging did not differ between direct and indirect bypass (8 vs 3.8 ml/100g/min, p=0.7). The ipsilateral MCA demonstrated significant improvement in CVR (6.9 ml/100g/min preoperatively vs 16.5 ml/100g/min postoperatively, p<0.01). No differences were observed in the ipsilateral ACA (p=0.13) and PCA (p=0.48) territories. Post-operative ipsilateral MCA CVR was higher in patients who achieved post-operative Matsushima grade A perfusion than in patients with Matsushima grades B or C (25.8 ml vs 17.5 ml, p=0.02).
Conclusion: Acetazolamide-challenged perfusion MR may be a useful tool for evaluating CVR changes after surgical revascularization in pediatric Moyamoya patients.

318. Fate-restricted Cell Population Predicted to Constitute Malignant Features in Diffuse Midline Gliomas.

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Introduction: Diffuse Midline Glioma (DMG) remains lethal with limited response to radiation a complete resistance to medical agents. DMG's resilience is believed to derive from the heterogenous tumor cell hierarchy arising from oncogenic stem cells. Targeting this stem cell population is appealing but their identity and vulnerabilities have been difficult to explore. Recent data suggests that growth and spread in high grade brain tumors is derived from more committed cell types downstream of stems cells promoting them as relevant treatment targets. We hypothesized that fate-restricted cells in DMG carry malignant biological programs such as proliferation and invasion. We further explored the treatment vulnerabilities of this cell population through prediction of enhancer profiles.
Methods: We analyzed RNA expression profiles of 2365 neoplastic cells from a published dataset of 6 distinct DMG tumors. We inferred their biological identity using SEURAT pipeline, cellular hierarchy through pseudotime ordering (monocle) or cellular entropy (SCENT) and enhancer profile based on inferred cis-regulatory elements (SCENIC).
Results: In keeping with previous studies we have identified a pluripotent stem cell population at the apex of the cellular hierarchy with limited proliferation and invasion capabilities. This population gave rise to a smaller oligodendrocyte-like and a larger astrocyte-like population. We detected a distinct cluster of cells committed to the astrocyte-like fate which was exclusively enriched in biological signatures of "proliferation" and "invasion". The activity of transcription factors such as E2F2 and FOXM1 were exclusively enriched in this cell population with several downstream target genes including EZH2.
Conclusion: Our results demonstrate a distinct astrocyte-like population that likely constitutes the proliferative and invasive cell population in DMG. We further identify master transcription factors E2F2 and FOXM1 specifically predicted to drive this malignant cell population through targetable downstream regulatory effects.

319. Surgical Decision Making in Brachial Plexus Birth Injuries

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Introduction: Brachial plexus birth injuries range from transient to profound neurologic impairment. Decision making can be divided into two parameters: first, when to operate and second, extent of repair. We present 34 patients who had a total of 36 operations (brachial plexus and/or Oberlin transfers) over 36 months and what guided these decisions.
Methods: Patients with partial injuries (isolated Bicep dysfunction) were considered for Oberlin transfer alone, while the more extensive injuries were best managed with brachial plexus repair. Decisions for surgery were made by 4 months of age when possible and ages were 4 months to 14 months at time of surgery. Two patients had Oberlin transfers only and the rest had Brachial Plexus repairs; 2 of these required an Oberlin transfer as a second operation to recover Biceps at 8 months.
Results: All patient's improvement was graded with the Mallet scale. The 2 patients with the Oberlin transfer alone improved the fastest and the earliest improvement in the upper trunk repairs (with or without middle trunk repairs) was 5 months post op. The patients with all three trunk injuries (ex. flail arm) had the slowest and most incomplete recovery.
Conclusion: Decision making in brachial plexus birth injuries can be in 2 parameters. The necessity to operate based on close physical exams and experience with spontaneous recovery vs surgical recovery and then, how extensive of repair. The second decision can be assisted by intraoperative findings (including nerve stimulation) and goals of functionality based also on preoperative physical exam.

320. Demographic Variables are Associated with Telemedicine Utilization by Pediatric Neurosurgical Patients

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Introduction: Telemedicine has taken on a new urgency during the COVID-19 pandemic. Preliminary studies have focused on telemedicine care implementation and patient/provider satisfaction. In the present study we analyze patient variables associated with increased use of telemedicine to better understand patients who may be willing to replace in-office care with a virtual experience within a pediatric neurosurgical practice.
Methods: All patients seen in the Connecticut Children's outpatient neurosurgery clinic between 4/1/20 and 7/31/20 were retrospectively reviewed. Demographic variables were collected from each patient's first completed encounter. Patients participating in telemedicine were compared to those who completed an in-person visit. A univariate analysis was performed using the Wilcoxon rank sum test for continuous variables and the Fischer's exact test for categorical variables. A logistic regression multivariate analysis was then performed.
Results: A total of 682 patients were included (374 telemedicine and 308 in-person). Univariate analysis demonstrated that patients completing telemedicine visits were more likely to be seen at earlier dates during the study period ($p < 0.0001$), be established patients rather than new patients ($p < 0.0001$), White or Caucasian ($p < 0.001$), not Hispanic or Latino ($p < 0.001$), English-speaking ($p < 0.0001$), non-Medicare/Medicaid recipients ($p < 0.001$), have lower no show rates ($p < 0.01$), and live further from the hospital ($p < 0.01$). Multivariate analysis demonstrated older age ($p < 0.05$), earlier appointment date ($p < 0.01$), established patient status ($p < 0.0001$), English-speaking ($p < 0.05$) and non-Medicare/Medicaid insurance ($p < 0.05$) were significant predictors of telemedicine use.
Conclusion: Significant demographic differences, including race/ethnicity, language, and insurance status, exist among pediatric patients who participate in telemedicine at our institution. As telemedicine becomes more widely used following the pandemic, addressing barriers to access will be crucial for promoting health equity in its utilization.

321. Intra-arterial Bevacizumab after Blood-brain Barrier Disruption for Refractory Radiation Necrosis

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Introduction: We piloted a Phase II, multi-center, single-arm, open-label prospective clinical trial with 10 adults diagnosed with medically refractory brain radiation necrosis (RN). Our purpose was to evaluate safety and efficacy of single low-dose targeted intra-arterial (IA) bevacizumab following osmotic blood-brain barrier disruption (BBBD).
Methods: After IRB approval, 10 adults underwent BBBD followed by targeted 2.5mg/kg IA bevacizumab. RN, vasogenic edema, headache, steroid dependency, and functional status were quantified at baseline and 12-months. Data (mean±SD) analyzed using Wilcoxon signed-rank tests and one-way repeated measures ANOVA test of linear trend within subjects. Null hypothesis was rejected for $p<0.05$.
Results: RN decreased by 74.4±14.7% with significant linear trend over time [$F(1)=10.940$, n=8, $p=0.013$, effect size=0.610]. Vasogenic edema decreased by 50.1±37.3% but linear trend did not reach significance [$p=0.102$]. Headache decreased by 84.4±18.2% with significant linear trend over time [$F(1)=9.299$, n=8, $p=0.019$, effect size=0.571]. Five/10 patients weaned completely off steroids post-treatment and remained steroid-free during remaining 12-months. There were significantly fewer days steroid usage overall 12 months after bevacizumab compared to before [$Z=-2.253$, $p=0.024$, $r=-0.531$]. Functional status was up-trending but did not reach significance [$p=0.100$]. 0/10 died or exhibited AEs attributed to bevacizumab alone. 4 AEs of moderate severity were probably related to BBBD (tonic/clonic seizures with altered mental status 2-hours post-procedure) or bevacizumab+BBBD (mono-ocular blurred vision with diplopia on day 1). 2/10 patients experienced RN recurrence requiring intervention (one patient surgery; one patient 2-cycles IV bevacizumab).
Conclusion: Single targeted low-dose intra-arterial bevacizumab led to durable radiographic and clinical improvement of refractory RN during 12-months follow-up. To our knowledge this is the first prospective report of this novel approach in adults. Randomized trial is needed comparing targeted low-dose IA bevacizumab to multiple cycles of IV bevacizumab at higher doses to determine which is longer-lasting safer alternative in treatment of brain RN.

322. Demographic, Clinical, and Radiographic Characterization of Intracranial Aneurysms in Patients with Marfan Syndrome

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Introduction: Prevalence of intracranial aneurysms (IAs) in patients with Marfan syndrome is variable, ranging from 6-14% and there is no definitive consensus on screening or management for IAs in Marfan patients. We report our multi-center experience with assessment of IAs in Marfan patients, including their demographic, clinical and radiographic characteristics.
Methods: Electronic medical records from adult patients with a confirmed diagnosis of Marfan and available brain imaging studies (MRI post-contrast, MRA, CT post-contrast, and/or CTA) from inception to November 2020 at the 3 main campuses of our institution were reviewed and patients with intracranial aneurysms were identified. Data was summarized using descriptive statistics, including percentages and counts for categorical data, mean as a measure of central tendency for continuous variables, and standard deviation (SD) as a measure of dispersion.
Results: A total of 218 patients with Marfan syndrome and available brain imaging studies were reviewed and 18 patients with Marfan syndrome and IAs were included. Prevalence of IAs in our cohort was 8.25%. Median age was 53.2 years (SD=17.04) and 50%(n=9) were male. Two patients (11%) had a history of aneurysmal subarachnoid hemorrhage and 6 patients (33.3%) had a family history of IAs. Six patients (33.3%) were active tobacco smokers at the time of diagnosis. Seven patients (38.9%) had hypertension and half of the cohort (9,50%) had coronary artery disease. In our cohort, patients had a mean of 1.33(SD=1.50) aneurysms in other sites, with the aorta as the most common location. All IAs were in the anterior circulation and were saccular (n=18,100%), with most common location at the paraclinoid-ICA. Mean maximal diameter was 3.35mm (SD=1.7). Four patients required intervention, comprised of one coil embolization, two flow diversions, and one clip ligation.
Conclusion: We report the largest known series of Marfan patients and IAs. Our results support the association between IAs and Marfan syndrome. In our cohort, all IAs were small, saccular lesions located in the anterior circulation. 2 patients presented with aneurysmal SAH and 4 patients underwent intervention.

323. Correlation between Intracranial Pressure and Venous Sinus Pressures in Patients Undergoing Cerebral Venography and Manometry

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Introduction: The pathophysiology of idiopathic intracranial hypertension (IIH) relates to cerebral venous hypertension. While studies suggest correlations between superior sagittal sinus (SSS) pressure and lumbar puncture (LP) opening pressure (OP) in IIH patients, few studies have simultaneously recorded venous sinus pressures and OP to understand the relationship between these factors without temporal confounding.
Methods: This retrospective review included patients with known or suspected IIH who underwent cerebral angiogram with manometry followed immediately by LP. Linear regression models were used to predict torcula, transverse sinus (TS), and SSS pressures by OP.
Results: 47 patients aged 16-68 years old met inclusion criteria. 91.5% were female. Mean BMI was 33.3 kg/m 2. Of the included patients, median OP was 21 cm H2O (IQR [15.5, 26.5]). Mean (SD) recorded SSS and torcular pressures were 25.5 (16.5) mmHg and 23.8 (16.6) mmHg, respectively. Twenty (42.6%) were discovered to have a trans-stenosis gradient of 8 mmHg or greater. Transverse sinus, torcula, and superior sagittal sinus (SSS) pressures were all significantly predicted by OP. On regression analysis, torcular pressures were best predicted by OP of the three measured sites. For patients with OP <20 cm H 2 O (n=17 (36.2%)), mean (SD) SSS and torcular pressures were 13.5 (4.2) mmHg and 15.4 (6.7) mmHg, respectively, suggesting that normally SSS pressures should measure <18 mmHg (80th percentile) in non-pathologic conditions.
Conclusions: This is the first study to correlate venous sinus pressures and OP in IIH patients with LP performed directly after manometry. In 47 patients, LP OP significantly predicted TS, torcula, and SSS pressures. Torcular pressures (mmHg) were most accurately predicted by OP (cm H 2 O) in a nearly 1-to-1 relationship.

324. Impact of Interfacility Transfer of AIS Patients Compared to Direct Admission for Mechanical Thrombectomy: Systematic Review and Meta-analysis

Isobel MacKenzie (Washington, DC); Toomas Arusoo, MD; Dimitri Sigounas, MD

Introduction: Mechanical thrombectomy (MT) is a proven treatment for large vessel ischemic stroke with improved functional outcomes when compared to intravenous thrombolytics.   However, access to thrombectomy-capable sites varies greatly by geography, often necessitating interhospital transfer of patients who first present to hospitals not able to deliver MT. The purpose of this meta-analysis is to examine the impact of interhospital transportation on patient outcomes to better inform recommendations for pre-hospital protocols.

Methods: A meta-analysis was completed following independent systematic literature searches in PubMed, Cochrane, and Scopus databases. Outcomes of interest included: successful reperfusion (TICI2b/3); symptomatic intracranial hemorrhage (sICH); 90-day mRS 0-2; 90-day mortality; onset-to-puncture times; and door-to-puncture times.

Results: Over 27,000 patients were represented in pooled analysis. Door-to-puncture time was 35.6 minutes shorter among transferred patients (p <0.001); however, symptom onset-to-puncture time was 91.6 minutes longer (p <0.001). Rate of successful reperfusion or sICH did not differ significantly between transferred and directly admitted patients (RR=0.99 [0.97,1.02]; RR=0.91 [0.80,1.03]) nor did 90-day patient mortality (RR=0.97 [0.75,1.25]). While the proportion of patients achieving good functional outcome at 90 days with mRS 0-2 did not differ by admission type, when mRS was narrowed to 0-1 direct transport showed 20% greater probability of achieving excellent functional outcome at three months (p <0.001).

Conclusions: This meta-analysis represents the largest pooled patient population examined to date to assess how transportation from referring facilities to thrombectomy capable sites affects patient outcomes. Our results indicate that interhospital transfer has negligible impacts on rates of reperfusion, sICH, and mortality. This is also the first meta-analysis to show that direct admission is a significant predictor of excellent functional outcome when compared to interfacility transfer. The findings presented here can be used to better inform quality improvement projects to streamline access to endovascular mechanical thrombectomy (EVT), minimizing treatment delays.

325. Effects of Quarantine and Social Distancing During the COVID-19 Pandemic on Neurotrauma Presentations among Western Pennsylvania Level I Trauma Centers

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Introduction: The 2020 COVID-19 pandemic resulted in state-specific quarantine protocols and introduced the concept of social distancing into modern parlance. We assess the impact of various isolation measures on neurotrauma presentations at level I trauma centers in Allegheny County.

Methods: The Pennsylvania Trauma Systems Foundation (PTSF) was queried for registry data from the Pennsylvania Trauma Outcomes Study (PTOS) between March 12th and June 5th in each year between 2017 and 2020. Neurotrauma included TBI, skull/facial fractures, spinal cord injury (SCI), neurovascular injury, and vertebral fractures.

Results: There were 721 neurotrauma presentations in 2020, a reduction in average neurotrauma volume of 26.5%. Mechanism of injury was less likely to be MVC and more likely to be fall-related during 2020 (p<0.05). Location of injury was less likely on roads or indoor public establishments and more likely at indoor private locations (p<0.05). The proportion of neurotrauma patients with blood alcohol concentration > 0.08 was unchanged; however, of those patients with BAC > 0.08, the median BAC was higher during 2020 (2017-2019 BAC 0.15 vs 2020 BAC 0.19; p<0.05). There was a 28.7% reduction in TBI volume during the 2020 index period (358 vs 502 TBIs). In 2020, patients suffering TBI were less likely to have midline shift associated with their injury (7.8% vs 13.3% vs 17.8% vs 11.0%) (p<0.05). However, there was no difference in relative likelihood of mild, moderate, or severe TBI among the years. Likelihood of injury leading to death was unchanged from 2020 compared to each of the prior three years.

Conclusion: Social isolation and stay-at-home orders decreased neurotrauma volume, reduced high-impact traumas, and increased low-impact traumas. Those patients presenting with alcohol-associated trauma had higher levels in their system. Identifying these shifts in trauma presentations allows improved resource allocation and understanding the effects these mandates have on public health.

326. Periodic Components of the Electroencephalography Signal Correlate with Recovery of Consciousness after Traumatic Brain Injury

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Introduction: The prognosis for recovery of consciousness secondary to traumatic brain injury (TBI) has historically been guided solely by clinical metrics such as the Glasgow Coma Scale (GCS) or the Coma Recovery Scale (CRS-R). However, advances in electrophysiological techniques and neuroimaging may now enable identification of preserved brain function in unresponsive patients. We demonstrate that parameterization of electroencephalography (EEG) signal to control for the aperiodic background can reveal otherwise hidden oscillations that predict recovery from coma secondary to TBI.
Methods: Seventeen patients admitted to Stony Brook University Hospital for prolonged loss of consciousness due to TBI were enrolled. Both GCS and continuous EEG were obtained. A one-hour period with minimal sedation was identified and preprocessed in MATLAB using the Fieldtrip toolbox for each patient. This data was parameterized into periodic and aperiodic components using the FOOOF python package. The aperiodic background was subtracted from the signal to give true periodic band power in putative frequency bands (e.g. alpha, beta). These results were k-means clustered into two distinct clusters associated with more favorable (following commands within 60 days of injury) and unfavorable short-term outcomes.
Results: K-means clustering of the parametrized EEG recordings into periodic signals revealed two areas in the power spectrum space associated with favorable and unfavorable outcomes. Patients with relatively higher theta power combined with lower beta power had poor outcomes. Interestingly, these results were not detectable on the unparameterized EEG signals, which underscores the importance of parameterization to control aperiodic backgrounds.
Conclusion: Controlling the EEG signal for aperiodic background reveals hidden oscillations that correlate with recovery from coma secondary to TBI that are otherwise not evident on unparameterized EEG.

327. Neurosurgical Care and Outcomes for Pediatric ATV and Dirt Bike Crashes: A 10-Year Experience at a Level 1 Pediatric Trauma Center in the Southeastern United States

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Introduction: All-terrain vehicle (ATV) and dirt bike crashes frequently result in traumatic brain injury (TBI). Consistently updated reporting informs public health and education initiatives. We performed a retrospective study to evaluate the role of helmets in neurosurgical outcomes among pediatric patients involved in ATV and dirt-bike crashes over the last decade.
Methods: Data on all patients, who were involved in ATV or dirt bike crashes and evaluated at a regional level 1 pediatric trauma center between 2010-2019, were analyzed. Patients were excluded if the crash occurred in a competition (70), or if helmet status could not be determined (18). Multivariable logistic regression analyzed the effects of age, sex, driver status, mechanism of injury, and helmet status on the primary outcomes of 1) neurosurgical consult, 2) intracranial injury (including skull fractures), 3) prolonged hospitalization (upper 25th percentile), and 4) moderate or severe TBI (MSTBI).
Results: 680 patients (230, 34% helmeted; 450, 66% unhelmeted) were included. Helmeted patients were more frequently male (81% vs 66%). Drivers were more frequently helmeted (44.3%) compared to passengers (10.4%). Head imaging was performed in 70.9% of unhelmeted patients and 48.3% of helmeted patients. MSTBI (8.0% vs 1.7%) and neurosurgical consults (26.2% vs 9.1%) were more frequent in unhelmeted patients. Neurosurgical injuries including intracranial hemorrhage (16% vs 4%) and skull fractures (18% vs 4%) were more common in unhelmeted patients. No neurosurgical procedures were required among helmeted patients, 2.7% of unhelmeted patients required a neurosurgical procedure. After accounting for age, sex, driver status, vehicle type, and injury mechanism, helmet use significantly reduced the odds of neurosurgical consult (OR=0.250,95%CI0.14-0.447,p<0.001), intracranial injury (OR=0.172,95%CI0.087-0.337, p<0.001), and MSTBI (OR=0.244,95%CI0.079-0.758,p=0.015). Prolonged hospitalization was similar between the two groups (OR=0.919,95%CI0.557-1.519,p=0.74).
Conclusion: Helmet use remains problematically low among young ATV and dirt bike riders, especially passengers. Expanding the use of helmets among these children could significantly reduce the likelihood and severity of head trauma. Promoting helmet use among recreational ATV and dirt bike riders must remain a priority for both neurosurgeons and public health officials.

328. Do Neurosurgeons Receive More Patient Complaints Than Other Physicians? Describing who is Most at Risk and How We Can Improve

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Introduction: The number of unsolicited patient complaints (UPCs) about surgeons correlates with surgical complications and malpractice claims. Using a large national patient complaint database, we sought to: 1) compare the rate of UPCs for neurosurgeons to other physicians, 2) analyze risk of UPCs by neurosurgeon factors, and 3) describe the type of UPCs made about neurosurgeons.
Methods: Patient/family complaint reports among 36,265 physicians, including 423 neurosurgeons, 8,292 other surgeons, and 27,550 non-surgeons who practiced at 33 medical centers (22 academic; 11 regional) from 1/1/14 – 12/31/17 were coded using a previously validated algorithm used by the Patient Advocacy Reporting System (PARS).
Results: Among 423 neurosurgeons, 93% were male, and most (71%) practiced in academic medical centers. Neurosurgical subspecialties included: general practice (25%), spine (25%), tumor (16%), vascular (13%), functional (10%), and pediatrics (10%). Neurosurgeons had more UPCs per physician (8.68; 95% CI: 7.68 to 9.67) than non-surgeons (3.40; 95% CI: 3.33 to 3.47) and other surgeons (5.01; 95% CI: 4.85 to 5.17) (p<0.001). Neurosurgeons also had a higher percentage of physicians receiving a UPC (71.6%; 95% CI: 67.3% to 75.9%) than non-surgeons (50.2%; 95% CI: 49.6% to 50.8%) and other surgeons (58.2%; 95% CI: 57.1% to 59.3%) (p<0.001). Factors most associated with increased UPCs were younger age, measured as median medical school graduation year (1990.5 in 0 UPC group vs. 1993 in 14+ UPC group, p = .009) and spine subspecialty (13.4 mean UPCs in spine vs 7.9 mean UPCs in others, 95% CI: 2.3 to 8.5, p<0.001). The most common complaints were surrounding care and treatment, communication, and accessibility (p<0.001).
Conclusion: Neurosurgeons were more likely to generate UPCs than other surgical specialties, and more than two out of three neurosurgeons (71.6%) had at least one UPC during the study period. Prior studies have shown that feedback to physicians about behavior can result in fewer UPCs. These results suggest that neurosurgeons have opportunities to reduce complaints and potentially improve the overall quality of care delivered.

329. The Effects of Various Medical Malpractice Reform Laws On Malpractice Rates, Payouts and Premiums.

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Introduction: There are various medical malpractice reforms throughout the United States, differing by state. This has led to drastically different medical liability climates among the states. This study attempts to determine which reforms have a measurable effect on the medical liability climate and the number of neurosurgeons.
Methods: The medical liability climate was measured by the rate of malpractice claims, the average payout for malpractice claims and the average malpractice insurance premium for both general surgeons and OB/GYN in the state. The claims rate and payouts are for all physicians. Neurosurgery specific claims data was not available. The number of neurosurgeons in each state was obtained from the Area Resource File. Median household income was obtained from US Census data. The following reforms were examined: damage capitation, contributory negligence, expert witness reform, presence of a medical review panel, collateral source reform, joint and several liability, and attorney fee capitation. Independent sample t-tests were used to compare the measures of the liability climate between states with and without the listed reforms. Pearson correlation was used to compare median household with the measures of liability climate and neurosurgeon density. Multivariate regression was performed, including any factors with p<.200 on univariate analysis or Pearson correlation.
Results: Multivariate regression modeling on insurance premiums revealed that the presence of damage capitation significantly decreases the average malpractice insurance premium for general surgeons (B=29,515;p =0.006) and OB/GYN (B=47,349;p=0.001). Regression analysis did not reveal any factors with a significant effect on the average claim payout or the number of neurosurgeons per capita. There was only one independent variable which was associated with the malpractice claims rate at p<0.200. This was household income, which showed a significant negative correlation (Pearson coefficient=-0.278,p=.050), so regression modeling was not run for claims rate.
Conclusion: States with malpractice damage capitation had lower malpractice insurance premiums. States with lower average median household income have increased rates of malpractice claims.

330. The Impact of Socioeconomics and Race on Access to Neurosurgical Care in the United States.

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Introduction: Access to neurosurgical care varies greatly across the United States. This study attempts to uncover socioeconomic and racial/ethnic factors that correlate with disparate neurosurgical coverage.
Methods: All data was compiled from public sources and aggregated at the county level. Socioeconomic data were provided by the Brookings Institute. Racial/ethnicity data were gathered from the Centers for Disease Control (CDC), with the variable labels kept as defined by the CDC. Physician density was retrieved from Health Resources and Services Administration. Catchment areas were defined by counties with neurosurgical coverage, with every county lacking coverage integrated with the nearest county with coverage based on inter-county distances. Socioeconomic variables (average income, poverty rate, housing vacancy rate, and prime-age employment (PAE) rate), race (proportion of the population who self-identify as American Indian, Asian, Black, White, and Hispanic) and ethnicity (Hispanic vs non-Hispanic) were chosen as independent variables for analysis. Characteristics for each catchment area were calculated as the population-weighted average across all contained counties. Linear regression analysis modeling assessed neurosurgeon density per capita, and average distance to care.
Results: Modeling revealed that catchment areas with higher poverty rates (CE=0.64,CI:[0.34,0.93]) and higher PAE rates (CE=0.58,CI:[0.40,0.76]) and areas with higher proportions of Black residents (CE=0.21,CI:[0.06,0.35]) were significantly associated with greater neurosurgeons per capita. Meanwhile, catchment areas with higher proportions of Hispanic residents displayed lower neurosurgeon density (CE=-0.17,CI: [-0.30,-0.03]). Additionally, residents of catchment areas with higher housing vacancy rates (CE=2.37,CI:[1.31,3.43]), higher proportions of American Indian residents (CE=4.97,CI:[3.99,5.95]) and higher proportions of Hispanic residents (CE=2.31,CI:[1.26,3.37]) must travel farther, on average, to receive neurosurgical care while people living in areas with lower income (CE=-2.28,CI:[-4.48,-0.09]) or higher proportion of Black residents (CE=-3.81,CI: [-4.93,-2.68]) travel a shorter distance.
Conclusion: Many Factors correlate with neurosurgical coverage in the United States, most notably with Hispanic and American Indian patients having reduced access to care. These findings highlight the interwoven associations between socioeconomics, race, ethnicity, and access to neurosurgical care nationwide.

331. Neurosurgeons in 2020: The Impact of Gender on Neurosurgical Training, Family Planning and Workplace Culture

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Introduction: A 2008 Women in Neurosurgery Committee white paper called for increased women applicants and decreased women's attrition in neurosurgery. However contributing factors (work-life balance, lack of female leadership, workplace gender inequality) have not been well characterized so specific actions cannot be implemented to improve these professional hurdles. We provide an update on the experiences of neurosurgeons in 2020 with these historical challenges.
Methods: An anonymous online survey was sent to all ACGME accredited U.S. neurosurgical programs, examining demographics and experiences with mentorship, family life, fertility, and workplace conduct.
Results: A total of 115 respondents (64 men, 51 women) 25-67 years old, from 49 different U.S. residencies. Mentorship rates were very high amongst men and women in medical school and residency. Women, however, were significantly more likely to have a woman mentor in residency than men. During residency, 32% of women versus 42% of men had children, and significantly fewer women interested in having a child were unable to have a child in residency, compared to men. Significantly more women versus men had a child only in a non-clinical year (56.3% versus 19.0%, respectively). 32% of women and 39% of men reported childbearing/rearing difficulty. The major difficulty for men was stress, whereas women reported physical challenges of pregnancy itself (workplace teratogens, morning sickness, etc.). Failed birth rates peaked during residency (0.33) versus before (0.00) and after residency (0.25). Women (80%) experience micro-aggressions in the workplace significantly more than men (36%) (p<0.001). 100% of micro-aggressions towards women neurosurgeons were regarding their gender or qualifications, compared to 3% for men (p<0.001). The most common overall perpetrators were senior male residents and attendings, followed by male patients (against women) and female nurses/mid-level providers (against men).
Conclusion: Accurate depictions of neurosurgery experiences, and open discussions of potential impacts of gender, may allow for 1) decreased attrition due to more accurate expectations and 2) improved characterization of gender differences in neurosurgery so the profession can work to address gender inequality.

332. Racial and Socioeconomic Minorities May Have Lower Quality of Life and Lower Chance of Returning to Work Following Surgery for Cervical Myelopathy: Analyses from the Quality Outcomes Database (QOD)

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Introduction: Race and socio-economic-status (SES) have been shown to impact not only access to care, but also outcomes of patients undergoing treatment for various pathologies. In the current study, we sought to investigate the differences in outcomes based on race and SES, among patients undergoing surgery for cervical myelopathy.
Methods: For the current study, we queried the Quality Outcomes Database (QOD) cervical module for patients undergoing surgery for cervical myelopathy between 2016 and 2018 at 14 of the highest enrolling sites. The primary predictors of interest for our study were race, ethnicity and socioeconomic status (SES) index.
Results: A total of 1,151 patients were included, of which 74.97%(n=863) were non-Hispanic Caucasians, 15.3%(n=176) were African Americans, 3.2(n=37) were Hispanic Caucasians while 65.8%(n=75) were included in other race group. Per SES grouping, 51.5% (n=593) were found to be from high SES quartiles (1 or 2), while 49.5% (n=558) were from low SES quartiles (3 or 4). On univariate analysis, among those belonging to low SES, African Americans and Caucasian Hispanic had significantly longer length of stay (p=0.041), African American patients had higher non-routine discharge (p=0.04), significantly lower patient satisfaction at 3 (p=0.01) and 12 months (p=0.014), and lower quality of life index at 3 (p=0.01) and 12-months (p<0.001). On multivariable logistic regression, African American patients, compared to non-Hispanic Caucasians, were less likely to return to work (OR: 0.348, 95% CI: 0.146-0.833,p=0.017). Moreover, we also found the interaction between race and SES for African American from low SES to be significant for quality of life at 1 year (B=-0.082,p=0.036).
Conclusion: After adjusting for all relevant demographic, clinical and operative characteristics, these results from a national spine-registry suggest that African-Americans may be less likely to return to work and that African-Americans from lower SES may have lower quality of life after surgery for cervical myelopathy. These findings highlight the need for addressing racial and socioeconomic disparities for patients undergoing cervical spine-surgery.

333. The Aging Neurosurgical Workforce

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Introduction: In recent years, an increased focus has been placed on the recruitment and retention of neurosurgeons to combat a workforce shortage. Trends in the neurosurgeon community must be continually analyzed to ensure adequate coverage of care for the general population. This study aims to characterize the average years of practice of neurosurgeons in 2020.
Methods: Data was obtained via the Physician Compare National database provided by the Center for Medicare and Medicaid Services. The year of graduation from medical school of each neurosurgeon is provided by this database and was used to calculate the years of practice. Surgeons were separated into groups that practiced for 0-10 years, 11-20 years, 21-30 years, 31-40 years, 41-50 years, and 51 or more years.
Results: In 2020 there were a total of 4,931 neurosurgeons in the US with an average age of practice of 33.4 years. Of this, a total of 522 surgeons (10.6%) had been practicing from 0-10 years, 1,604 surgeons (32.5%) from 11-20 years, 1,311 surgeons (26.6%) from 21-30 years, 1,002 surgeons (20.3%) from 31-40 years, 396 surgeons (8%) from 41-50 years, and 12 surgeons (1.7%) from 51-60 years.
Conclusion: We believe this data contributes to the sense of urgency in the need for greater neurosurgical recruitment efforts. With almost 30% of neurosurgeons practicing for over 30 years, it becomes concerning whether the current level of incoming residents will be enough to replenish the aging workforce. Additionally, as the US population continues to grow, so too does the demand for neurosurgical care. Future studies are warranted into how to adequately address the disparity between neurosurgical workforce supply and demand in coming years.

334. Gender Equity of Promoting Practices in Academic Neurosurgery in the United States

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Introduction: We investigated any potential association between gender and promoting practices, and identified factors associated with full professorship and chair/directorship among academic neurosurgeons in neurosurgical training institutions across the United States.

Methods: This is a cross-sectional study of the current clinical faculty at academic institutions from the AANS Neurosurgical Residency Training Program Directory. Neurosurgical faculty from academic institutions within the US with sufficient available data (time out of residency, professorship status, specialty information, and h -index) were included. Differences in demographics, training, and appointments were compared between male and female neurosurgeons. Predictors of professorship and chair/directorship were identified using multivariable models.

Results: 1606 faculty members were examined (female n=167; male n=1439). Women were more likely to have completed training more recently (p<0.0001), to have received fellowship training (p=0.003), to have trained in pediatrics (p<0.0001), and to hold the title of assistant professor (p<0.0001) compared to men. Men were more likely to be full professors (p=0.0002), to hold chair/directorship positions (p=0.003), and to have a higher Scopus h -index (p<0.0001). In a multivariable analysis, years out from residency training was a significant positive predictor of full professorship (p<0.001), but not for chair/directorship (p=0.193).Chair/directorship was a significant positive predictor of full professorship (p<0.001), and h -index was a significant positive predictor of full professorship (p<0.001) and chair/directorship (p<0.001). Gender was not found to be a significant predictor of full professorship (p=0.115) or chair/directorship (p=0.391).

Conclusion: While significantly more men currently hold higher leadership positions in academic institutions in the US, gender was not a significant predictor of either full professorship or chair/directorship in multivariable analysis. This suggests a lack of identifiable gender discrimination in promoting practices at academic neurosurgical institutions within the US. These results may serve as encouragement to female neurosurgeons who are looking to advance their careers in academic neurosurgery.

335. Economic Impact of Pre-Operative Opioid Use in Neurosurgery

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Introduction: The opioid epidemic has led to a rapid increase in associated morbidity and mortality, but its impact on neurosurgical patients remains unclear. We sought to assess the economic impact of pre-operative opioid use following craniotomy.

Methods: All patients undergoing craniotomy or craniectomy between January 2013 and October 2018 were retrospectively evaluated. Baseline demographics, socioeconomic factors, and surgical metrics were collected. Outcome variables included length of ICU duration, length of hospital stay (LOS), and readmission rates. Pearson chi-square, independent t-test, and Mann-Whitney U test analyses assessed differences in categorical, continuous, and ordinal variables. Univariate and multivariable regression analyses were used to correlate between variables and outcome measures. Daily incurred costs of ICU and hospitalization stays were estimated from hospital averages.

Results: A total of 1715 patients were included, with 27.7% utilizing pre-operative opioids. Opiate naïve patients were more likely to be female and employed, and less likely to be uninsured or use IV drugs or tobacco. Patients with a pre-operative history of opioid use were more likely to have higher American Society of Anesthesiologists physical classification (ASA) scores.   After controlling for these confounders, patients with pre-operative opioid use required longer ICU care (median 3 [IQR 1,8] v 1 [0,3]; β 2.699, 95%CI 1.980-3.418, p<0.001), longer LOS (median 11 [IQR 6,20] v 5 [3,10]; β 7.535, 95%CI 6.270-8.801, p<0.001), and higher readmission rates (31.9% v 23.7%; OR 1.509, 95%CI 1.190-1.913, p<0.001). Given hospital daily average costs of ICU ($4000) and regular ward ($2900) stays, pre-operative opioid use would be expected to incur an additional $24,500 per patient.

Conclusion: Patients with a pre-operative history of opioid use require greater utilization of healthcare resources following craniotomy. Given the increase in opioid use and additional costs incurred during hospitalization and potential readmission, this generates a significant burden on the healthcare system.

336. The Availability and Utility of Online Cost Information for 15 Non-Emergent Neurosurgical Procedures in 8 Major U.S. Healthcare Markets

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Introduction: There is a paucity of evidence regarding the cost information that neurosurgical patients may use to inform their choices regarding surgical care. Building on recent literature, we sought to characterize the amount and utility of publicly-available cost information for non-emergent neurosurgical procedures.

Methods: Using Google, we searched for and recorded geographically-relevant cost information for 15 non-emergent neurosurgical procedures across 8 major U.S. healthcare markets. Cost information was characterized by website type and by the disclosure of itemized costs and discounts. In comparing cost estimates between websites, we took note of differences in presentation and accessibility of cost data.

Results: Of 2356 included websites, 228 (9.7%) yielded geographically-relevant cost information. Although accounting for only 15.8% of total search results, price transparency websites provided the highest proportion of cost information (74.1%), followed by clinical sites (19.3%), and other related sites (5.3%). Cleveland and Philadelphia had the largest proportion of clinical (5.2%) and price transparency (13.5%) sites with geographically-relevant price information, respectively, demonstrating city-specific variability in cost data. Most price transparency sites offered "fair" procedure prices, although data sources and analytical methods were not consistently disclosed. Most clinical websites, save two Houston-based clinical sites, provided only bundled price ranges, without clear itemized cost breakdowns, while healthcarebluebook.com was the only price transparency site to delineate services included in cost bundles. Moreover, only one clinical site provided information on discounts (low-cost MRI for the uninsured) that might be available to patients.

Conclusion: Under 10% of websites generated through targeted web searches yield geographically-specific cost information for non-emergent neurosurgical imaging and operative procedures. Available cost information varies widely by region and website type, often fails to credit its data sources, and rarely includes itemized breakdowns or discount availability. Variability and ambiguity of these data—as currently disclosed—likely limits their benefits to cost-conscious healthcare decision-making.

337. Impact of Race on Care, Readmissions, and Survival for Patients with Glioblastoma: A National Analysis

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Introduction: It has previously been reported that race is associated with survival in various types of primary cancer. In glioblastoma specifically, previous analyses have demonstrated that Non-Hispanic Whites may have poorer long-term survival compared to other races. However, these prior studies do not examine variation in short term survival or issues related to quality of care as reflected by readmissions.

Methods: The NCDB was queried for patients diagnosed with glioblastoma over the past decade, which covers approximately 70% of all new cancer diagnoses in the United States. Multivariable Cox regression analyses were performed to evaluate patient (such as age at diagnosis, race, Charlson-Deyo score) and treatment variables (such as treatment modality and facility type) associated with outcomes, which included 30-day readmission, 30- and 90-day mortality, and overall survival.

Results: A total of 103,652 glioblastoma patients were identified. White Non-Hispanics had the highest rates (p<0.001) of treatment, including total resection (31%) and radiation (70%). Black non-Hispanics had the highest rates of unplanned re-admission (7.6%) within 30 days (p<0.001). Asian Non-Hispanics had the lowest 30-day (3.2%) and 90-day mortality (9.8%) when compared to other races, whereas White non-Hispanics had the highest (p<0.001). Compared to White Non-Hispanics, Black Non-Hispanics (HR: 0.88, p<0.001), Asian Non-Hispanics (HR: 0.72, p<0.001), and Hispanics (HR: 0.69, p<0.001) had longer overall survival.

Conclusion: Differences in treatment and outcomes exist between races. Despite the higher rates of treatment and lower readmissions, White Non-Hispanics exhibited the lowest overall survival, and this finding was durable even after excluding from analysis the patient who died within the first 90-days, suggesting possible biological differences. Non-Hispanic whites were less likely than Hispanics and non-Hispanic Blacks to be re-admitted within 30 days, suggesting disparities in short term outcomes. Further studies are needed to elucidate the etiology of these race-related disparities and to improve outcomes for all patients.

338. Medicaid Expansion is Associated with Increased Administration of Standard-Of-Care Therapy and Lower Uninsured Rates in Glioblastoma Patients

Jonathan Wesley Borden (Provo, UT); Alister Sharp; Adela Wu, MD; Michael Jin, BS; Erqi Pollom, MD; Scott Soltys, MD; Reena Thomas, MD; Susan Hiniker, MD; Seema Nagpal, MD; Melanie Hayden-Gephart, MD; Michael Lim, MD; Gordon Li, MD

Introduction: The Patient Protection and Affordable Care Act (ACA) allowed states to expand Medicaid eligibility to include low-income adults. Glioblastoma is the most common form of malignant brain cancer with a median survival of 19.8-24.5 months. Our study was developed to explore how the state-level ACA adoption impacted insurance coverage and patient care to uncover future avenues for care optimization.

Methods: With a cohort of 70,553 GBM patients treated during 2007-2015 across the United States from the National Cancer Database, we assessed patterns of administration of standard-of-care therapy, healthcare insurance coverage, and temporal patterns of care and their relationships with the ACA.

Results: Medicaid expansion was associated with an increase in the proportion of patients receiving standard-of-care therapy in expansion states (from 52.2% in 2010-2013 to 54.2% in 2014-2015 ($p<0.001$)), but not in non-expansion states ($p=0.178$). Medicaid expansion was also associated with a decrease in uninsured rate (4.2% in 2013, 3.0% in 2014, $p<0.001$). Medicaid expansion was not associated with any changes in time to first treatment for our cohort ($p=0.621$), but it was loosely associated with an increase in time from first treatment to adjuvant therapy ($p<0.001$).

Conclusion: Medicaid expansion was associated with increased administration of standard-of-care therapy and lower uninsured rates in glioblastoma patients. As increasing attention is directed towards the impact of healthcare policy on clinical outcomes, describing the implications of past policy changes may help guide legislators and clinicians towards more efficient and effective approaches to provide quality healthcare to patients. Funding: We gratefully acknowledge the Simmons Center for Cancer Research for their funding in assistance of this project

339. An Assessment of Neurosurgery Resident Clinic and Socioeconomic Training: The 2013 Council of State Neurosurgical Societies Post-Residency Survey Results

Owoicho Adogwa, MD, MPH (Dallas, TX); James Caruso, MD; Catherine Mazzola, MD; Michael Steinmetz; Scott Simon, MD; Clemens Schirmer, MD, PhD; Owoicho Adogwa, MD, MPH

Introduction: The Council of State Neurosurgical Societies (CSNS) surveyed neurosurgeons applying for oral board certification in 2008 to assess their preparedness to practice. This survey was repeated in 2013 for a subsequent group of board applicants to evaluate the quality of neurosurgery training and identify opportunities for improvement.

Methods: Applicants for the American Board of Neurological Surgeons (ABNS) oral examination from 2008-2013 were provided an anonymous survey focused on clinical and socioeconomic skills. Survey responses were compared with the published results of a similar survey using an inferential statistical analysis.

Results: 110/655 neurosurgeons responded (response rate 16.8%). Significantly more respondents from the 2013 survey felt prepared to perform the following techniques: Angiography, endoscopic surgery, anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), kyphoplasty, deep brain stimulation. Significantly more respondents in 2013 attested to receiving appropriate education on Health Insurance Portability and Accountability Act (HIPAA) and pay-for-performance practice models of healthcare. However, significantly fewer respondents in 2013 felt prepared in open vascular neurosurgery techniques. In both surveys, fewer than 35% of respondents felt adequately prepared in endovascular neurosurgery techniques, medical coding, negotiating an employment contract, and issues regarding practice management and the economics of neurosurgery.

Conclusion: The 2013 survey suggests that candidates for board certification in neurosurgery perceive themselves to be adequately prepared to independently perform nearly all neurosurgical procedures. However, additional work is required to optimize neurosurgery training in endovascular procedures and the socioeconomic aspects of neurosurgery practice..

340. Toward Diversity, Equity, and Inclusion: A Worldwide Survey of Female Neurosurgeons

George William Koutsouras, MPH, MD (Syracuse, NY); Zulma Tovar Spinoza, MD; Sandi Lam, MD; Lu Zhang, PhD; Nelci Zanon

Introduction: The global neurosurgery workforce is a dynamic group of individuals. We sought to characterize the demographic features of the women in the global neurosurgery community and to better understand the factors important in career and personal development.

Methods: A 58 item cross sectional survey was developed based on precedent surveys published in medical and surgical fields on career development, career satisfaction, and work-life balance. It was distributed internationally, targeting female neurosurgeons between October 2018 until December 2020 via an anonymized online platform. We utilized descriptive statistics and chi square analyses where appropriate: a p value of <0.05 was established for significance.

Results: There were 237 total responses. 40% were between the ages of 26-35. 45% identified themselves as the only female neurosurgeon in their practice. 43% stated that their department was supportive in advancing female neurosurgeons into leadership roles. 38% had been involved in leadership positions in organized neurosurgery groups. The vast majority were satisfied with their profession. Sixty three percent reported a salary comparable to their male colleagues. Among respondents holding an academic position, there was a significant difference between career satisfaction and various factors commensurate with more years in practice, fewer hours worked or clinic days per week, and operating room days per month. In personal life, 40% were without children in their families. 60% of respondents postponed their decision to get pregnant because of resident or work-related influences. In regard to pregnancy, 45% believed their work environment supported them.

Conclusion: The survey presents perspectives from 237 women about the different aspects of gender equity in the profession of neurosurgery. This is an initial step to describing the state of the global neurosurgery workforce and its gender representation. Through quantitative and qualitative data, this survey may provide preliminary information that could be applied locally and internationally to promote diversity, equity, and inclusion for a stronger field to serve our patients and advance health and science.

400. Trigeminal Nerve Stimulation Mitigates the Consequences of Cortical Spreading Depolarizations after Subarachnoid Hemorrhage

Kevin A. Shah, MD (Manhasset, NY); Timothy White, MD; Keren Powell, BA; Raj Narayan, MD; Chunyan Li, PhD

Introduction: Cortical spreading depolarizations(CSD)and neurovascular decouplinghaverecently gained interest as pathologic mechanisms of delayed cerebral ischemia(DCI)after aneurysmal subarachnoid hemorrhage(SAH).The trigeminal nerve richly innervates cerebral blood vessels and can dramatically augment cerebral blood flow in the setting of cerebrovascular disease. We investigated the ability ofelectricaltrigeminal nerve stimulation (TNS) tolimitCSDs and improve CSD-induced hypoperfusionin an animal model of DCI.

Methods: An endovascular perforation model of the left middle cerebral artery was used to induced SAH in21Sprague-Dawley rats.In the peak DCI period,craniotomies were performed over the left middle cerebral artery (MCA) territory for implantation of Ag-AgCl electrodes to monitor for CSDs.A bipolar electrode was inserted into the left infraorbital nerve and rectangular biphasicstimulationpulses were delivered(50 Hz, 0.5 – 2.5 V,5 secON/5 secOFF)for 1 minuteevery 10 minutes. DC-ECoGrecordings were obtainedover70 minutes.After 48 hours, HIF-1a immunopositive neurons were quantifiedwithinthe CA1 region of the ipsilateral hippocampus.

Results: TNS decreased thenumberof CSDeventsby 58.8% (4.0vs. 9.7 events persession, p<0.05). There was no difference in the amplitude or duration of individual CSDeventsbetween theTNSgroup andcontrols(amplitude: 4.2 vs. 3.7 mV, p=0.09;duration: 110 vs 115 sec, p=0.60). TNS treatment augmented the hyperemic response to episodes of CSDscompared with controls (+139%vs. +70% over baseline, p<0.05), and maintained cerebral perfusion in the distalMCAterritory (94% vs. 70% of baseline, p<0.05).Animals that received TNS displayed substantially reduced HIF-1a immunopositivity (0.9 vs. 45.5 neurons per HPF, p<0.05).

Conclusion: TNS suppresses CSDs after SAH and minimizes cerebral hypoperfusion associated with DCI. These resultssuggest a novel therapeutic strategy in preventing delayed cerebral ischemia.

401. PPIL4, A Novel Wnt Signaling Molecule, is Indispensable for Cerebrovascular Development and Mutated in Intracranial Aneurysm Patients.

Tanyeri Barak (New Haven, CT); Emma Ristori; Danielle Miyagishima; Andrew Prendergast; Kristopher Kahle; Stefania Nicoli; Murat Gunel

Introduction: Intracranial aneurysm (IA) is a significant health burden affecting nearly 6 million people in the United States with an estimated prevalence of 3.2% worldwide. However, conclusive identification of specific genes or molecular pathways involved in brain aneurysm formation and rupture has yet to be elucidated.   Using whole exome sequencing (WES) of over 400 European IA patients, we identified significant enrichment of rare and deleterious mutations of PPIL4. Furthermore, using in-vivo models we identified a novel PPIL4-dependent WNT signaling mechanism in IA pathogenesis.
Methods: We performed WES on 434 European IA cases followed by a mutational burden analysis between IA cases and a European control group of 1443 unaffected individuals, and European subjects in the gnomAD database.   Two-sided Fisher exact test was used to determine the significance of the enrichment of rare (ExAC MAF<0.0001) and deleterious variants consisting of loss of function and deleterious missense mutations (MetSVM-D). Mutant ppil4 line was generated using Crispr-CAS9 in zebrafish.
Results: Burden analysis revealed a significant enrichment of rare & deleterious PPIL4 variants in European IA cases when compared to 1443 controls (OR=INF., Fisher P= 2.9 x10-4) and gnomAD (OR= 11.51, Fisher P= 5.34 x10-4). Compared to wildtype zebrafish, ppil4-/- model displayed cerebral hemorrhage (P<0.001) and loss of cerebrovascular branches (P<0.001). Using transgenic zebrafish line Tg(7xTCF-Xla.Siam:nlsmCherry; kdrl:eGFP)   we demonstrated that ppil4 abrogation reduces Wnt signaling activity dramatically in zebrafish cerebrovascular endothelial cells in vivo (P<0.001). Furthermore, using co-immunoprecipitation experiments we showed that wildtype PPIL4 binds to JMJD6, an angiogenesis regulator and a WNT signaling molecule, and potentiates WNT signaling activity (P<0.0001), while this interaction and WNT signaling transactivation were lost with IA-mutations.
Conclusion: Our findings identify a novel PPIL4-dependent Wnt signaling mechanism indispensable for cerebrovascular development and shed novel insight into the pathogenesis of human IA, with diagnostic and clinical implications.

402. White Matter Integrity of Ipsilesional Cerebellar Lobule V Correlates with Motor Recovery in Chronic Stroke Patients Undergoing Brain-Computer Interface Therapy

Sarah Chiang (Saint Louis, MO); Siddharth Rana, BA; Joseph Humphries, BS; Eric Leuthardt, MD

Introduction: We aimed to determine if white matter (WM) tract integrity in chronic stroke patients with upper extremity weakness prior to brain-computer interface (BCI) rehabilitation predicted motor recovery. Mean diffusivity (MD) was calculated from diffusion tensor imaging (DTI) as an indication of axonal and myelin integrity in WM and is a biomarker for motor recovery in subacute stroke.
Methods: DTI scans were performed with 9 chronic (≥6 months post-stroke) hemiplegic stroke patients within 2 weeks of initiating a 12-week BCI rehabilitation program. Pre-therapy MD was calculated using DSI-Studio for WM tracts in each patient. Motor function was evaluated pre- and post-therapy using the upper extremity portion of the Fugl-Meyer Assessment (UEFM). Relationships between pre-intervention MD for cerebral and cerebellar hemispheres and changes in UEFM scores were estimated with Spearman correlations. Region-based and tract-based statistical analyses were conducted for atlas-defined segments of the significantly correlated hemispheres. A multiple linear regression model using region-based and tract-based MD values was applied to the significantly correlated cerebellar regions.
Results: Ipsilesional pre-therapy cerebellar MD values were positively correlated with UEFM change (ϱ=0.78, p=0.01). Three regions within this hemisphere showed strong correlations (ϱ>0.7) between pre-therapy MD and UEFM change for both region-based and tract-based statistical analyses: lobules V, VIIb, and VIIIa. The lobule V multiple linear regression correctly classified each patient's recovery or non-recovery (R^2=0.64, p=0.049).
Conclusion: Pre-therapy, ipsilesional cerebellar mean diffusivity is a stronger correlate to motor recovery than contralesional cerebellum and both cerebral hemispheres. Within the ipsilesional cerebellum, lobule V demonstrated significant correlation to motor recovery and correctly classified motor recovery or non-recovery in all patients. Lobule V has previously been shown to play a role in execution of voluntary hand movements and sensorimotor processing. These results suggest pre-therapy WM integrity in lobule V may predict motor recovery.

403. Incidence and Outcomes of Posterior Circulation Involvement in Moyamoya Disease

Seth Stravers Tigchelaar, PhD (Stanford, CA); Allan Wang; Yiping Li; Gary Steinberg

Introduction: Moyamoya disease (MMD) is a progressive, occlusive disease of the internal carotid arteries and their proximal branches, with the subsequent development of an abnormal vascular network of small, weak blood vessels that are prone to rupture. Steno-occlusive changes in the posterior cerebral arteries (PCA) may contribute to worse outcomes in MMD patients, however, there is a paucity of information on the incidence and natural history of MMD patients with PCA disease.

Methods: We retrospectively reviewed the charts of patients with MMD treated between 1987 and 2019. Demographics, peri-operative outcomes, and radiological phenotypes were recorded for 450 patients. PCA disease was scored as either 0 (no disease), 1 (mild), 2 (moderate), or 3 (severe, or occluded).

Results: Out of 450 patients, 164 (34.4%) had concurrent PCA disease. In patients with PCA disease, the extent of occlussion was mild in 56 (34%), moderate in 41 (25%), and severe in 67 (40.9%) patients. In total, there were 319 females (70.9%), with a higher proportion of female MMD patients having severe or moderate PCA disease ($p=0.038$). Patients with worse PCA disease had higher Suzuki grades ($p<0.0001$), more extensive collateral angiopathy ($p<0.0001$), more frequent cerebrovascular accidents ($p=0.012$), and a greater frequency of post-operative ischemic complications ($p=0.019$). Peak modified Rankin Scale (mRS) scores were higher in patients with any severity of PCA disease ($p=0.0006$). Over a mean follow-up of 6.94 ± 4.16 years, 28 patients (8.86%) developed new or progressive PCA disease. Bilateral disease was present in 66 patients (14.7%) and was associated with higher Suzuki grades ($p<0.0001$), more extensive collateral angiopathy ($p<0.0001$), and greater post-operative ischemic complications ($p=0.011$). Peak mRS scores were higher in patients with bilateral disease compared to patients with no PCA disease ($p<0.0001$).

Conclusion: PCA disease involvement is associated with higher rates of ischemic peri-operative complications and poor functional outcomes likely due to reduced collateral flow. Progression of PCA disease is not uncommon. Future studies are needed to assess the impact of PCA disease progression on long-term outcomes.

Cerebrovascular Section Best Basic Scientific Paper Abstract Award

404. Cannabis Use and Delayed Cerebral Ischemia Following Aneurysmal Subarachnoid Hemorrhage: A Propensity-score Adjusted Analysis

Joshua Catapano, MD (Phoenix, AZ); Kavelin Rumalla; Visish Srinivasan, MD; Ashutosh Jadhav, MD; Andrew Ducruet, MD; Felipe Albuquerque, MD; Michael Lawton, MD

Introduction: There is a growing body of evidence linking cannabis use to cerebrovascular disease, including stroke. Pathophysiology is unknown but recent studies suggest a role of multifocal intracranial stenosis, oxidative stress, and cerebral mitochondrial dysfunction. The present study sought to investigate the effect of cannabis and other commonly used recreational drugs on outcomes in patients with aSAH.

Methods: Records were reviewed for all patients with aSAH treated at a single quaternary center from August 1 st , 2007 to July 31 st , 2019. The predictor variable of interest was substance use (cannabis, cocaine, amphetamines, tobacco). The primary outcomes analyzed were delayed cerebral ischemia (DCI), poor functional outcome (modified Rankin Score, mRS > 2), and mortality. Propensity scores for outcome variables were computed with adjustment for age, sex, pre-existing comorbidities, GCS score, Hunt-Hess score, Fisher grade, aneurysm type/size/location, and type of treatment (endovascular vs. microsurgery).

Results: Of the 1014 patients treated for aSAH the rate of DCI was 36.2%. The rate of DCI was significantly higher in patients with UDS+ for cannabis (51.1% vs. 35.5%, P=0.033). Tobacco, methamphetamine, and cocaine use were not associated with DCI. In propensity score adjusted multivariable regression analysis, cannabis use was independently associated with increased likelihood of DCI (OR: 2.30, 95% CI: 1.18-4.50, P=0.014). In further multivariable analysis, DCI was an independent predictor of mortality (OR: 2.19, 95% CI: 1.41-3.41, P<0.001) and poor long-functional outcomes (mRS > 2, OR: 2.79, 95% CI: 2.08-3.78, P<0.001).

Conclusion: The present study demonstrates a significant relationship between cannabis use and development of DCI, which is a significant contributor to morbidity and mortality following aSAH. This study contributes to existing evidence of linking cannabis to cerebrovascular disease.   Given recent popular trends, it is essential to evaluate the risks and benefits of this potential therapeutic agent and recreational drug.

Vesalius Award

405. An early case of successful peripheral nerve repair in 1880: Francis L. Parker MD

Zachary S. Hubbard, MD (Charleston, SC); Fraser Henderson, MD; Sunil Patel, MD

Introduction: The modern technique of epineural suture repair, along with detailed reporting of functional restoration, came from Heuter in 1873. While there is extensive history of peripheral nerve surgery throughout the recorded history leading up to the 1800s, there is little reported American literature available. It was at the same time that Schwann, Nissl, and Waller were publishing their work on nerve anatomy and physiology that Francis Lejau Parker was born. The South Carolina native would go on to describe one of the first American cases of peripheral nerve repair with restoration of function. Francis L. Parker was born in 1836 in Abbeville, South Carolina. He attended the South Carolina Military Academy in 1855 and graduated from the Medical College of Charleston in 1858. He volunteered for military service at the beginning of the Civil War. At the end of the War, Parker returned to Charleston, South Carolina where he joined faculty of the Medical College as Professor of Anatomy in 1870. He ultimately became Dean of the College in 1891, where he served until his retirement in 1906. Under his leadership, Women were admitted for the first time in 1894. He opened the Dental School in Charleston in 1900. While notable for his tenure at the Medical College, he also gained local notoriety with being the first American surgeon to suture a severed nerve with restoration of function. The case dated back to 1880, in his 10th year as professor when a patient presented to his clinic with severing of the posterior interosseous nerve. The details of this case come from the archives of the South Carolina Medical Association, available through the Waring Historical Library at the Medical University of South Carolina. The authors reviewed these records in detail and provide a case illustration not previous reported in modern literature involving nerve repair. The history, neurological examination, and detailed description of the case provide insight to the adroit surgical skills of Dr. Parker.

406. Shocking Revelations: Failures in the Management of Head Injury during World War I

T Forcht Dagi, MD, DMedSc, FRCSEd, FAANS(L) (Newton, MA); Alexander Dagi

Introduction: The surgical management of penetrating head injury made huge advances during World War I (WWI). Nevertheless, a pervasive confusion around the neurological effects of blast injury and the psychiatric syndrome called "shell shock" blocked comparable progress in the management of closed head injury.
Methods: This study analyzes the overlapping histories of the concepts, classifications and management of penetrating and closed head injury during and immediately after the War.
Results: Notwithstanding the introduction of artillery to Western warfare in the 14th century, nothing compared to the cannonade of 432,000 shells during the Battle of the Marne, between the 6th and 12th of September, 1914. Of the two million combatants, close to 25% were killed or wounded. Disturbingly, some casualties, including many killed in action, bore no visible wounds. It appeared as though a "dark, invisible force had… passed through the air and was inflicting novel and peculiar damage to men's brains." These casualties seemed to suffer from "the actual explosion itself, and not…the missiles set in motion." This constitutes as an early description of blast injury to which the term "shell shock" was quickly and uncritically applied. The medical community was bewildered. The "shell shock" nosology propagated a number unfortunate concepts rooted in the 18th and 19th centuries that wrongly attributed shock to neurological, rather than to cardiovascular causes. It also disregarded distinctions between neurological and psychiatric pathology; overlooked the etiological contributions of traumatic stress; and promoted a self-righteous, virtue-laden view of combat and courage that incorporated and encouraged a dismissive attitude to injuries without wounds.
Conclusions: Even as the surgical treatment of penetrating head injury successfully reduced mortality rates, elevated the status of neurosurgery and changed attitudes to neurosurgical intervention, and neurological rehabilitation, decades would pass before the consequences of the "dark invisible force" would be substantially unraveled.

407. A Scientific and Historical Study of Michelangelo's Life, Renaissance Neurosciences and Vesalius' Dissections to Decode Encrypted Neuroanatomical Visual Language in the Sistine Chapel.

Luis E. Savastano, MD (Rochester, MN); Robert Morreale, MS; Philip Eliasoph, PhD; Teo Forcht Dagi, MD; Daniel Nijensohn, MD, PhD

Introduction: Michelangelo's frescos in the Sistine Chapel have been traditionally considered to represent the catholic dogma of the Creation. However, studies have suggested that Michelangelo concealed anatomical information of human brains in these drawings. This study was conducted to scientifically analyze and interpret these frescos in the appropriate historical, anatomical and philosophical context.
Methods: Brain function theories during the Renaissance were reviewed to contextualize Michelangelo's work in time and space. Anatomical representations and dissection techniques of that specific timeframe, available to Michelangelo were identified and reproduced in ten cadaveric human brains. Anatomical specimens were used as art models to analyze Sistine Chapel's frescos in light of contextual philosophical ideas.
Results: Galen's Ventricular Theory of brain function was still dominant during the Renaissance, as evidenced by Da Vinci's folios. Michelangelo performed human dissections together with anatomist Colombo, who trained under Vesalius, author of "De humani corporis fabrica". This work includes extensive neuroanatomical iconography embodying Galen's theory. We replicated Vesalius' dissections to generate neuroanatomical models. We support the following contextual interpretations: 1) "Separation of light from darkness": represents the dorsal brainstem, known to control arousal and when damaged, to cause coma; 2) "Creation of the Sun and the Moon": represents the eyes, optic nerves and chiasm, the organ of sight, known to result in blindness if damaged; 3) "Creation of Adam": representation of the mid-sagittal section of the human brain depicting the ventricular system, providing mankind with the ability of thought; 4) "The Last Judgement": A coronal section of a brain with lateral and third ventricles   provides the substrata to interpret and judge the environment. In addition, the "Last Judgement" presents Colombo starting a dissection on the body of Jesus.
Conclusions: We conclude that Michelangelo's frescoes evoke philosophical meaning through an encrypted neuroanatomical visual language.

408. The Historic Evolution of Intracranial Pressure Concepts: 2 Centuries of Challenges

Josué da Silva Brito (Paracatu, Brazil); Jassiara da Silva; Lara Mariana Rosa; Sérgio Brasil; Gustavo Frigeri; Nícollas Rabelo

Introduction: There is a consensus on the importance of monitoring intracranial pressure (ICP) during neurosurgery, and this monitoring is responsible for reducing mortality during procedures. Current knowledge about ICP has been built thanks to more than two centuries of research on brain dynamics. Different anatomists and physiologists have contributed to the understanding of how intracranial volumes behave under normal and pathological conditions.
Methods: This historical note revisits the history of the Monro-Kellie doctrine through the re-reading of classic manuscripts and articles.
Results: The construction of the Monro-Kellie doctrine combined different researchers and is a result of investigations of human and animal brain circulation carried out in different centuries. Monro secundus started the theory by proposing, in 1783, that: the brain tissue volume was static and the blood volume inside the skull hardly varied, regardless of the individual health conditions. Kellie, in 1824, also linked to the Universiade of Edinburgh, deepened Monro's assessment of cerebral circulation, adding the conclusions that the skull was firm and inflexible in adults, capable of isolating the interior from external mechanical pressures. Kellie's conclusions came at a similar time to Abercrombie's. This pathologist stressed that a cranial depression would result in a reduction in blood volume or compression of the brain mass. Burrows added cerebrospinal fluid to the theory, suggesting that its drainage is the main mechanism for regulating intracranial pressure. After him, Duret described other mechanisms of adaptation, such as vertebral ligament extensibility and venous sinus collapse. Cushing, in turn, demonstrated the clinical importance of the theory and legitimized Burrows' findings. Since Cushing, only Mascarenhas raised doubts about the theory by demonstrating that the skull has mild extensibility.
Conclusion: Monro-Kellie theory is a unique contribution to neurosurgery. Anatomists and pathologists worked to understand brain dynamics. It fell to Cushing, a neurosurgeon, his eternity.

409. Nancy Davis (Reagan): First Lady and a Neurosurgical Legacy

Lena Mary Houlihan, MDMCH, MRCS(I) (Phoenix, AZ); Ann Staudinger Knoll, BS; Jubran Jubran, BS; Dara Farhadi, BS; Dimitri Benner; Joseph Zabramski, MD; Robert Spetzler, MD; Mark Preul, MD

Nancy Davis Reagan is recognized for endeavors against drug abuse, Alzheimer's disease, and polio. Less known is her life connected to neurosurgery. Nancy recorded poignant memories growing up with remarkable neurosurgeon father and educator, Loyal Davis. At age 14 Nancy herself initiated adoption by Davis, whose home was often a home away from home for medical students and residents. Nancy's early exposure to neurosurgery formed intimate memories. Loyal allowed Nancy to accompany him on neurosurgical calls in the northern central Illinois area that also reinforced their relationship as father and daughter: "I often went along on these calls to keep my father company, and as a result we became close." Davis' training and research with Allen Kanavel, Harvey Cushing, and Lewis Pollock produced an extraordinary career of neurosurgical influence. He formed the first neurosurgical service in Chicago. As Barrow Neurological Institute director from 1966-1967 during BNI founder John Green's illness, animosity developed when Davis did not want to give up the lead. After Davis' death in 1982, and having been his Northwestern ethics professor and now BNI director, Robert Spetzler convinced Green, despite his misgivings, to support a neurosurgical laboratory recognizing Davis. In 1988, Nancy, then First Lady, dedicated The Loyal and Edith Davis Neurosurgical Research Laboratory. At the dedication Nancy remarked on her time spent in Phoenix from a young age: "My parents were devoted supporters of the [BNI], and, now, to have their names associated with the institute – well, I know how proud they would be. My father believed deeply in the importance of research to develop new methods for treating patients." Green and Spetzler's unified efforts supported by Nancy Reagan as the First Lady to honor the extraordinary career of Davis would leave a lasting and visionary mark on progress for the science and education of neurosurgery.

410. Reconstructive surgery of peripheral nerve injuries during the Chaco war, Bolivia-Paraguay 1932-1935

Edgar M. Carrasco, MD, IFAANS (Santa Cruz, Bolivia)

Introduction: The Chaco War was a conflict between Paraguay and Bolivia, from 09/09/1932 to 06/14/1935. It was the most important war in South America during the twentieth century. In the three-year period, Bolivia mobilized 250,000 soldiers and Paraguay 120,000, who faced fighting in which there were large numbers of casualties (60,000 Bolivians and 30,000 Paraguayans). The historian Juan Miguel Balcazar described it: the Chaco War was a true field of experimentation for surgery. That all doctors had to become surgeons to save the soldiers wounded and sick.
Methods: A descriptive analysis and bibliographic review of the book "REPAIR SURGERY FOR INJURIES OF THE PERIPHERAL NERVES", written by the Bolivian physicians Abelardo Ibañez Benavente and Valentin Gomez, and published by the Bolivian Government in 1936, was performed.
Results: 176 cases of nerve injuries in 151 patients are described, where upper limb injuries predominate. Nerve lesions are described with the terms "contusion" and "complete or incomplete section". In 126 pages Dr. Ibañez Benavente describe the diagnosis, the surgical and clinical follow-up of war wounds, treatment against infections, the exploration of wounds and the definitive surgical approach, emphasizing the end-to-end suture and neurolysis
Conclusion: We present a beautiful monograph with the description of 176 peripheral nerve surgeries during the Chaco War, considering this work as revolutionary for its time (1932-1936) taking into account the limitations of anesthesia, the discovery and use of antibiotics and even knowledge of the nerve injury Seddon (1943) and Suderland (1951)

411. Foraminal Origin of the Dorsal Scapular Nerve: An Anatomical Study

Andrew Steven Jack, MD, MSc, FRCSC (San Francisco, CA); Vinil Shah, MD; Line Jacques, MD, MSc, FRCSC

Introduction: Although distal dorsal scapular nerve (DSN) anatomy has been well characterized, a paucity of literature exists detailing its proximal origin. To our knowledge, this is the first study examining the DSN origin and its anatomy relative to the C5 nerve root which may help localize pathology and provide insight into timing of DSN or C5 nerve root clinical and electrophysiological recovery.
Methods: Eighteen cadaveric dissections were performed using a posterior-midline approach. Calipers were used for DSN branching and course characterization with statistical analysis completed for the following measurements: DSN diameter, C5 nerve root diameter, distance of DSN branch-point from the C5 ganglion, dural edge, and posterior foraminal tubercle (intra- vs extraforaminal origin), as well as C5 root-SC branch-point distance.
Results: Average (mean) measurements (standard error) were as follows: DSN diameter: 3.7mm (0.3mm), C5 nerve root diameter: 6.2mm (0.5mm), DSN origin to C5 DRG: 12.4mm (1.9mm) distal, DSN origin to dural edge: 19.6mm (1.8mm), DSN origin to C5 root origin: 23.3mm (2.2mm), DSN origin to the posterior foraminal tubercle: 2.3mm (2.5mm) proximal/intraforaminal (first branch from C5 in all cases, and the majority [12/18, 67%] of DSNs originating from the C5 spinal nerve root within the foramen).
Conclusion: The C5 nerve root contributed to the DSN in all specimens which originated from the proximal, intraforaminal, C5 nerve root in the majority of specimens. As the first C5 nerve branch, surgeon knowledge of this proximal DSN pattern will help localize lesional pathology, as well as may help monitor clinical and electrophysiological recovery.

412. Declining Reimbursement Rates for Peripheral Nerve Procedures from 2000-2020

Parth P Parikh (Phoenix, AZ); Brandon Nguyen, BS; Rohin Singh, BS; Pelagia Kouloumberis, MD; Naresh Patel, MD

Introduction: Peripheral nerve surgery is a unique sub-specialty that can be performed by neurosurgeons, plastic surgeons, and orthopedic surgeons. Reimbursement rates for these procedures can directly impact workforce recruitment, and access to care for patients. Therefore, these trends must be continually monitored to assure fair and adequate compensation is provided. In this study, we aim to characterize the reimbursement rates for the top five peripheral nerve procedures conducted by neurosurgeons from 2000-2020.
Methods: Data for peripheral nerve procedures conducted by neurosurgeons was obtained from the Medicare Provider Utilization Database from 2012-2017. The database was filtered by 84 HCPCS codes for specific procedures, and then by primary specialty to only include "Neurological Surgery." The five most common procedures were identified and entered into the Physician Fee Schedule Look-Up Tool for years 2000-2020, to determine an unadjusted reimbursement rate. These rates were then adjusted for inflation using the CPI Inflation Calculator.
Results: The top five peripheral nerve procedures were release and relocation of median nerve of hand (64721), release of ulnar nerve at elbow (64718), release of nerve of arm or leg (64708), implantation of peripheral nerve neurostimulator electrodes (64555), and release of unspecified nerve (64722). Between 2000 and 2020, the average reimbursement for codes 64721, 64718, 64722, and 64718 decreased by 17.1%, 8.0%, 27.8%, and 22.8%, respectively. The average change in reimbursement for these four codes is -18.9%. The reimbursement for 64555 (implantation of neurostimulators) increased by 582.6%.
Conclusion: Over the twenty years, the average reimbursement for most peripheral nerve procedures has decreased. Implantation of a neurostimulator is the only code to have increased substantially due to the recognition of heightened practice expenses and work value associated with this procedure. Declining rates for all other procedures are a troubling trend that must be addressed to assure sufficient compensation moving forward.

413. Carboxyl Terminal Modulator Protein Knockout Mitigates Denervation Atrophy in a Mouse Model of Sciatic Nerve Injury

Christopher D. Wilson, MD (Indianapolis, IN); Christopher Wilson, MD; Junmei Wang, PhD; Chandler Walker, PhD

Introduction: Carboxyl Terminal Modulator Protein (CTMP) is an endogenous inhibitor of Akt kinase activation. Akt activation promotes cell survival and prevents cell degradation and is downregulated in skeletal muscle afflicted by trauma and neurodegeneration. Because Akt activation prevents pro-atrophic gene expression downregulation is associated with muscle atrophy. CTMP is upregulated and Akt activation is decreased in denervation-mediated muscle atrophy. Inhibition of CTMP rescues Akt activity in vit ro. In the present study, we hypothesize that CTMP knockout (KO) will limit denervation-mediated muscle atrophy in mice after sciatic nerve injury (SNI) compared with wildtype (WT) mice.
Methods: TMP-KO and WT mice underwent right-sided (n=10/group) SNI and were euthanized seven days postoperatively. Ratios of gastrocnemius muscle weight from injured and uninjured sides were compared between groups. Muscle protein was isolated, prepared, and ran on SDS-polyacrylamide gel electrophoresis. Expression of total and activated Akt and Murf1 (E3 ubiquitin ligase and pro-atrophic protein) were compared between CTMP-KO and WT mice using Western blot.
Results: The ratio of injured to uninjured gastrocnemius muscle weight was greater in CTMP-KO mice than WT mice (0.74±0.02g vs 0.52±0.3g, p<0.001). The ratio of active Akt to total Akt in the injured to uninjured hindlimb muscle was also greater in the CTMP-KO mice than WT mice (0.67±0.04 vs 0.41±0.05, p=0.001). The ratio of Murf1 expression in the injured to uninjured side was lower in CTMP-KO mice than WT mice (0.69±0.14 vs 1.4±0.14, p=0.02). All data indicate mean ± standard error of the mean.
Conclusion: Anatomic analysis indicated CTMP-KO mice suffer less atrophy than WT mice after SNI. Western blot analysis indicated atrophy is regulated by CTMP and mitigated by Akt upregulation and Murf1 downregulation in the absence of CTMP. Therefore, CTMP inhibition may be a viable target to limit neurogenic muscle atrophy after peripheral nerve injury.

414. The Efficacy and Safety of Different Surgical Techniques for Cubital Tunnel Decompression: A Systematic Review and Network Meta-Analysis

Timothy T Griffiths (Leeds, United Kingdom); Ryckie Wade; Robert Flather; Nicholas Burr; Mario Teo; Grainne Bourke

Introduction: Cubital Tunnel Syndrome (CuTS) is the 2nd most common compressive neuropathy, affecting 6% of the population. There are numerous different operations performed globally to treat CuTS. To-date, conventional (pairwise) meta-analyses have been unable to determine which procedure is the most effective and safe. Network meta-analysis (NMA) provides more precise estimates than standard pairwise meta-analysis and can rank interventions, to inform clinical decisions. The primary objective was to determine which operation is most likely to provide symptomatic cure.
Methods: We searched PubMed, Embase and CENTRAL for studies comparing any surgical treatments for adults with primary CuTS. The primary outcome was response to treatment (i.e. symptomatic improvement). The secondary outcomes were peri-operative complications, reoperation and recurrence. We performed NMA to estimate the relative efficacy of interventions using relative risks (RR). Surgical techniques are ranked by their probability of being the best.
Results: We included 31 studies of 2420 patients undergoing 8 different operations. Overall, 85% of patients improved with surgery; all forms of in-situ decompression were more effective than any type of transposition procedure; for example, open in situ decompression with epicondylectomy was associated with 13% higher success rates than subcutaneous transposition (RR 1.13 [95%CI, 1.01-1.25]). Postoperatively, 3% of patients developed complications and again, in-situ decompressions were the least risky. Overall, 2% of patients required reoperation; open in-situ decompression was associated with the fewest reoperations; in comparison, submuscular transposition was associated with 5 times the risk of reoperation (RR 5.08 [95% CI 2.06-12.5). During surveillance, 3% developed recurrence and open in situ decompressions with epicondylectomy were the safest
Conclusion: Open in-situ decompression (with or without medial epicondylectomy) appears to be the most effective and safe procedure for patients with primary CuTS. Future research should focus on better defining this disorder and developing core outcome measures.

Philip L. Gildenberg Resident Award
415. Microglial Replacement Enhances Motor Function and Improves Overall Survival in a Mouse Model of Gaucher's Disease

Kevin K. Kumar, MD, PhD (Stanford, CA); Yohei Shibuya, PhD; Mu Zhou, PhD; Yongjin Yoo, PhD; Adrian Rodrigues, BA; Ying Sun, PhD; Thomas Südhof, MD; Marius Wernig, MD, PhD

Introduction: Gaucher's disease (GD) is the most common lysosomal storage disease with an incidence of 1/40,000 births. Children with GD have progressive neurodegeneration which is recalcitrant to conventional therapy. We have developed a bone marrow transplantation (BMT) protocol that utilizes small molecule inhibition of CSF1 receptor (CSF1R) to repopulate microglia within the CNS with circulation derived microglia-like cells (CDMCs). We hypothesized that CDMCs could serve as a novel cellular delivery platform to the brain, allowing restoration of dysfunctional proteins in GD. Using the prosaposin (Psap)/glucocerebrosidase (Gba1) mouse model of GD, we assessed the impact of microglial replacement on motor function and survival.
Methods: Bone marrow isolation from Psap/Gba1 mice was performed followed by retro-orbital injection into 6-week-old recipient mice pre-treated with busulfan. Recipients were subsequently treated with PLX5622, a CSF1R inhibitor, to deplete endogenous microglia. Behavioral characterization was performed at 10 and 20 weeks by open field, elevated beam test, and gait analysis. Brains were harvested to assess CDMC chimerism and Psap expression.
Results: BMT mice demonstrated high efficiency repopulation of microglia niches by Iba1+ Psap+ CDMCs. BMT ameliorated the decline in area measured from 10 to 20 weeks compared to untransplanted mutant mice ($p<0.0001$). BMT from Psap/Gba1 control donors to mutant recipients prevented decline in unilateral forelimb and hindlimb stride from 10 to 20 weeks ($p<0.0001$). BMT-treated mice had no increase in falls from 10 to 20 weeks and significantly less falls at 20 weeks compared to untransplanted mutants ($p<0.0001$). BMT from Psap/Gba1 control donors to mutant recipients improved overall survival compared to untransplanted mutants ($p<0.05$).
Conclusions: We report the successful replacement of microglia with CDMCs in the Psap/Gba1 mouse model of GD. Transplanted CDMCs express Psap, ameliorate multiple motor phenotypes, and enhance survival. Microglial replacement has great potential as a therapeutic strategy for a variety of neurodevelopmental disorders.

416. Machine-learning Approach to Differentiation of Benign and Malignant Peripheral Nerve Sheath Tumors: A Multicenter Study

Michael Zhang, MD(Stanford, CA); Elizabeth Tong, MD; Forrest Hamrick, BS; Courtney Pendleton, MD; Brandon Smith, MD; Nicholas Hug, BA; Sarah Mattonen, PhD; Sandy Napel, PhD; Robert Spinner, MD; Kristen Yeom, MD; Thomas Wilson, MD; Mark Mahan, MD

Introduction: Clinicoradiologic differentiation between benign and malignant peripheral nerve sheath tumors (PNSTs) has important management implications. Benign lesions can be observed or undergo nerve sparing resection, whereas malignant lesions require en bloc nerve resection. This research reports the first machine-learning, radiomics classifier for these two pathologies.
Methods: We identified PNSTs from patients treated at 3 institutions and extracted high-dimensional radiomics features from gadolinium-enhanced, T1-weighted MRI sequences. Training and test sets were selected randomly in a 70:30 ratio. 900 image features were automatically extracted using the PyRadiomics package from the Quantitative Imaging Feature Pipeline, as defined by the Imaging Biomarker Standardization Initiative. Clinical data including age, sex, neurogenetic syndrome presence, spontaneous pain, and motor deficit were also incorporated. Features were selected using sparse regression analysis by a least absolute shrinkage and selection operator. Retained features was further refined by gradient boost modeling to optimize the area under the curve (AUC) for diagnosis. We evaluated the performance of radiomics-based classifier models with and without clinical features and compared model performance against human readers.
Results: Ninety-five malignant and 171 benign PNSTs were included. The final classifier model included 21 imaging and clinical features. Sensitivity, specificity, and AUC of 0.676, 0.882, and 0.845, respectively, were achieved on the test set. Using additional imaging and clinical features, human readers collectively achieved sensitivity, specificity, and AUC of 0.684, 0.742, and 0.704, respectively.
Conclusion: Radiomics using routine MRI sequences and clinical features can aid in evaluation of PNSTs, particularly by increasing the specificity for diagnosing malignancy. Further improvement may be achieved by incorporating additional imaging sequences and clinical variables into future models.

417. Patient-Operated Brain-Computer Interface for Hand Grasp Restoration at Home

Kevin C. Davis (Miami, FL); Benyamin Meschede-Krasa; Shovan Bhatia; Sebastian Gallo; John Abel; Noeline Prins; Michael Ivan; Abhishek Prasad; Jonathan Jagid; Emery Brown; Iahn Cajigas

Introduction: Approximately 5.4 million patients live with paralysis. These patients often suffer decreased independence and face significant social and economic adversity. Brain- Computer Interface (BCI) research has shown potential in restoring sensorimotor deficits in these patients. Despite recent advances, BCIs have been limited to laboratory settings due to hard-wired equipment, the need for clinician-assisted recalibration, complex donning and doffing procedures, and non-continuous decoding. Addressing these challenges, we developed a portable BCI for a patient with cervical spinal cord injury (C5 ASIA A) to regain volition of hand grasp for at-home use.
Methods: Two four-contact electrodes implanted over the dominant hand region of the primary motor cortex and connected to a subclavicular transmitter, allowed for real-time data acquisition of 4 ECoG channels (Resume II leads/Activa PC+S, Medtronic). A nanocomputer (M90n, Lenovo) and battery pack (Krisdonia), fixed to the patient's wheelchair, processed ECoG signals for decoder training and drove an orthosis to actuate hand grasp. A mobile phone application enabled the patient to collect data remotely, calibrate the decoder, and adjust BCI system preferences.
Results: Using the mobile phone application, the patient successfully operated and adjusted settings to the BCI independently. This design minimized caretaker involvement to merely fitting the patient with the device and turning the system on. It also completely removed the need for in-person clinician administration and allowed for remote data analysis. Functional activity tests at home improved with BCI use. The patient independently performed previously unattainable activities of daily living (e.g., brushing their hair or teeth).
Conclusion: We successfully demonstrate the use of a patient-operate BCI for at-home use in a chronic spinal cord injury patient. Future work investigating the efficacy of long-term at-home ECoG signal acquisition will elucidate the feasibility of long-term use and may better address the role BCI plays in rehabilitative therapy.

Byron Cone Pevehouse Young Neurosurgeon Resident Award

418. Implementation of a Novel Enhanced Recovery after Surgery (ERAS) Protocol for Transsphenoidal Surgery Improves Patient Outcomes and Hospital Financial Performance

Christina Sarris, MD (Phoenix, AZ); Scott Brigeman, MD; Estelle Doris; Deborah Astemborski; Margaret Bobrowitz; Thomas Rowe; Eva Duran; Kevin Yuen, MD; William White, MD; Andrew Little, MD

Introduction: Our center embarked on an evidence-based quality improvement initiative guided by enhanced recovery after surgery (ERAS) principles to improve patient outcomes and optimize healthcare value after transsphenoidal surgery. In this abstract, we describe our program and its impact on quality and hospital financial performance over the last five years.

Methods: Length of stay (LOS), unplanned readmissions, and financial performance were identified as surrogate endpoints for healthcare value for the surgical epoch. Foundational elements of the program include evidence-based care pathways, patient education, multidisciplinary team care, checklists, multimodal pain control, a steroid-sparing protocol, prophylactic fluid restriction, high-touch post-discharge care, a patient-navigator, among other items. To assess the impact of these protocols, we retrospectively reviewed all patients undergoing elective transsphenoidal surgery for pituitary tumors and Rathke's cleft cysts between January 2015 and December 2019.

Results: 609 patients were identified. There were no significant changes in patient demographics, comorbidities, or payer mix over the study period (p>.1). Mean LOS was significantly shorter in 2019 versus 2015 (1.63 midnights ± 1.03 vs 2.94 midnights ± 2.24, p<.001). The percentage of patients discharged after one midnight was significantly higher in 2019 versus 2015 (75.4% vs 15.6%, p<.001). 30-day unplanned hospital readmissions decreased from 8.3% to 2.8% over the 5 year period. Per patient hospital profit increased 71.3% and contribution margin increased 42.3%, while costs increased only 3.4%.

Conclusion: This study demonstrates that implementing a quality program based on ERAS principles delivers improved healthcare value for elective transsphenoidal surgery patients. This study is the largest and most comprehensive description to-date of applying ERAS principles to pituitary surgery. Details of our center's program will be presented at the meeting.

419. Pilot of a Randomized, Blinded, Placebo-Controlled Trial of Shunting in Idiopathic Normal Pressure Hydrocephalus

Mark G. Luciano, MD, PhD, FAANS, FACS (Baltimore, MD); Richard Holubkov, PhD; Sean Nagel, MD; Thomas Zwimpfer, MD; Michael Williams, MD; Jan Malm, MD; Abhay Moghekar, MD; Anders Eklund, PhD; Heather Katzen, PhD; Mark Hamilton, MD

Introduction: While multiple prospective non-randomized studies have shown that 60-70% of patients improve with shunt surgery, no multi-center placebo-controlled trial has been performed. Without this evidence some have called for a restriction or cessation of iNPH shunting. We present the preliminary results of a multi-center randomized, blinded, placebo-controlled, pilot trial of shunt surgery in idiopathic normal pressure hydrocephalus (iNPH).

Methods: Five sites of the Adult Hydrocephalus Clinical Research Network, enrolled 18 patients scheduled for ventriculoperitoneal shunting based on response to CSF drainage. Patients were randomized to a Codman® Certas® Plus valve with SiphonGuard® at either setting 4 (Active, N=9) or setting 8 /"virtual off" (Placebo, N=9). Patients and assessors were blinded to the shunt setting. Outcomes included 10-meter gait velocity (primary outcome), cognitive function, bladder activity, depression, Modified Rankin scale, and Lawton ADL/IADL scores. The primary analysis was gait velocity improvement in the Active versus Placebo groups at 4-months. Afterwards all shunts were blindly adjusted to the active setting. The long term evaluation of active shunting in all patients is ongoing.

Results: At the 4-month primary outcome evaluation, gait velocity increased by 0.28 ± 0.28 m/s in the Active Group and 0.06 ± 0.15 m/s in the Placebo Group (p=0.078), a treatment difference of 0.21 m/s (95% CI: -0.03, 0.45). Overactive Bladder (OAB-q) significantly improved in Active versus Placebo (p=0.007). No significant between-group differences were found for the other outcome measures.

Conclusion: This multi-center, randomized pilot study demonstrates the feasibility of a placebo controlled trial in iNPH and a trend suggesting gait velocity improves more at an active shunt setting than a placebo shunt setting. A larger, sufficiently powered, study is indicated and planned to confirm the efficacy of shunting.

420. Using Machine Learning to Predict Seizure Onset Zones in Focal Epilepsy from Interictal ECoG Features

Thomas Luo (Milwaukee, WI); Manoj Raghavan, MD, PhD

Introduction: Localization of the epileptic seizure onset zone (SOZ) prior to epilepsy surgery often requires electrocorticographic (ECoG) recordings of seizures using intracranial electrodes. While seizure (ictal) recordings represent the clinical gold standard to identify surgical targets, several interictal features of the ECoG signal possibly represent biomarkers of the epileptogenic cortex. Since individual feature may lack sensitivity and specificity, we aimed to determine if machine learning applied to channel-level ECoG features could identify signals from the SOZ.
Methods: Multichannel interictal ECoG data and the SOZ determinations established during clinical evaluations were retrieved for 10 patients (N=807). The following ECoG features were extracted from all channels using custom MATLAB scripts: epileptic spike-rates and mean-amplitudes; high frequency oscillation (HFO)-rates and mean-amplitudes; power spectral density in six frequency bands; node-strength and eigenvector centrality (EC) based on cross-channel signal-envelope correlations in four bands; node-strength and eigenvector centrality based on phase-locking values (PLV) for the same four bands. The known SOZ classification of 75% of channels was used as the output for training. The generalizability was evaluated on the remaining 25% of channels.
Results: Several algorithms including k-nearest neighbor, decision trees, ensemble, shallow neural network, and support vector machine (SVM) were trained on the ECoG feature data. An SVM using a Gaussian kernel showed the highest AUROC of 0.93 and captured ~90% of channels from the SOZ with a false positive rate of ~17%, using 15 features including: envelope-correlation node-strength and EC, PLV node-strength and EC, and power spectral density.
Conclusion: Our results suggest that spectral and connectivity-based features likely carry more information relevant to identifying epileptogenic regions of the brain than traditional markers of epileptic cortex such as spike discharges. Accurate interictal SOZ prediction could allow localization of surgical targets from brief intraoperative ECoG recordings, eliminating the need for multiday invasive recordings.

421. Deep Brain Stimulation for Treatment Resistant Depression: A Decade of Clinical Follow-up

Frederick Luke Hitti, MD, PhD (Philadelphia, PA); Andrew Yang, MD; Mario Cristancho, MD; Gordon Baltuch, MD, PhD

Introduction: Major depressive disorder (MDD) is a prevalent and debilitating disease that is a significant source of morbidity and mortality. While many treatments are available including psychotherapy, medication, and electroconvulsive therapy (ECT), a sizeable number of patients (30-40%) remain symptomatic despite treatment. These patients are diagnosed with treatment-resistant depression (TRD). Deep brain stimulation (DBS) is an emerging therapy for TRD that has shown variable efficacy. In this study, we describe our long-term clinical outcomes of DBS for TRD.
Methods: A consecutive series of 8 patients with severe TRD were implanted with DBS systems targeting the ventral capsule/ventral striatum as part of the Reclaim clinical trial (NCT00837486). This study included a 16-week blinded phase followed by an open-label long-term phase. Outcomes were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS). Demographics, MADRS scores, and adverse events were collected via retrospective chart review.
Results: This cohort of patients had severe TRD- 75% had trials of ECT and all had at least 4 failed medication trials. Mean follow-up for patients who kept their devices was 10.53±0.17 years and it was 7.45±1.41 years for the entire cohort. At last follow-up, mean improvement in MADRS scores was 42.9±13.7%. Response (≥50% improvement) and remission (MADRS≤10) rates at last follow-up were 37.5% and 25%, respectively. Two patients discontinued stimulation due to lack of efficacy and one committed suicide. The majority of the cohort (63%) continues to receive stimulation.
Conclusion: While enthusiasm for DBS treatment of TRD has been tempered by recent randomized trials, this open-label study demonstrates that many patients achieve meaningful and sustained clinical benefit from DBS. Further trials are required to determine the optimal stimulation parameters and patient populations for which DBS would be effective. Particular attention to factors that include electrode placement technique, patient selection, and long-term observation (i.e., 1-5 years) is essential for future trial design.

422. Voluntary Movement-Related Neural Oscillations in the Intact Human Spinal Cord

John Fredrick Burke, MD (San Francisco, CA); Nikhita Kunwar, BSE; Doris Wang, MD, PhD

Introduction: Voluntary movement isassociatedwith neuraloscillations in the motor cortex, however it is not knownwhether such oscillations are also present in the spine.Here, weused implanted spinal epidural electrodes toinvestigatethe electrophysiological basis ofnaturalistic leg and arm movement in the intact human spinal cord.

Methods: Six patients with chronic pain who underwent implantation of percutaneous epidural electrodes as part of a test trial for spinal cord stimulation therapy were recruited for this study. Spinal epidural potentials (SEPs) were recorded using an external amplifier. Electromyographic and accelerometry data from the upper and lower extremities were collected using wireless sensors. Patients were engaged in naturalistic movement tasks including flexion and extension of bilateral elbows and knees, stepping in place, and ambulation. SEP time-frequency activity were performed using wavelet transforms, and then correlated with individual muscle movements.

Results: We found that voluntary movement was associated with a specific spatiotemporal spectral pattern for each patient. This activity was characterized by an overall decreased level of low frequency oscillatory activity during movement, and varied as a function of spinal level. A multivariate unsupervised classifier was used to decode movement (upper vs. lower extremity, flexion/extension vs. walking), and successfully predicted ambulation compared to non-ambulatory movement using spinal electrical activity. Amplitudes of movement-related SEPs changes were also correlated with the side of limb movements.

Conclusion: These findings represent the first evidence that neural oscillations from intrinsic spinal circuits are associated with naturalistic movements, and suggest thatspinal oscillations can decode ambulatory state.

423. Cross-Regional Phase Amplitude Coupling Supports the Encoding of Episodic Memories

Kelsey Schmitt (Dallas, TX); David Wang, MS; Sarah Seger, BS; Carlos Davila, PhD; Bradley Lega, MD

Introduction: Phase amplitude coupling (PAC) between theta and gamma oscillations represents a key neurophysiological mechanism that promotes the temporal organization of oscillatory activity. Thus, PAC has been implicated in item/context integration for episodic processes, and data in rodents have revealed evidence that the phase of the hippocampal theta oscillation modulates gamma oscillations in the cortex (and vice versa). This pattern, termed cross-regional PAC (xPAC), has not previously been observed in human subjects engaged in mnemonic processing. We aimed (1) to test for the presence of significant xPAC in the hippocampus and seven cortical regions in humans, (2) to establish that the magnitude of xPAC predicts memory encoding success, (3) to describe specific frequencies within the broad 2-9 Hz theta range that govern hippocampal-cortical interactions in xPAC, and (4) to compare anterior versus posterior hippocampal xPAC patterns.

Methods: We used a unique dataset with intracranial electrodes inserted simultaneously into the hippocampus and seven cortical regions across 40 human subjects engaged in a free recall task. xPAC was quantified as a modulation index (MI) value. Mixed effects models were used to identify connections with significant xPAC effects on either successful or unsuccessful encoding and to characterize the functional effects of xPAC at each theta frequency for those regions previously identified as displaying significant xPAC.

Results: Significant xPAC occurs between the hippocampus and cortex, especially for other mesial temporal regions (ERC and PHC). In the left hemisphere, posterior hippocampal xPAC with the ERC and PHC was stronger than for the AH. The preferred phase of coupling for xPAC differs between the AH and PH for several connections.

Conclusion: xPAC supports successful memory encoding. Strong functional xPAC occurs principally between the hippocampus and other mesial temporal structures, namely entorhinal and parahippocampal cortices, and that xPAC is overall stronger for posterior hippocampal connections.

424. Stimulated Raman Histology for Rapid Intraoperative Diagnosis of Meningiomas

Long Di (Cape Coral, FL); Daniel Eichberg, MD; You Park, BS; Ashish Shah, MD; Aria Jamshidi, MD; Evan Luther, MD; Victor Lu, MD, PhD; Ricardo Komotar, MD; Michael Ivan; Sakir Gultekin, MD

Introduction: Frozen section is the current standard for intraoperative pathologic diagnosis in neurosurgery but remains a labor and time-intensive process. With current and projected shortages of board-certified neuropathologist servicing neurosurgical centers, there exists a need to expedite the acquisition and analysis of diagnostic histologic data. Stimulated Raman histology (SRH) is a novel technology that my offer an alternative approach to rapid intraoperative histopathologic diagnosis. The purpose of this study was to evaluate the accuracy and efficiency of simulated SRH intraoperative diagnosis compared to frozen section and permanent section diagnosis.

Methods: Following IRB approval, 82 patients undergoing resection for CNS tumors were enrolled in a blinded, prospective cohort study. Of these, 26 patients were diagnosed with meningioma on frozen, SRH, or permanent section diagnosis. For these patients, accuracy and time to diagnosis was compared between simulated SRH histology images and frozen section. Agreement of SRH and frozen section diagnosis with permanent section ("true") diagnosis was also compared.

Results: SRH-mediated mean time-to-diagnosis (TTD) was statistically significantly shorter than TTD with frozen section (9.2 vs 35.8 minutes, $p < 0.0001$). Despite improved time-savings, methods did not significantly differ in diagnostic accuracy ($p=.15$). Diagnostic agreement was not significantly different between SRH vs. frozen, SRH vs. permanent, or frozen vs. permanent section methods. ($p=0.5$; $p=0.5$; $p = 1.00$).

Conclusion: SRH is a promising adjuvant to traditional frozen section in the intraoperative diagnosis of meningiomas that allows for expedited surgical neuropathologic consult without sacrificing diagnostic accuracy.

425. RNA Polymerase II Meningioma Mutations Dysregulate Transcriptional Pause-Release and Exhibit Susceptibility to CDK9 Inhibition

Victoria Clark, MD (Boston, MA), PhD; Lazaris Charalampos, PhD; Richard Young, PhD

Introduction: Recurrent mutations in the dock domain of RNA polymerase II, which transcribes DNA into mRNA, drive 6% of benign meningioma formation and localize to the surgically-challenging tuberculum sellae. Meningioma mutations are adjacent to DSIF, which facilitates transcriptional elongation upon phosphorylation by CDK9 (pause-release). If Pol II mutations alter pause-release, then CDK9 inhibition by AZD4573 (currently in Phase I clinical trials for hematologic malignancies) represents a novel therapeutic target.

Methods: Using CRISPR-Cas9, the POLR2A Q403K meningioma mutation was modeled in mouse embryonic stem cells (100% identity to human dock domain). Pol II ChIP-seq was performed on wildtype and POLR2A Q403K cells. To quantify pause-release, the traveling ratio was calculated by the normalized density of Pol II ChIP-seq reads in the gene promoter divided by the normalized density of Pol II ChIP-seq reads in the gene body. To determine the effect of CDK9 inhibition on nascent transcription, wildtype and POLR2A Q403K cells were treated with either AZD4573 or DMSO, nascent RNA was metabolically labeled with 4-thiouridine, RNA was extracted then alkylated with iodoacetamide, and next-generation sequencing libraries were created and sequenced (SLAMseq). T>C conversions, reflecting nascent RNA, were digitally unmasked using SlamDunk.

Results: For active genes, the traveling ratio distribution for mutant Pol II was significantly left-shifted compared to wildtype Pol II (mean 10.79 vs. 13.97, $p < 2.2e-16$), reflecting a greater proportion of mutant Pol II undergoing active elongation compared to wildtype. Pol II mutant cells showed a significantly higher decrease in nascent transcription after treatment with AZD4573 compared to wildtype (75.1% vs 67.1%, $p < 2.2e-16$).

Conclusion: Pol II meningioma mutations dysregulate transcriptional pause-release, promote elongation, and are sensitive to selective CDK9 inhibition by AZD4573. These findings represent a novel therapeutic target for the most common primary brain tumor and provide new insight into the function of the dock domain.

Synaptive Preuss Research Award

426. Rational Development of Synergistic Therapies alongside BMI1 Inhibition for Group 3 Medulloblastoma.

David Bakhshinyan (Hamilton, Canada); David Bakhshinyan, PhD; Ashley Adile; Chitra Venugopal, PhD; Kevin Brown, PhD; Katherine Chan; Maleeha Qazi, PhD; Chirayu Chokshi; David Tieu; Jason Moffat, PhD; Sheila Singh, MD, PhD

Introduction: Medulloblastoma (MB) is the most common pediatric brain tumor. Of its four distinct molecular subgroups, Group 3 MBs are associated with increased risk of recurrence, metastasis and overall poor patient outcome. In recent years, small molecule inhibitors targeting BMI1 have shown to be efficacious against several types of malignant tumors including pediatric MB. Although in vivo studies provide a promising proof-of-concept for the therapeutic targeting of BMI1 in Group 3 MB, mice that receive treatment eventually succumb to their disease. These/Such results suggest that additional mechanisms may underlie the maintenance of MB and underscores the main obstacle in treating a constantly evolving tumor.

Methods: After initial preclinical validation of BMI1 inhibitor PTC-596, DNA barcoding clonal tracking technology was leveraged to profile in vivo clonal dynamics of Group 3 MB in response to the established chemoradiotherapy regimen alone and in combination with PTC-596. Subsequently, we undertook an in vitro genome-wide CRISPR/Cas9 screening to identify context-specific MB regulatory pathways to be synergistically targeted along with BMI1.

Results: Profiling clonal dynamics of Group 3 MB growth post-treatment revealed the persistence of a small number of clones with the ability to escape therapy and drive subsequent tumor expansion. By comparing the results of the in vitro genome wide CRISPR/Cas9 screen to the essential genes in human neural stem cells (hNSCs), we identified several context specific regulators of mTOR, AKT and PLK1 pathways. The combined treatment alongside PTC-596 has demonstrated synergistic efficacy against MB cells with minimal toxicity to hNSCs in vitro and is currently being evaluated in preclinical studies.

Conclusion: This study provides the foundation for clinical validation of small-molecule inhibitors synergistic with PTC-596 to improve the durability of remissions and extend survival of patients with treatment-refractory Group 3 MB.

Brainlab Neurosurgery Award

427. Long-term Survival Following PDT for HGG Depending on MGMT

Artemii Rynda (Saint-Peterburg, Russian Federation); Victor Olyushin, MD, PhD; Dmitrii Rostovtsev, MD, PhD; Yulia Zabrodskaya, MD, PhD

Background: The aim of the study was to increase the survival rate and duration of the relapse-free period in patients with malignant brain gliomas by using PDT as part of complex treatment.

Methods: The study included patients with glial brain tumours with a high degree of malignancy (Grade IV), undergoing treatment at the RNSI named after Prof. A.L. Polenova. The study group consisted of 50 patients and there were 50 patients in the control group. Patients in the study group were injected intravenously 1.5 hours before the operation with a photosensitizer of the chlorine E6 group (2nd generation). After resection of the tumour, a PDT session was performed using a Latus-2.5 laser as a radiation source. The average dose was 180 J/cm2. In the postoperative period, patients in both groups received adjuvant therapy. Long-term results (interrecurrence period, overall survival) were evaluated depending on the results of immunohistochemical studies (the presence of IDH mutation and MGMT).

Results: The median survival for patients with Grade IV gliomas (MGMT +) using PDT was 23.3 ± 4.1 months; in the control group (without PDT) the median survival was 16.5 ± 3.3 months (P = 0.0002). The median survival for patients with Grade IV gliomas (MGMT-) using PDT was 18.2 ± 3.5 months; in the control group (without PDT) this was 11.2 ± 2.4 months (P = 0.0001). The median duration of the inter-relapse period for patients with Grade IV gliomas (MGMT +) was 13.5 ± 2.3 months in the study group and 9.1 ± 1.4 months in the control group (P = 0.0003). The median duration of the inter-relapse period for patients with Grade IV gliomas (MGMT-) was 10.1 ± 2.2 months in the study group and 7.0 ± 1.1 months in the control group (P =0.0001).

Conclusions: Photodynamic therapy increases life expectancy in patients with malignant gliomas. In patients expressing MGMT life expectancy was significantly higher in the group receiving PDT.

428. Dose to Neuroanatomical Structures Surrounding Pituitary Adenomas and the Effect of Stereotactic Radiosurgery on Neuro-endocrine Function: An International, Multicenter Study

Isaac Jonathan Pomeraniec, MD (Bethesda, MD); Zhiyuan Xu, MD; Mary Vance, MD; Darrah Sheehan; Kimball Sheehan; International Radiosurgery Research Foundation; Jason Sheehan, MD, PhD

Introduction: Stereotactic radiosurgery (SRS) provides a safe and effective therapeutic modality for patients with pituitary adenomas. The mechanism of delayed endocrine deficits based on targeted radiation to the hypothalamic-pituitary axis remains unclear. Radiation to normal neuro-endocrine structures likely plays a role in delayed hypopituitarism after SRS.
Methods: This is a multicenter retrospective review of patients with pituitary adenomas who underwent single fraction SRS from 1997 to 2019 at 16 institutions within the International Radiosurgery Research Foundation. Dosimetric point measurements of 14 predefined neuroanatomical structures along the hypothalamus, pituitary stalk, and normal pituitary gland were made. Statistical analyses were performed to determine the impact of doses to critical structures on clinical, radiographic, and endocrine outcomes.
Results: The study cohort comprised 521 pituitary adenomas treated with SRS. Tumor control was achieved in 93.9% of patients over a median follow-up period of 60.1 months. 22.5% of patients developed new loss of pituitary function. Median maximal radiosurgical doses were to the hypothalamus, pituitary stalk, and normal pituitary gland were 1.4, 7.2, and 11.3 Gy, respectively. Nonfunctioning adenoma status, younger age, higher margin dose, and higher doses to the pituitary stalk and normal pituitary gland were independent predictors of new or worsening hypopituitarism. Neither the dose to the hypothalamus nor the ratio between doses to the pituitary stalk and gland were significant predictors. A threshold of median dose to the pituitary stalk for new endocrinopathy was 10.7 Gy in a single fraction (odds ratio [OR] = 1.77, 95% CI = 1.17 – 2.68, p = 0.006).
Conclusion: SRS for the treatment of pituitary adenomas affords a high tumor control rate with an acceptable risk of new or worsening endocrinopathy. Doses to the pituitary stalk, with a threshold of 10.7 Gy, and normal gland significantly increased the risk of post-SRS hypopituitarism. In patients with preserved pre-SRS neuro-endocrine function, limiting the dose to the pituitary stalk and gland while still delivering an optimal dose to the tumor appears prudent.

429. Next-Generation Modality for Intraoperative Tumor Histoarchitecture Discrimination: Prospective Utilization of In Vivo Confocal Laser Endomicroscopy

Irakliy Abramov (Phoenix, AZ); Alexander Dru; Evgenii Belykh; Jennifer Eschbacher; Kris Smith; Andrew Little; Randall Porter; Laura Snyder; Michael Lawton; Mark Preul

Introduction: This study assesses the feasibility of a confocal laser endomicroscope (CLE) system for intraoperative real-time in vivo identification of pathologic tissue and integration into surgery for primary and dural-based intracranial neoplasms in 30 patients.
Methods: FDA-approved CLE system was used in 14 patients to date. CLE was performed after intravenous injection of fluorescein sodium (FNa). CLE images obtained within the neoplasm body and margins were classified as interpretable or noninterpretable. Images were compared descriptively and quantitatively to corresponding frozen and permanent histology sections, with image correlation to biopsy location using neuronavigation. Specificities and sensitivities of CLE and frozen sections for gliomas and meningiomas were calculated using permanent histological sections as the standard. Surgery-pathology workplace allows real-time image remote display and interpretation.
Results: CLE images (5033 total, 359 average/case) were obtained on all 14 patients (5 male; 9 female; mean age 52.5 years). Permanent histology identified 5 meningiomas, 5 primary glial neoplasms, 3 recurrent malignant gliomas, and 1 case of radiation necrosis. Mean duration of intraoperative CLE system use was 5.8 minutes (range 3.1–9.5 minutes). CLE images were correlated with 22 biopsy specimens from 14 patients. 32.9% (average) of CLE images were interpretable per patient; overall, 1551 and 3481 images were interpretable vs uninterpretable. After CLE initiation, 6.8 images (average, mean duration 6.0 seconds) were acquired before identification of first interpretable image. CLE was 100% sensitive and specific for positive identification of histologically abnormal tissue. CLE diagnostic sensitivity/specificity were 100%/83% for glial neoplasms and 100%/90% for meningiomas with optimal instrument use.
Conclusion: CLE with FNa provided efficient actionable histological analysis during tumor removal. Specificities and sensitivities for CLE diagnosis of neoplasms were comparable to frozen sections. This ongoing study demonstrates the feasibility of CLE to guide extent of tumor resection and may significantly impact surgeon-pathologist workflow in the OR.

American Brain Tumor Association Young Investigator Award

430. Intra-operative Microdialysis for Tumor Biomarker Discovery--A Candidate Platform for Accelerated Pharmacodynamic Feedback.

Terence Calvin Burns, MD, PhD, FAANS (Rochester, MN); Lucas Carlstrom; Rajani Rajani

Introduction: Progress for gliomas is slowed in part by the paucity of mechanistic feedback during teatment with experimental therapies. Access to CSF or extracellular tumor pharmacodynamic biomarkers could provide an avenue to accelerate progress. We have initiated a program of intra-operative microdialysis to accelerate biomarker discovery and to identify candidate outcome measures for translational therapies.

Methods: Intraoperative microdialysis was performed with M-dialysis 100kDA catheters and 107 variable rate pumps under an IDE. 4 IDH-mutant and 2 IDH-WT lesions were studied intraoperatively with 3 divergently placed catheters. Microperfusate (artifical CSF+ 3% dextran) was perfused at 2uL/min and collected in 20 min increments. Paired CSF was also obtained when accessible. A parallel cohort of nude mice bearing human IDH-mutant, IDH-WT, or sham intracranial xenografts (n=6-12) underwent intratumoral microdialysis. A pilot murine study of intracranial drug delivery was performed via convection-enhanced delivery (CED) saline or the IDH-inhibitor AG120 during concurrent microdialysis (1mm from CED catheter) on consecutive days.

Results: Microdialysate from IDH-mutant murine GBMs revealed >100 differentially abundant metabolites (compared to 20 for IDH-WT) including D2-HG (21x) and MTA(18x), $p<10^{-5}$. The most significantly abundant metabolite was DMA (4x, $p<10^{-10}$). 15-1000nM D2HG was recovered from human IDH-mutant tumors, and <1nM in IDH-WT tumors and 2-12uM in CSF and 1-2uM in normal brain adjacent to IDH-WT gliomas. Lower D2HG was found in enhancing than non-enhancing tumor. Serial aliquots of microdialysate during saline CED yielded steady D2-HG levels whereas CED with AG120 yielded undetectable D2-HG within 6 hours.

Conclusion: The extracellular metabolic landscape of glioma is diverse, dynamic and reflects tumor biology and response to therapy. Collectively, these studies suggest that intra-tumoral drug testing should be feasible with realistic expectation of gaining metabolic feedback within a short timeframe. Leveraging this paradigm is an untapped future avenue to accelerate therapeutic translation for gliomas.

William H. Sweet Young Investigators Award

500. Long-term Durability of Restorative Neurostimulation for Chronic Mechanical Low Back Pain – Two-Year Pivotal Trial Results

Christopher J. Gilligan (Boston, MA); Shivanand Lad, MD

Introduction: Chronic mechanical low back pain (CMLBP) can be caused by impaired neuromuscular control and degeneration of the multifidus muscles resulting in functional instability of the lumbar spine. Available treatment options often lack long-term effectiveness and prognosis is unfavorable. An implantable Restorative Neurostimulation system (ReActiv8® by Mainstay Medical), that stimulates the L2 medial branches of the dorsal rami to reactivate neuromuscular control, received FDA Premarket Approval based on evidence from the ReActiv8-B pivotal trial (clinicaltrials.gov/show/NCT02577354). Here we report the two-year results of the open-label phase of this trial.

Methods: Participants had refractory, activity limiting CMLBP with average low back pain VAS≥6cm, Oswestry Disability Index ODI≥21 points, evidence of multifidus inhibition (prone-instability-test) and no indication for spine surgery. Participants self-administered up to 60-minutes of stimulation per day and were followed-up through two years.

Results: At baseline (N=204), participants were 47±9 years of age, had backpain for 14±11 years, average LBP-VAS of 7.3±0.7cm, ODI of 39.1±10.3 points, EQ-5D (quality-of-life) of 0.585±0.174 and had LBP on 97±8% of days during the year before enrollment. At two-years (N=159), all prespecified outcome measures showed statistically significant (P <0.0001) and clinically substantial improvements compared to baseline. Average LBP-VAS improved by -4.8±2.4cm (-65.9±32.6%), ODI by -21.7±16.8points (-54.7±39.2%) and EQ-5D by 0.215±0.215; 71% of participants had ≥50% LBP-VAS improvement; 66% had VAS≤2.5cm (LBP-resolution); 62% had ≥20points ODI improvement; 77% had ≥50% improvement in LBP-VAS and/or ODI; 80% was "Definitely satisfied" with the treatment and 59% voluntarily eliminated or reduced opioid consumption. The overall safety profile is favorable, and no lead migrations were observed.

Conclusion: Long-term restorative neurostimulation is an effective, durable, and safe treatment for patients with refractory, activity limiting CMLBP, impaired multifidus motor control and no indications for spine surgery. Clinically substantial improvements, which progressively accrue through two years, are consistent with the restorative mechanism of action.

501. Peri-operative Thalamus Structure and Metabolism Predict Response to Surgical Treatment for Trigeminal Neuralgia

Tejas Sankar, MD, FAANS (Edmonton, Canada); Hayden Danyluk, BSc; Jennifer Andrews, PhD; Rohit Kesarwani, MD; Peter Seres, PhD; Robert Broad, MD; Blaise Wheatley, MD, PhD

Introduction: A non-trivial proportion of patients undergoing surgery for trigeminal neuralgia (TN) are non-responders, experiencing early disabling pain recurrence even after a technically successful procedure. Surgical non-response has been linked to clinical factors (such as pain type and duration of TN) and structural variations of the trigeminal nerve seen on imaging (such as degree of neurovascular compression and alterations in diffusivity metrics at the root entry zone). The thalamus is a key component of the trigeminal sensory pathway involved in transmitting facial pain, but the influence of the thalamus on outcome after TN surgery is relatively understudied.
Methods: We performed a prospective, longitudinal, peri-operative neuroimaging study of the thalamus in medically-refractory TN patients undergoing microvascular decompression or percutaneous balloon compression rhizotomy. Patients underwent structural MRI and MR spectroscopy scans pre-operatively and at 1-week following surgery, and were classified as responders or non-responders based on 1-year post-operative pain outcome (responder --> BNI pain intensity scale ≥ IIIa). Thalamus volume, shape, and metabolite concentration (choline/creatine [Cho/Cr] and N-acetylaspartate/creatine [NAA/Cr]) were evaluated at both time points, and compared between responders, non-responders, and healthy controls.
Results: Twenty healthy controls and 23 TN patients treated surgically (17 responders, 6 non-responders) from 2017-2020 were included. Pre-operatively, TN patients showed significantly larger thalamus volume contralateral to the side of facial pain, and there were also significant contralateral thalamic shape differences between responders and non-responders prior to surgery. As early as 1-week after surgery, long-term non-responders showed distinct decreases in contralateral thalamic Cho/Cr and NAA/Cr, while these changes were not observed in responders.
Conclusion: Durable pain relief after surgery for TN is linked to pre-operative variations thalamic structure, and immediate post-operative changes in thalamic metabolism.

502. Optogenetic Motor Cortex Stimulation Alleviates Neuropathic Pain in Trigeminal Neuralgia Rat Model

Young Seok Park, MD PhD (Cheongju-si, Republic of Korea); Byeong Ho Oh, MD; Hyeong cheol Moon, PhD; Dong Wook Kim, MD; Youn Joo Lee, MD, PhD; Jaisan Islam, MSc; Elina KC, MSc

Introduction: Previous studies have reported that electrical stimulation of the motor cortex is effective in reducing trigeminal neuropathic pain; however, the effects of optical motor cortex stimulation remain unclear. The present study aimed to investigate whether optical stimulation of the primary motor cortex can modulate chronic neuropathic pain in rats with infraorbital nerve constriction injury.
Methods: Animals were randomly divided into a trigeminal neuralgia group, a sham group, and a control group. Trigeminal neuropathic pain was generated via constriction of the infraorbital nerve and animals were treated via selective inhibition of calcitonin gene-related peptide in the trigeminal ganglion. We assessed alterations in behavioral responses in the pre-stimulation, stimulation, and post-stimulation conditions. In vivo extracellular recordings were obtained from the ventral posteromedial nucleus of the thalamus, and viral and α-CGRP expression were investigated in the primary motor cortex and trigeminal ganglion, respectively
Results: We found that optogenetic stimulation significantly improved pain behaviors in the trigeminal neuralgia animals and it provided more significant improvement with inhibited α-CGRP state than active α-CGRP state. Electrophysiological recordings revealed decreases in abnormal thalamic firing during the stimulation-on condition.
Conclusion: Our findings suggest that optical motor cortex stimulation can alleviate pain behaviors in a rat model of trigeminal neuropathic pain. Transmission of trigeminal pain signals can be modulated via knock-down of α-CGRP and optical motor cortex stimulation.

503. Efficacy of Ultra-microdose Intrathecal Morphine Delivery in the Treatment of Chronic Pain

Muhammad Ibrahim Jalal (Horseheads, NY); Muhammad Jalaluddin, MD

Introduction: The use of low dose intrathecal morphine via a morphine drug delivery system has been shown as a promising alternative treatment of chronic pain. A definition for what constitutes a low or "microdose" of intrathecal morphine and its efficacy has not been made clear.This study sought to elucidate the efficacy of "ultra-microdoses" of intrathecal morphine, which we define as less than 0.20 mg, in the treatment of chronic pain.
Methods: Patients were enrolled at St. James Mercy Hospital, University of Rochester, New York from February 2016 to February 2020. An out-patient intrathecal morphine trial was performed by injecting a single dose of 0.1-0.3 mg of preservative free morphine in the lumbar intrathecal space. Following at least 60% reduction in pain compared to baseline, a permanent intrathecal catheter and morphine pump was implanted. The drug delivery system was programmed to deliver "ultra-microdoses" of morphine ranging from 0.065 mg to 0.195 mg over 24 hours in a simple continuous or flexible mode. Follow up visits occurred between 12 and 60 months, and the efficacy of the "ultra-microdoses" was assessed.
Results: Of 58 patients enrolled, 33 met the criteria for "ultra-microdose" treatment (13 male, 20 female, median age 57). The "ultra-microdose" of morphine had a mean dose of 0.13 mg and a median of 0.15 mg. Following treatment with "ultra-microdoses" there was a mean reduction in pain of 8.8 points and median reduction of 9 points on the 0-10 pain scale. 17 of 33 patients reported 100% reduction in pain. There were no infections or complications present in the study.
Conclusion: "Ultra-microdoses" of intrathecal morphine administered via a morphine drug delivery system have a high success rate in the reduction of chronic pain in the patient population without complication. A future multi-center study with a larger sample size is desired.

504. Opioid Use and Discrepancies in the Electronic Medical Record in Patients Undergoing Elective Spine Surgery

Daniel Cummins, BS (San Francisco, CA); Sigurd Berven, MD

Introduction: Significant pre-operative opioid use is associated with adverse outcomes following elective spine surgery, including long-term opioid dependence and peri-operative complications. Daily opioid use >50 and >90 morphine milligram equivalents (MME) may indicate moderate and high-risk, respectively. Accurate quantification of opioid use in the electronic medical record (EMR) is thus essential to optimize surgical outcomes.
Methods: Patients undergoing elective spine surgery May-August 2020 at one academic institution were retrospectively collected. Opioid medications and use were compared between the EMR and California's Controlled Substance Utilization Review and Evaluation System (CURES), a state-wide mandated opioid reporting system. Prevalence and risk factors for daily opioid use >50MME and >90MME were assessed using Chi-squared statistics.
Results: Elective spine surgery was performed for 440 patients, 236 (53.64%) of which had a pre-operative opioid prescription. EMR-recorded opioid data was compared to CURES for 99 of these patients. EMR medications or use was inaccurate for 57.2% of patients, with use underestimated for 25.3%. CURES data showed 31.3% of patients with daily opioid use >50MME and 17.2% of patients >90 MME. Patients taking two opioid medications were significantly more likely than those taking one opioid medication to use >50 MME per day (Two opioids = 91.7%, One Opioid = 28.4%, p<0.001) and >90 MME per day (Two opioids = 58.3%, One Opioid = 14.9%, p=0.002). Age, gender, number of comorbidites, and BMI were not associated with daily opioid use >50 or >90 MME.
Conclusion: In this single-center review of patients undergoing elective spine surgery, pre-operative opioid use in the EMR was inaccurate for over 50% of patients. 31.3% of patients were found to have daily pre-operative opioid use >50MME (moderate risk) and 17.2% >90MME (high risk). Use of >1 opioid medication may serve to screen for moderate to high risk pre-operative opioid use.

505. Graft Length Does Not Impact the Degree of Revascularization with Pial Synangiosis for Moyamoya Disease in Children

Arka N. Mallela, MD, MS (Pittsburgh, PA); Hussam Abou-Al-Shaar, MD; Enyinna Nwachuku, MD; Daniel Tonetti, MD; Stephanie Greene, MD

Introduction: Moyamoya disease is a chronic progressive cerebrovascular disease characterized by progressive occlusion of the distal internal carotid arteries, dilation of the lenticulostriate arteries, and formation of spontaneous collateral blood supply. Pial synangiosis is a technique that involves surgically grafting a donor artery, typically the superficial temporal artery (STA), to the pia to facilitate new vascular ingrowth to supply the subjacent ischemic brain. This neovascularization may occur in response to local vascular growth factors. This study aims to elucidate the role that the length of the donor artery might play in the degree of neovascularization achieved by pial synangiosis.
Methods: In a retrospective case series of 19 patients, 27 pial synangioses were performed. All patients underwent pial synangiosis and were followed for at least one year. Graft length was measured intraoperatively and on 1-year post-operative angiogram. Matsushima grade was determined at the same time and compared with graft length.
Results: Patients in this series were 58% female, with a median age of 10±9.3 years (range: 2-17 years). The primary diagnosis was idiopathic moyamoya disease in 47% of cases. The remaining 53% had conditions associated with moyamoya. The presenting symptom was new neurological deficit attributable to an ischemic event in 37% of cases. Suzuki stage ranged from 2-5. All patients had Matsushima Grade A (93%) or B (7%) revascularization. Intraoperative superficial temporal artery length was a median of 8±1.0 cm in all patients and angiographic length was a median of 6.0±2.2 cm. Patient age, sex, diagnosis, presenting symptom, and intraoperative and angiographic length did not vary significantly by Matsushima grade.
Conclusions: Pial synangiosis is an effective revascularization technique in pediatric patients. The length of the arterial graft does not correlate with degree of revascularization in our series, nor did preoperative Suzuki classification or patient age. The degree of revascularization may depend on the degree of cerebral ischemia and concentration of vascular growth factors, as opposed to arterial length apposing the cortical surface.

506. Feasibility of Cerebello-Cortical Stimulation for Intraoperative Neurophysiological Monitoring of Cerebellar Mutism

Francesco Sala, MD (Verona, Italy); Davide Giampiccolo; Federica Basaldella; Andrea Badari; Giovanna Maddalena Squintani; Luigi Cattaneo

Introduction: Cerebellar mutism can occur in a third of children undergoing cerebellar resections. Recent evidence proposes it may arise from uni- or bilateral resection of cerebellar efferents to the cortex along the cerebello-dento-thalamo-cortical pathway. At present, no neurophysiological procedure is available to monitor this pathway intraoperatively. Here we specifically aimed at filling this gap.
Methods: We assessed 10 patients undergoing posterior fossa surgery using a conditioning-test stimulus paradigm. Electrical conditioning stimuli (cStim) were delivered to the exposed cerebellar cortex at interstimulus intervals (ISIs) of 8-24 ms prior to transcranial electric stimulation of the motor cortex that served as test stimulus (tStim). The variation of motor evoked potentials (MEP) to cStim+tStim compared to tStim alone was taken as a measure of cerebello-cortical connectivity.
Results: cStim alone did not produce any MEP. cStim preceding tStim produced a significant inhibition at 8 ms (p<0.0001) compared to other ISIs when applied to the lobules IV-V-VI in the anterior cerebellum and the lobule VIIB in the posterior cerebellum. Mixed effects of decrease and increase in MEP amplitude were observed in these areas for longer ISIs.
Conclusion: The inhibition exerted by cStim at 8 ms on the motor cortex excitability is likely to be the product of activity along the cerebello-dento-thalamo-cortical pathway. We show that monitoring efferent cerebellar pathways to the motor cortex is feasible in intraoperative settings. This study has promising implications for paediatric posterior fossa surgery with the aim to preserve the cerebello-cortical pathways and thus prevent cerebellar mutism.

507. Often a Big Head is Just a Big Head: Imaging Infants with Macrocephaly

Joseph H. Piatt, Jr., MD, FAANS (Wilmington, DE); Jessica Rohde, MD; Jeffrey Campbell; Joseph Piatt

Introduction: By definition 2.3% of all infants are macrocephalic, but the prevalence of conditions requiring treatment is very small. There are no evidence-based guidelines for selecting macrocephalic infants for imaging.
Methods: A health system imaging registry was queried for requests that mentioned 'macrocephaly,' 'macrocephalia,' or 'head growth' over an 8-year period. Studies reported to show findings of possible neurosurgical concern were reviewed independently by 4 neurosurgeons. If any reviewer judged that the study merited intervention or follow-up, that study became a case. Electronic health records of cases and randomly selected controls were reviewed by 2 independent, blinded reviewers. After exclusions controls were matched to cases by date of study in a 3:1 ratio. Conditional logistic regression identified factors associated with imaging concerns. A predictive scoring system was developed with points proportionate to parameter estimates. Sensitivities, specificities and confidence intervals were calculated for score thresholds.   A parallel secondary analysis was performed for cases that actually required surgical intervention.
Results: Out of 1381 studies of unique patients, there were only 46 (3.3%) cases of neurosurgical concern. Predictive factors entered into the scoring system were bulging fontanel, prematurity < 34 weeks, any developmental delay, and head circumference-weight discrepancy. The optimal score threshold yielded a sensitivity of 0.93 (0.83 – 0.98) and a specificity of 0.28 (0.21 – 0.36).   Only 15 patients (1.1%) required surgery. Factors entered into the scoring system were bulging fontanel, sleep disturbance, and head circumference-weight discrepancy. The optimal score threshold yielded a sensitivity of 0.93 (0.70 – 0.98) and a specificity of 0.83 (0.77 – 0.88).
Conclusion: The proposed scoring systems, incorporated into the electronic record, may augment clinical judgment to reduce unnecessary brain imaging in infancy. Historical growth data and parental head measurements were sparse in the current data set and must be captured in future prospective investigations.

Young Neurosurgeons Abstract Award
508. TRIM71 Mutations Cause Congenital Hydrocephalus by Impairing Prenatal Neural Stem Cell Regulation

Duy Phan; Sheng Jin; Stefan Weise; Claudi Marini; Lucia Torres-Fernandez; Hao Le; Bettina Jux; Haifan Lin; Gregory Wulczyn; Richard Lifton; Waldemar Kolanus; Kristopher Kahle (New Haven, CT)

Introduction: Lack of understanding into the pathogenesis of congenital hydrocephalus (CH) hinders patient care and development of clinically-relevant animal models. Given that 40% of CH cases are thought to have a genetic etiology, human genetics is perhaps the most clinically relevant and unbiased approach to understanding biological mechanisms of CH. However, the overwhelming majority of patients remain genetically undefined, highlighting the urgent need for continued gene discovery. We sought to identify novel disease genes that cause human CH and to understand the biological functions of CH genes in brain development using stem cell and mouse genetic models.
Methods: We recruited 475 neurosurgically-treated primary CH probands, including 284 parent-offspring trios, and subjected them to whole exome sequencing (WES). We also generated mutant mouse and stem cell models harboring CH-causing mutations in genes identified by WES.
Results: We identify the TRIM71/lin-41, encoding an RNA-binding protein enriched in mammalian embryonic neural stem cells (NSCs), to be the most commonly mutated gene in human CH. Three novel Trim71 mutant mouse models that harbor the homologous CH-causing point mutation localized to the TRIM71 RNA-binding domain or NSC-specific Trim71 deletion all exhibited severe neonatal-onset communicating hydrocephalus with cortical thinning observed in human patients. Strikingly, although local CSF flow was normal in hydrocephalic Trim71 mutant mice, cortical neurogenesis was profoundly reduced due to impaired NSC proliferative expansion in the embryonic neural tube. In vitro, CH-causing mutations disturbed NSC self-renewal andTRIM71's posttranscriptional regulation of RNA targets involved in stem cell pluripotency
Conclusion: Our data comprising of human genetics with functional validation in cell lines and three novel mutant mouse models (including the first-ever animal model in which a human-specific disease mutation has been shown to cause hydrocephalus) demonstrate TRIM71 is a bona fide CH gene and support a NSC paradigm of hydrocephalus independent of CSF hydrodynamics.

509. No Woman Alone – Dorothy Russell's Legacy for Neurosurgery

Lena Mary Houlihan, MDMCH, MRCS(I) (Phoenix, AZ); Jubran Jubran, BS; Ann Staudinger Knoll, BS; Dara Farhadi, BS; Richard Leblanc,MD; Mark Preul, MD

Dorothy Russell's contributions to neuropathology are pivotal in the evolution of modern neurosurgery. In an era preferential to men in medicine, she entered the first medical school class to include women at the London Hospital Medical College in 1919. While in the laboratory of Hubert Turnbull, she met Hugh Cairns, a pioneer of neurosurgery who would become her professional neurosurgeon-neuropathologist partner. In 1928, she travelled to North America on a Rockefeller scholarship to study with pathologists and physicians interested in the brain. In 1929 she began to learn the "Spanish method" of histological staining with Wilder Penfield and William Cone, recently arrived at McGill's Royal Victoria Hospital to begin a neurosurgical service. Arguably the world's first neurosurgery research fellow, Russell performed cellular brain studies elucidating the origin and activity of microglia in the nervous system and in philosophical and practical connections between neuropathology and neurosurgery promoted by Penfield and Cone. In London, Russell worked closely with Cairns for many years, participating in the first culturing of gliomas and meningiomas, and analyzing effects of fatal head injuries on soldiers during World War II leading to helmet requirements for army motorcyclists 30 before rules for the general public. She became the first woman to hold a chair in an English university as London Hospital Director of the Institute of Pathology and Professor or Morbid Anatomy, influencing neuropathology as a distinct clinical specialty. Her textbook with Lucien Rubinstein, Pathology of the Tumors of the Nervous System, is a landmark manuscript in neurosurgery, neuropathology and neurooncology. Maintaining a close relationship throughout her career, Penfield and Cone honored Russell and considered her a favorite of the Montreal Neurological Institute: "From London has come our most distinguished pupil." Dorothy Russell's extraordinary career elucidating the mysteries of neurosurgical pathology has made an enduring mark on neurosurgery's legacy. .

510. Evaluating the Impact of Preoperative Epidural Steroid Injections on Postoperative Morbidity and Reoperation Rates Following Lumbar Degenerative Surgery

Kunal Varshneya (San Jose, CA); Jack Michaud, BS; Daniel Herrick, MD; Parastou Fatemi, MD; Jay Nathan; Zachary Medress; John Ratliff, MD; Anand Veeravagu, MD

Introduction: The objective of this study is to determine the postoperative complications and quality outcomes of patients who receive an epidural steroid injection (ESI) prior to undergoing surgical management for lumbar degenerative disease (LDD).
Methods: This study identified patients with who underwent surgery for LDD between 2007 – 2016.   Patients were stratified based on whether the patients received an ESI prior to time of surgery.   Propensity score matching (PSM) was then utilized to mitigate intergroup differences between patients who were given an ESI or ESI naïve. Patients who underwent three or more levels surgical correction, were under the age of 18 years, or those with any prior history of trauma or tumor were excluded from this study.
Results: 3125 patients were surgically treated for LDD including 625 (25%) patients that received an ESI in the 2-year window prior to surgery. There were no baseline differences after PSM. The 90-day composite complication rate was higher in the cohort that received a preoperative ESI compared to the cohort that did not (10.4% vs. 7.8%, p= 0.0385). The rates of post-operative infection between the groups were not statistically different (1.8% in the preoperative ESI cohort vs 1.3%, p = 0. 3569).   Patients that received an ESI in the 2-years prior to surgery had longer length of stay (2.9 days vs. 2.4 days, p < 0.0001) and higher rates or revision surgery at 2 years (6.6% vs. 4.2%, p = 0.0143). The rates of readmission were significantly higher in the patients with preoperative ESI at all time points (30, 60, and 90 days). At 90 days, total costs for preoperative ESI patients was $52,599 compared to $46,852 for patients that did not have an ESI prior to surgery (p = 0.041).
Conclusion: Patients who were ESI naïve at the time of LDD surgery had shorter lengths of stay, lower rates of reoperation and readmission, and led to lower healthcare resource utilization through 2 years of follow-up.

511. Influence of Race on Early Outcomes of Elective Lumbar Interbody Fusions: Propensity-Matched and Subgroup Analysis

Safwan Alomari, MD (Baltimore, MD); Ali Bydon, MD ,FAANS; Jose Porras, MD; Brendan Judy, MD; Timothy Witham, MD

Introduction: Several studies have consistently found that black patients, when compared to white patients, were more likely to have postoperative morbidity and mortality. This updated analysis was conducted to investigate the impact of race (black vs. white) on 30-day peri-operative complication rates of elective lumbar interbody fusions.
Methods: Patients who underwent (PLIF/TLIF) or (ALIF/LLIF) between 2015-2018 were reviewed from ACS-NSQIP database. Propensity score matching and subgroup (single/multi-level) analysis were used.
Results: 17,471 PLIF/TLIF cases and 8,760 ALIF/LLIF cases met inclusion criteria and were reviewed. In both single/multi-level PLIF/TLIF and ALIF/LLIF, black patients were more likely to be younger, have higher BMI, be of female gender, have inpatient admission status, have an ASA class 3 or more, be a smoker, have baseline dyspnea, have hypertension and be functionally dependent. In both single/multi-level ALIF/LLIF, black patients were more likely to have diabetes mellitus. In both groups (single/multi-level PLIF/TLIF and ALIF/LLIF), except for the higher incidence of DVT in the black cohort, there were no significant differences in morbidity and mortality measures between the black and white cohorts.
Conclusion: In contrast to prior literature, our analysis did not identify black race as an independent risk factor for higher perioperative morbidity or mortality in patients undergoing elective lumbar fusion, except for the higher incidence of venous thromboembolism. The findings of the present study are important for clinicians and spine surgeons while counseling patients undergoing these types of procedures. It is important to address patient's concerns and to explain that the previously reported inferior perioperative morbidity and mortality outcomes in black patients might be due differences in baseline health status, and not due to the race difference itself.

512. Focused Ultrasound Mediated Blood Brain Barrier (BBB) Opening of the Hippocampus, Frontal and Parietal Lobes in Mild Alzheimer's Disease: Long-term Safety and Clinical Outcome of a Multi-center Phase II Clinical Trial

Ali R. Rezai, MD, FAANS; Vibhor Krishna; Umer Najib; Manish Ranjan; Mark Haut; Douglas Scharre; Jeffrey Carpenter; Pierre D'haese; Daniel Claassen; Peter Konrad; Sally Hodder; Michael Kaplitt (Morgantown, WV)

Introduction: Magnetic resonance (MR)-guided low intensity focused ultrasound (FUS) is shown to reversibly open the blood-brain barrier (BBB), reduce amyloid-beta plaque, and improve memory in preclinical Alzheimer's disease (AD) models. We present longitudinal safety, imaging, clinical, and amyloid PET outcomes in this on-going multi-center trial of FUS BBB opening of the hippocampus, frontal and parietal lobes in patients with AD.
Methods: Patients with mild AD and positive amyloid PET underwent MRI-guided low intensity FUS (ExAblate Neuro) with concomitant IV microbubble (Definity®) administration during three separate sessions (each 2 weeks apart) targeting hippocampus, frontal and parietal lobes (up to 30cc treatment volume). In this Insightec sponsored study, outcome assessments included safety, BBB status (opening and closure), cognitive evaluations, and amyloid PET. Cognitive evaluations were compared to an age and sex matched cohort of patients with mild AD (Alzheimer's Disease Neuroimaging Initiative - ADNI).
Results: Fifteen subjects completed three treatments each for a cumulative total of 45 separate FUS treatments. All subjects had immediate BBB opening demonstrated by parenchymal IV gadolinium contrast enhancement and BBB closure within 24-48 hours. Treatments were well tolerated with no neurological adverse events (follow-up up to 28 months). Less cognitive decline was observed among participants with > 1-year follow-up (n=7) as compared to a matched ADNI cohort subset; however, the limited sample size precludes meaningful statistical comparison.PET analysis of 9 subjects showed reduction in brain amyloid at 60 days in the regions treated by FUS.
Conclusion: Focused ultrasound mediated BBB opening is feasible, reversible, and safe in multiple large brain regions among persons with AD. Our data suggest that brain amyloid is decreased and cognitive decline may be slowed. Additional participants and further long-term studies are needed to determine clinical significance. FUS provides a unique, non-invasive opportunity for novel and targeted therapeutics.

513. Implant-Free Regulation of CNS Circuit with Magnetogenetic Gene Therapy

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Introduction: Modified ion channels provide powerful opportunities to regulate neuronal circuits with light (optogenetics) or drugs (chemogenetics). Magnetogenetics uses a modified Trpv1 receptor fused to a ferritin nanoparticle, which permits channel control by a magnetic field, allowing more rapid neuronal regulation than chemogenetics while eliminating light implants required for optogenetics. Here we demonstrate that magnetogenetic gene therapy can non-invasively regulate striatopallidal neurons and subthalamic nucleus (STN) projection neurons, resulting in consequent changes in motor behavior.

Methods: Striatopallidal neurons were first targeted via bilateral injection of a adeno-associated virus (AAV) vector encoding a floxed excitatory Trpv1 Ca+ magnetogenetic channel in A2a-Cre mice, which express Cre-recombinase in D2 neurons, followed by motor testing. To target the same neurons in wild type (WT) mice, bilateral injection of the same floxed AAV into the striatum was combined with a bilateral injection of a retrograde AAV (AAVretro) encoding Cre in the globus pallidus externus (GPe). To test this in a disease model, nigral lesions were generated in PitX-2-Cre mice, which express Cre in the STN, followed by ipsilateral injection of an AAV with a floxed inhibitory Trpv1 Cl- magnetogenetic channel. A 3T MRI was the source of direct magnetic field (DMF) for behavioral assessments.

Results: Magnetogenetic activation of indirect pathway upon DMF exposure caused profound freezing in both A2a-Cre and WT mice that was reversible post-DMF. Striatal c-fos expression and fluorodeoxyglucose uptake on PET were both increased following DMF consistent with activation. Magnetogenetic inhibition of the STN reduced drug-induced rotations in lesioned mice, consistent with therapeutic normalization of STN function.

Conclusion: Magnetogenetics is a robust, reversible, and implant-free method to regulate brain circuits. Combining AAVretro-Cre and floxed-AAV constructs allowed regulation of specific circuits in normal animals to the same degree as in cre-driver mice, which creates the potential for translation into humans.

514. Diffuse Axonal Injury and Cerebral Contusions on MRI are Associated with Poorer Functional Outcome in CT-Negative TBI

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Introduction: Intracranial pathology on MRI after traumatic brain injury (TBI) is heterogeneous, and prior studies have shown associations between contusions, axonal injury and poorer 3-month outcome. We assessed correlations between radiographic injury patterns and 6-month outcome in a prospective cohort of acute TBI patients with negative initial head CT (CT-) presenting to US Level 1 trauma centers.

Methods: CT- TBI subjects from the prospective Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) who completed a 2-week research MRI and 6-month Glasgow Outcome Scale-Extended (GOSE) were included. GOSE was dichotomized to good recovery (7-8) vs. moderate disability or worse (<7). MRIs were scored according to NINDS Common Data Elements by a central board-certified neuroradiologist, and included traumatic axonal injury (TAI, 1-3 foci of shear) and diffuse axonal injury (DAI, >3 foci of shear). Odds ratios (OR) and [95% confidence intervals] are provided.

Results: In 108 CT- subjects, 29% were MRI+ (18% TAI-only, 4% DAI-only, 3% subdural hematoma (SDH)-only, 2% TAI+Contusion, 2% DAI+Contusion+SDH, 1% Contusion-only). Subjects were aged 36.8±14.9 years, 31% male, 72% Caucasian, with mean GCS 14.6±1.4, and 40% were admitted to hospital, which did not differ by MRI+/-. At 6 months postinjury, 32% had moderate disability or worse (GOSE <7), which did not differ significantly by MRI+/- but differed by DAI+/- and Contusion +/- on subgroup analyses (MRI-: 28.6%, MRI+ without DAI/Contusion: 27.3%, DAI+: 80%, Contusion+: 60%). The combined DAI/Contusion+ group was more likely to have GOSE<7 compared to those without DAI/Contusion (66.7% vs. 28.3%, OR=5.07 [1.19-21.69]).

Conclusion: In a cohort of TBI patients with negative initial head CT, presence of diffuse axonal injury and contusion on MRI was associated with significantly worsened 6-month clinical outcomes. MR imaging in acute TBI may be a more sensitive assessment tool for predicting persistent functional disability.

515. Trigeminal Nerve Stimulation Promotes Neurovascular Coupling in a Rat Model of Stroke

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Introduction: Ischemic stroke causes decreased neurovascular coupling, leading to a failure of cerebral autoregulation. As such, neuroprotective therapies that restore neurovascular coupling could reduce brain damage. The trigeminal nerve directly innervates key vascular structures. We aim to investigate the effect of electrical trigeminal nerve stimulation (TNS) to rescue cortical neurovascular coupling responses to spontaneous and induced cortical spreading depolarization (CSD).

Methods: Studies were performed on 25 male Sprague-Dawley rats. Animals were randomized to two groups with middle cerebral artery occlusion (MCAO): (1) control animals; (2) animals with 1-h TNS. Susceptibility to CSD was evaluated by measuring spontaneous CSD frequency and CBF responses for the first 3-h after MCAO. Cortical neurovascular coupling responses were analyzed by application of 1M KCl for 1-h at 23-h after MCAO. CBF responses immediately before and after KCl application were compared between stimulated and non-stimulated animals. Brains were collected for measurement of lesion volume and eNOS mRNA expression at 24-h.

Results: During the 3-h after MCAO, spontaneous waves of CSD appeared in peri-infarct zone. TNS treatment significantly reduced CSD frequency (9±2.9 vs. 2.2±0.9). Upon occlusion, CBF immediately fell by ~67%. After 3-h MCAO, CBF further decreased in control animals, while TNS treatment prevented further CBF declines (fell by 81% vs. 69%). At 23-h after MCAO, CBF changes in response to KCl-induced CSD were significantly decreased in control rats compared with TNS rats (-23% vs 57%). TNS decreased lesion volume (31% vs. 13%) and increased eNOS mRNA expression (1.3-fold vs. 3.7-fold). These results indicate that neurovascular coupling was impaired at 24-h in MCAO-control rats, and TNS restored eNOS-mediated neurovascular coupling.

Conclusion: Our results demonstrate TNS suppresses susceptibility to CSD after MCAO and restores cortical neurovascular coupling by upregulation of eNOS expression ultimately salvaging penumbral tissue.

516. Glymphatic System Alteration Following Circadian Rhythm Disruption Impacts Chronotherapy

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Introduction: The glymphatic system is a network of paravascular spaces (PVS) surrounding the brain vasculature. The cerebrospinal fluid (CSF) passes from the subarachnoid space surrounding the brain into these PVS. Aquaporin-4 (AQP4) channels on the glia surrounding the PVS move CSF into the brain parenchyma. Large proteins are removed through this flow. Glymphatic impairment has been implicated in a multitude of neurosurgical conditions including neurodegeneration, hydrocephalus, stroke and subarachnoid hemorrhage. Little is known about whether circadian rhythm disruption impairs glymphatic flow and whether drug modulation of the glymphatic transport could alter glymphatic impairment.

Methods: Intracisternal injection of Texas Red dextran (TRd3) and confocal imaging to assess diurnal variation of glymphatic transport within the hippocampus and SCN. We subjected rats to circadian disruption by maintaining in a 10h:10h light-dark cycle. Vasopressin was injected subcutaneously followed by intracisternal injection of TRd3. TRd3 spread into the parenchyma was analyzed along with AQP4 paravascular expression.

Results: SCN and hippocampus displayed diurnal variation in glymphatic flow; however, they are in antiphase to each other-- the TRd3 intensity is higher in the SCN during night and the hippocampus during day. The hippocampus AQP4 peaks during nighttime. Glymphatic flow and AQP4 expression were assessed after circadian disruption. Hippocampus from 10:10 LD rats displayed diminished glymphatic flow and AQP4 expression compared to controls. Paradoxically, TRd3 accumulated within the DG granular cell layer. A similar shift in amyloid β accumulation in grey matter has been reported in brains of Alzheimer's patients (Klunk et al., 2004). Vasopressin administration reversed the lower glymphatic flow within the hippocampus during the night and the SCN during the day.

Conclusion: SCN and hippocampus displayed diurnal variation in glymphatic flow. Circadian-rhythm disruption altered the glymphatic flow and AQP4 levels in SCN and hippocampus. Vasopressin administration enhanced the glymphatic flow within the hippocampus and SCN.

517. Induced Suppression of Platelets Activity in Aneurysmal SAH Management (ISPASM) to Prevent Delayed Cerebral Ischemia

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Introduction: Microthrombosis could play a role in delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (aSAH). Tirofiban has shown promising results in reducing DCI in retrospective studies. However, the safety and efficacy of tirofiban in aSAH is not rigorously established.

Methods: A phase 1/2a double-blinded randomized controlled trial (2:1 randomization) was conducted to assess the safety of a 7-day intravenous infusion (IV) of tirofiban compared with placebo, in patients with aSAH treated with ventriculostomy and coiling. The primary safety outcome was any intracranial hemorrhage during the hospital stay. The secondary efficacy outcome was the incidence of DCI in the 2 groups to determine the need for a phase 2b trial. Other secondary outcomes were also evaluated.

Results: Eighteen patients received IV tirofiban and 12 received placebo. There was no difference in baseline characteristics except for higher male proportion in the tirofiban group. There was no difference in death, in development of new or change in existing intracranial hemorrhages, in thrombocytopenia, or in need for shunts between the two arms. On the other hand, the tirofiban arm had a lower incidence of DCI compared with placebo [6% (1/18) vs. 33% (4/12); p=0.04], and less radiographic vasospasm as detected by catheter angiogram or CT angiography (p=0.01) and CT perfusion (p=0.01).

Conclusion: Our results suggest that 7-day IV infusion of tirofiban is safe and resulted in substantial reduction in DCI. These findings endorse tirofiban as a synergistic intervention to nimodipine to prevent DCI after SAH and warrant a pivotal phase 2b/3 trial.

518. Intervention for Unruptured High-grade Intracranial Dural Arteriovenous Fistulas: A Multicenter Study

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Introduction: The risk-to-benefit profile of treating an unruptured high-grade dural arteriovenous fistula (dAVF) treatment is not clearly defined. The aim of this multicenter retrospective cohort study is to compare the outcomes of different interventions to observation for unruptured high-grade dAVFs.

Methods: We retrospectively reviewed dAVF patients from 12 institutions participating in the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR). Patients with unruptured high-grade (Borden type II or III) dAVFs were included, and they were categorized into four groups (observation, embolization, surgery, and stereotactic radiosurgery [SRS]) based on the initial management. Primary outcome was defined as modified Rankin Scale (mRS) at final follow-up. Secondary outcomes were good outcome (mRS 0–2) at final follow-up, symptomatic improvement, all-cause mortality, and dAVF obliteration. We compared the outcomes of each intervention group against those of the observation group as a reference, with adjustment for differences in baseline characteristics.

Results: The study included 415 dAVF patients, comprising 29, 324, 43, and 19 in the observation, embolization, surgery, and SRS groups, respectively. The mean radiological and clinical follow-up durations were 21 and 25 months, respectively. Functional outcomes were similar for embolization, surgery, and SRS compared to observation. With observation as a reference, obliteration rates were higher after embolization (aOR=7.147, p=0.010) and surgery (aOR=33.803, p<0.001) and all-cause mortality was lower after embolization (aOR=0.171, p=0.040). Hemorrhage rates per 1000 patient-years were 101 for observation versus 9, 22, and 0 for embolization (p=0.022), surgery (p=0.245), and SRS (p=0.077), respectively. Non-hemorrhagic neurological deficit rates were similar between each intervention group versus observation.

Conclusion: Embolization and surgery for unruptured high-grade dAVFs afforded a greater likelihood of obliteration than observation. Embolization also reduced the risk of death and dAVF-hemorrhage compared to conservative management over a modest follow-up period. Our findings support embolization as the first-line treatment of choice for appropriately selected unruptured Borden type II and III dAVFs.

519. Examining Aneurysmal Healing after Flow Diversion Treatment using Endovascular Optical Coherence Tomography

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Introduction: The mechanism of aneurysmal healing after flow diversion treatment of cerebral aneurysms remains unknown. The two hypothesized mechanisms of healing include: 1) Altered hemodynamics causing subsequent aneurysmal thrombosis, and 2) Endothelialization over the stent across the aneurysm neck. To improve our understanding of healing after flow diversion, we utilized structural and doppler optical coherence tomography (OCT) in a rabbit aneurysm model, enabling real-time endovascular examination of endothelialization over stent-struts, and hemodynamic conditions within the aneurysm sac.

Methods: Saccular aneurysms were created in 10 New Zealand white rabbits. The aneurysms were treated with a flow diverting stent 28 days after creation. Structural and doppler OCT images were acquired before and after stent placement. Repeat structural and doppler OCT images were acquired 28 days after stent placement. The subjects were subsequently euthanized and the aneurysm/stent specimen was harvested for histologic processing, specifically examining for endothelialization across the stent, organized thrombus formation within the sac, and comparing histology with OCT findings.

Results: Aneurysms were successfully created, treated with flow diverting stents, and imaged with structural and doppler OCT. Structural OCT revealed endothelialization across the stent, appearing to originate from the parent vessel, along with small amounts of thrombus on the stent-struts. Minimal thrombus was visualized within the aneurysm sac, and doppler OCT revealed ongoing flow in all aneurysms where incomplete neck endothelialization was observed. Histologic examination revealed OCT can accurately define endothelialization across the sent, and define patent segments across the neck.

Conclusion: Aneurysmal healing appears to originate at the parent vessel/stent interface, using the stent as a scaffold for endothelial growth across the neck of the aneurysm. Minimal thrombus was visualized within the aneurysm sac, with ongoing flow observed in the setting of incomplete neck endothelialization. OCT can reliably reveal stent/vessel malapposition and differentiate between endothelium and thrombus.

520. Patient and Spine Surgeon Perceptions on Shared Decision Making in the Treatment of Older Adults Undergoing Corrective Surgery for Adult Spinal Deformity

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Introduction: Surgery for correction of adult spinal deformity is often beneficial, however, in over 20% of older adults' (age>65 years), outcomes from surgery are less desirable. Deciding between treatment strategies presents a considerable decision-making challenge for older adults, however to date, patients' and spine surgeons' perspectives on shared-decision making in older adults considering spinal surgery remain poorly understood.

Methods: Using purposive sampling we identified older adult patients who underwent deformity correction surgery and were both satisfied and not satisfied with outcomes based on their responses to the Ottawa decision regret questionnaire. We conducted semi-structured, in-depth interviews with six older adult patients, and five fellowship trained spine surgeons. Two investigators independently coded the transcripts using constant comparative method, and an integrative, team-based approach to identify themes.

Results: Three patient themes emerged: (1) patients mentally committed to surgery prior to the initial encounter with their surgeon and felt that surgery was their only choice; (2) patients felt that the current decision support tools were not effective in preparing them for surgery; and (3) patients felt that pain management was the most difficult part of recovery from surgery. Three surgeon themes emerged: (1) spine surgeons did not consider patients' chronological age as a major contraindication to undergoing surgery, however, preoperative functional limitations were strongly considered; (2) while spine surgeons intuitively understood the concept of shared decision making, they varied substantially in their interpretations; (3) spine surgeons felt that patient expectations from surgery were often established prior to their initial surgery visit, frequently required recalibration, and there is a goal mismatch where patients prioritize complete pain relief while surgeons prioritize concrete functional improvement.

Conclusion: Older adult patients' felt they were "running out of time" and surgery as the "only choice"; whereas spine surgeons expressed the need for recalibrating patient expectations and balancing the risks and benefits when considering surgery. The variability in the discussions surrounding deformity correction surgery highlights the need for improved understanding of both sides of shared decision making.

521. Baseline Myelopathic Severity is an Independent Determinant of Adverse Outcomes, Complications and Functional Recovery Following Adult Cervical Deformity Corrective Surgery

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Introduction: Little is known of the impact of myelopathy severity in CD patients on patient-reported outcomes when taking into account symptomatic presentation.

Methods: Surgical CD patients with baseline HRQLs and radiographic follow-up [1-yr]. mJOA assessed baseline myelopathy severity, Tetreault et al.(Severe <12). Ratios of baseline myelopathy groups to neck disability groups (Vernon et. al:), assessed myelopathy in conjunction with neck disability. A ratio >1 indicated that myelopathy severity weighed more than neck disability, and vice versa. In a subanalysis, Severe and Not Severe myelopathy groups were PSM for cSVA. Univariate analyses were performed to determine whether myelopathy severity impacted postop outcomes.

Results: 136 CD patients included (56.6yrs, 49%F, 29.9kg/m 2). Baseline mJOA: 13.1±2.9, NDI of 58.9±18.8. 28.7% had Severe baseline myelopathy, 71.3% Not Severe. Severe patients had greater baseline NDI scores (68.2 vs Not Severe: 55.1, p<0.001). Ratios distribution can be seen in Table 1. Patients more impacted by myelopathy had greater postop neurological complications (25%, vs greater NDI: 3%, p=0.042) and DJK (25%), p=0.034. After PSM for cSVA in the subanalysis, 26 patients remained in Severe and Not Severe myelopathy groups. Severe had increased neuro complications(15.4%) and met MCID for EQ5D significantly less than the Not Severe baseline myelopathy patients (11.5% vs 34.6%), both p<0.05. From baseline to 1-year, 31.5% improved, 49.3% same, and 19.2% deteriorated in their myelopathy severity. Patients who improved in mJOA severity by 1-yr had less incidence of DJK (0% vs 8.3 vs 28.6).

Conclusion: Patients who report more severe myelopathy over neck disability preoperatively are at increased risk for neurologic complications and distal junctional kyphosis occurrence. When controlling for baseline deformity severity, this remained true for patients with severe myelopathy presentation along with decreased overall quality of life at follow up.

522. Fusion Technique Affects Patient Satisfaction Scores for Patients with Degenerative Lumbar Disease

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Introduction: In addressing degenerative lumbar disease, surgeons may opt for transforaminal lumbar interbody fusion (TLIF) or anterior lumbar interbody fusion (ALIF) approaches as they offer similar outcomes but pose distinct complication profiles such as operative time, vessel injury, and incidental durotomy. However, the Value Based Purchasing (VBP) reimbursement model has made it increasingly important for surgeons to additionally understand how these techniques compare with newly emphasized metrics, such as the patient satisfaction Hospital Consumer of Assessment of Healthcare Providers and Systems (HCAHPS) survey. This study aims to compare patient satisfaction scores and patient reported outcomes between TLIF and ALIF.

Methods: This is a retrospective study of patients who underwent spine surgery between 2010 and 2020 at a tertiary care center. Operative reports were reviewed for lumbar interbody fusions and patients who underwent TLIF or ALIF were included for analysis. Gathered data included patient demographic, PROMIS Global Health scores, Visual Analog Scale scores for Back Pain, and overall provider rating score on the HCAHPS survey. Outcome and satisfaction measures were analyzed using standard statistical methods.

Results: 185 patients were included in the final analysis. Overall patient satisfaction was significantly higher in those undergoing TLIF versus ALIF operations (80% vs 59%, p = 0.005). Additionally, no differences were found between groups with regards to improvement in VAS or PROMIS-GH scores at three and six months postoperatively.

Conclusion: Since the implementation of VBP, patient satisfaction is increasingly used as a measure of the quality of care. The surgical management of lumbar degenerative disease is unique in that there are several ways to treat the same pathology. The present study demonstrates that while improvements in patient reported outcomes in the early post-operative period are similar, significant differences in patient satisfaction are present. These findings can serve as an added variable in clinical decision-making.

523. Spinal versus General Anesthesia for Minimally-Invasive Transforaminal Lumbar Interbody Fusion (MIS-TLIF): Implications on OR time, Pain and Ambulation

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Introduction: Recently there has been increasing interest in the use of spinal anesthesia for spine surgery. Despite the wide adoption of spinal anesthesia by the orthopedic practices, it has not gained wide acceptance in spine surgery. Studies in lumbar laminectomy and discectomy have found that spinal anesthesia reduces perioperative costs, and leads to a reduction in analgesic use, shorter anesthesia and surgery time. This retrospective, case-controlled study was conducted to assess the notion that spinal anesthesia is both safe and efficacious in the treatment of patients undergoing minimally-invasive transforaminal lumbar interbody fusion (MIS-TLIF).
Methods: We analyzed 40 consecutive patients that underwent MIS-TLIF by a single surgeon, 20 under spinal anesthesia, 20 under general anesthesia. We collected procedure times, intraoperative and postoperative adverse events, length of stay, 3-hour PACU pain VAS, opioid medications and time to first ambulation.
Results: The groups were homogeneous for clinical characteristics. We found a decrease in total OR time for patient that underwent an MIS-TLIF under spinal anesthesia, mean OR time 156.5±18.9 minutes versus 213.6±47.4 (p<0.0001), a reduction of 27%. A reduction in total procedure time, 122 ± 16.7 minutes versus 175.2 ±10 (p<0.0001). No significant differences were found in intraoperative and postoperative adverse events. A difference in max VAS pain score during the first 3 hours in the PACU, with the spinal anesthesia group with 4.8±3.5 versus 7.3±2.7 (p=0.018), even though there was no significant difference in morphine equivalents received by the groups. A difference was also observed in mean VAS pain score during the first 3 hours in the PACU, with the spinal anesthesia group with 2.4±2.1 versus 4.9±2.3 (p=0.001). A difference was observed in time to first ambulation, with the spinal anesthesia group ambulating on average after 385.8±353.8 minutes after leaving the OR, versus 855.9±337.4 minutes (p<0.0001).
Conclusion: Our study demonstrates that spinal anesthesia is safe and effective for performing MIS-TLIF, offering unique advantages to general anesthesia, including reduced postoperative pain, reduced OR time and faster postoperative mobilization.

524. Local Delivery of an IL-15 Superagonist Using a Replicating Retrovirus Significantly Improves Survival and Lymphocyte Infiltration in a Mouse Model of Glioblastoma

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Introduction: Glioblastoma (GBM) leads to severe systemic and local immunosuppression, limiting T cell-mediated killing of tumor cells. IL-15 is a promising immunocytokine with the ability to stimulate T cell activation and proliferation. In this study, we evaluate the treatment efficacy of RLI (an IL-15 superagonist) delivered to tumor cells using a tumor-selective retroviral replicating vector (RRV) in the poorly immunogenic murine SB28 model of GBM.
Methods: First, the ability of RRV-RLI to replicate and spread in cultured SB28 cells was confirmed by intracellular staining and analysis by flow cytometry. Production and function of RLI expressed from RRV-transduced SB28 cells was confirmed by ELISA and T cell proliferation in culture, respectively. Next, tumor growth inhibition in vivo was assessed after stereotactic intratumoral delivery of RRV-RLI to luciferase-expressing SB28 orthotopic intracerebral tumors established in syngeneic C57BL/6 mice. Changes in the tumor immune microenvironment were evaluated by flow cytometry.
Results: RRV-RLI replicated and spread to >95% of cultured SB28 cells. Transduced SB28 cells expressed high levels of RLI (73.3 ng/mL), which sustained T cell growth   in culture. Treatment with RRV-RLI by stereotactic injection into intracerebral murine SB28 tumors significantly reduced tumor growth on bioluminescence imaging, and increased median survival relative to control mice (19 vs. 55 days, p=0.0016), leading to long-term survival in a subset of treated mice. RRV-RLI treated tumors showed significantly increased CD3+ immune cell and CD8+ T cell infiltration, without changes in immunosuppressive cell populations, including myeloid-derived suppressor cells or T regulatory cells.
Conclusion: Local RLI immunotherapy delivered with an RRV results in anti-tumor changes to the tumor immune microenvironment associated with a significant survival benefit in a poorly immunogenic model of GBM. This localized tumor-specific immunomodulatory gene therapy has the potential to safely reverse the T-cell depleted immunophenotype of GBM.

525. Single Cell Sequencing of Tumour Infiltrating Lymphocytes Reveals Low and Variable Tumour-Reactivity in Glioblastoma

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Introduction: Glioblastoma (GBM) is the most common and malignant primary brain tumour in adults. Its poor prognosis is due to the inevitability of recurrence, which is thought to be, in part, due to a highly immunosuppressive environment. Bulk T cell receptor (TCR) repertoire analysis of the highly exhausted tumour infiltrating lymphocytes (TIL) has shown increased clonality. It has been assumed that these expanded clonotypes are tumour reactive but without functional data to support this. Here we present our novel single cell TCR sequencing (scTCRseq) technique that allows for in depth TCR repertoire analysis, including testing of tumour specificity.
Methods: Fresh tumour samples and blood was taken at the time of surgery. Peripheral blood mononuclear cells (PBMC) were separated out using a ficoll gradient. Tumour samples were dissociated into single cell suspension and were used to establish primary cell lines. PBMC/TIL were single-cell sorted by FACS and subjected to scTCRseq. scTCRseq analysis was performed using an in-house pipeline. Expanded TCR were cloned into both reporter Jurkat cell line and primary T cells. Tumour specificity was defined by activation markers and intra-cellular cytokine staining on flow cytometry.
Results: The TIL population exhibited high levels of PD-1 and HLA-DR expression compared to PBMC. scTCRseq reveals MAIT cell infiltration across multiple patients. There are no other shared TCR motifs between patients. There isincreased clonality and reduced diversity in TIL. Several expanded TCR in TIL are known public TCR specific to viral or tumour-associated antigens. Interrogation of the expanded TCR reveals that there are very few tumour specific TCR present in TIL and they are not highly expanded.
Conclusion: We present, for the first time, the TCR repertoire of TIL in GBM at a single cell level. We show that, although the TCR repertoire in TIL is more clonal and less diverse, the assumption that this represents increased tumour reactive T cells is not correct and may explain the lack of efficacy of current immunotherapeutic strategies.

526. Locally Proliferating Macrophages in Angiogenic Niches of Adult Glioblastoma: A New Cell Population Supporting Tumor Microenvironment.

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Introduction: The immune landscape of adult glioblastomas (GBM) is central to shaping clinical phenotypes. We currently believe that the most abundant immune cell type in GBM, tumor associated macrophages (TAM) are populated by conversion of resident microglia or recruitment of bone marrow derived macrophages. Analysis of non-neoplastic conditions have suggested locally proliferating macrophages contribute to pathogenesis in atherosclerosis and chronic infections. In this study we hypothesize the existence of a locally proliferating TAM population in adult GBM and investigate their geographical distribution, microenvironmental correlates and associations with outcome.
Methods: We surveyed 2 distinct single cell gene expression datasets using standard computational pipelines comprising of 10 GBMs from distinct patients yielding total of 11922 cells. Cell identity, proliferation labels, and treatment resistance features were derived from established gene signatures. Correlates with geographic distribution, cellular microenvironment and survival correlates were derived from two distinct bulk datasets (total 192 samples from 80 patients).
Results: We found a cell cluster of TAMs in five tumors which enriched in proliferative signatures constituting 4,3%-9,7% of TAMs population. Further analysis of bulk tumor datasets with topological labels found cycling TAM enrichment in areas of microvascular proliferation. Investigating microenvironmental drivers of proliferating TAM found good correlations with abundance of mesenchymal tumor cells (R=0.52, p<2.2e -16). Finally, the inferred abundance of cycling TAM was significantly higher in short versus mid and long-term survivors (meta gene score 0.005 vs 0.020 vs -0.045 p=0.012, Kruskal – Wallis test).
Conclusion: We present multiple lines of evidence using single cell and tumor bulk gene expression data regarding a new population of immune cells that may be supporting TAMs by local proliferation. We further demonstrate that this proliferating pool of macrophages are highly abundant in areas of vascular proliferation and are potentially stimulated by neoplastic cells carrying mesenchymal identity. We finally show significantly higher enrichment of proliferating macrophages in short-term survivors of GBM implying pro-oncogenic functions.

527. Vaccination with Irradiated Whole Tumor Cells Pulsed With Phagocytic Agonists, TLR Ligands and Anti-CD40 Antibody Stimulates Antitumor Immune Response Against Metastatic and CNS Tumors

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Introduction: Vaccination with irradiated whole tumor cells (rWTC) mixed with immunostimulatory adjuvants has been identified as a promising immunotherapeutic strategy against solid tumors. Optimization of the rWTC vaccine strategy with amphiphilic phagocytic agonists and immunostimulatory adjuvants to target metastatic and CNS tumors has not been explored. Here, we assessed the therapeutic efficacy of an rWTC vaccine, pulsed with a phagocytic agonist (Mannan-BAM), TLR ligands and anti-CD40 antibody (collectively abbreviated as rWTC-MBTA) to control tumor growth and improve survival in micewith metastatic lesions or CNS tumors.
Methods: Syngeneic glioma (GL261) and colon carcinoma (CT26) models were established to assess the rWTC-MBTA vaccine's efficacy in generating immune responses against metastatic lesions and CNS tumors.
Results: In the glioma model, subcutaneous injection of irradiated GL261 cells pulsed with MBTA (rGL261-MBTA) resulted in the complete regression of intracranial gliomas in 70% (7/10) of treated animals. In the colon carcinoma model, subcutaneous injection of irradiated CT26 cells pulsed with MBTA (rCT26-MBTA) significantly reduced metastatic CT26 tumor growth rates and induced complete remission (CR) in 28.6% (2/7) of treated animals. Tumor infiltrating leukocyte analyses demonstrated significantly increased CD8+ cytotoxic T-lymphocytes (CTL) in metastatic tumors with higher percentages of TNFα and IFNγ positive cells. Therapeutic effect of MBTA was abrogated in CD4 + and CD8 + lymphocyte depleted mice. Further assessments with MHC I tetramers revealed significantly increased CT26-associated peptide (AH1) specific CTLs in the blood and tumors of rCT26-MBTA Vaccine treated animals. All animals that achieved complete remission in the colon carcinoma model resisted subsequent peripheral and intracranial challenges with CT26 cells, confirming the induction of immunological memory against CT26 tumors.
Conclusion: Collectively, our investigation demonstrates that rWTC-MBTA Vaccines can effectively induce a tumor-specific adaptive immune response that can target metastatic and CNS tumors.

528. Equivalent Radiographic and Clinical Outcomes with Particle or Liquid Embolic Agents for Middle Meningeal Artery Embolization of Nonacute Subdural Hematomas: Experience from A Multi-Institutional Database of 208 Patients

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Introduction: Middle meningeal artery (MMA) embolization is an efficacious minimally invasive treatment for nonacute subdural hematomas (NASHs). It remains unclear whether outcomes differ depending on embolic agent used. The objective of this study was to evaluate radiographic and clinical outcomes after particle or liquid MMA embolization.
Methods: Patients who had MMA embolization for NASH in November 2017–February 2020 were retrospectively identified from 15 institutions. Three subgroups were evaluated based on embolization timing: upfront (without surgical intervention), after recurrence, or with concomitant surgery (prophylactic). The primary radiographic and clinical outcomes—50% NASH thickness reduction and need for surgical retreatment within 90 days, respectively—were compared for liquid and particle embolizations.
Results: The upfront, recurrent, and prophylactic subgroups included 133, 59, and 16 patients, respectively. The primary radiographic outcome was observed in 61.8%, 61%, and 72.7% of particle-embolized patients and 61.3%, 55.6%, and 20% of liquid-embolized patients, respectively (p=0.457, 0.819, 0.755). Hazard ratios comparing time to reach radiographic outcome in the particle and liquid groups were 1.31 (95% CI 0.78-2.18; p=0.310), 1.09 (95% CI 0.52-2.27; p=0.822), and 1.5 (95% CI 0.14-16.54; p=0.74), respectively. Among patients who underwent particle embolization, 8.0%, 2.4%, and 0% required surgical retreatment, respectively, compared with 0%, 5.6%, and 0% who underwent liquid embolization (p=0.197, 0.521, 1.00).
Conclusion: MMA embolization with particle and liquid embolic agents appears to be equally effective in treatment of NASHs as determined by the percentage who reach, and the time to reach, 50% NASH thickness reduction and the incidence of surgical reintervention within 90 days.

529. A Propensity-adjusted Comparison of Middle Meningeal Artery Embolization versus Conventional Therapy for Chronic Subdural Hematomas

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Introduction: Middle meningeal artery (MMA) embolization is a promising treatment strategy for chronic subdural hematomas (cSDHs). However, studies comparing MMA embolization and conventional therapy (surgical intervention and conservative management) are limited. The authors aim to compare MMA embolization versus conventional therapy for cSDHs using a propensity-adjusted analysis.
Methods: A retrospective study of all patients with cSDH who presented to a large tertiary center over a 2-year period was performed. MMA embolization was compared with surgical intervention and conservative management. Neurological outcome was assessed with modified Rankin Scale. A propensity-adjusted analysis compared MMA embolization versus surgery and conservative management for all individual cSDHs. Primary outcomes included change in hematoma diameter, treatment failure, and complete resolution at last follow-up.
Results: A total of 231 patients with cSDH met the inclusion criteria. Of these, 35 (15%) were treated using MMA embolization, and 196 (85%) were treated with conventional treatment. On latest follow-up, there were no statistically significant differences between groups in the percentage of patients with worsening mRS. Of the 323 total cSDHs found in 231 patients, 41 (13%) were treated with MMA embolization, 153 (47%) were treated conservatively, and 123 (38%) were treated with surgical evacuation. After propensity adjustment, both surgery (odds ratio [OR] 12, 95% confidence interval [CI] 1.5-90, p=0.02) and conservative therapy (OR 13, 95% CI 1.7-99, p=0.01) were predictors of treatment failure and incomplete resolution on follow-up imaging (OR 6.1, 95% CI 2.8-13, p<0.001, and OR 5.4, 95% CI 2.5-12, p<0.001, respectively) when compared with MMA embolization. Additionally, MMA embolization was associated with a significant decrease in cSDH diameter on follow-up relative to conservative management (-8.3 mm, 95% CI -10.4 to -6.3, p<0.001).
Conclusion: This propensity-adjusted analysis suggests that MMA embolization for cSDH is associated with a greater extent of hematoma volume reduction with fewer treatment failures than conventional therapy.

530. Neuro-immunomodulation after Moderately Severe Traumatic Brain Injury Prevents Post-traumatic Hydrocephalus

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Introduction: People who suffer severe traumatic brain injury (TBI) are at risk for developing post-traumatic hydrocephalus (PTH). PTH causes a lifelong need for CSF diversion and consumes substantial healthcare resources. Typically, PTH occurs in the subacute period, opening a window of opportunity to intervene medically to enhance restoration of healthy CSF dynamics. Given that PTH is more likely to occur along with systemic inflammation, we hypothesized that a subacute neuro-immunomodulatory cocktail given after TBI can prevent PTH.
Methods: Juvenile rats of both sexes received systemic immune system priming doses of lipopolysaccharide on postnatal day 21 (P21) and P23. On P25, under anesthesia rats received an incision and midline closed skull impact. Shams underwent similar anesthesia and incision without impact. Injured rats were randomized to treatment (erythropoietin (EPO) 1000U/kg on P26-P30, P32, P34 plus melatonin (MLT) 20 mg/kg P26-35), or vehicle. Observers were blinded. Opening pressure was measured on P45. Serum and brain were collected. Ex vivo MRI was performed to quantify ventricular volume. Serum biomarkers were quantified electrochemiluminescence. Data were compared with two-way ANOVA with Bonferroni or Kruskal-Wallis with Dunn's correction, with p<0.05 considered significant.
Results: At P45 PTH-veh rats (n=18) exhibited elevated opening pressure compared to controls (n=13,p<0.001) and PTH-EPO+MLT rats (n=8,p=0.04). Similarly, PTH-veh rats had ventriculomegaly compared to shams (n=10/group,p<0.001). PTH-veh rats also had elevated serum levels of chemokine CCL2, and interleukin 1-beta compared to shams that normalized with EPO+MLT treatment (n=7/group, all p<0.001).
Conclusion: PTH contributes significant burden to people who suffer severe TBI. Using a novel preclinical model, we show neuro-immunomodulation with EPO+MLT after TBI prevents symptomatic PTH and normalizes serum biomarkers. These results demonstrate that the injury that causes PTH can be modulated, potentially preventing the need for shunt dependence.

531. Improved Pressure Equalization Ratio Following Mannitol Administration in Severe TBI Patients – A Potential Bedside Marker for Response to Therapy

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Introduction: Performing a CSF drainage challenge can be used to measure the pressure equalization (PE) ratio which describes the extent to which cerebrospinal fluid (CSF) drainage can equalize pressure to the height of the external ventricular drain and may serve as a correlate of cerebral edema. We sought to assess whether treatment with mannitol improves PE ratio in severe TBI patients with elevated intracranial pressure (ICP).
Methods: We studied consecutive patients with TBI and brain edema on CT scan and an EVD, admitted to the neurointensive care unit. PE ratio, defined as ICP prior to CSF drainage minus ICP after CSF drainage divided by ICP prior to CSF drainage minus EVD height, was measured as previously described. Patients were treated with mannitol for raised ICP based on clinical indication and PE ratio measured before and after mannitol administration.
Results: We studied 20 severe TBI patients with raised ICP. Mean ICP prior to mannitol treatment was 29 ± 7 mm Hg. PE ratio rose substantially after mannitol treatment (0.62 ± 0.24 vs. 0.29 ± 0.20, $p<0.0001$), indicating an improved ability to drain CSF and equalize ICP with the preset height of the EVD. The combination of mannitol and CSF drainage led to an improved reduction in ICP compared with that seen before mannitol therapy (11 ± 2 mm Hg vs. 6 ± 2 mm Hg, $p < 0.01$), and led to a decrease in ICP below the 20 mm Hg threshold in 77% of cases.
Conclusion: Treatment with mannitol leads to a substantial increase in PE ratio that reflects the ability to achieve a greater decrease in ICP when CSF drainage is performed after mannitol administration. PE ratio may be useful to follow response to therapy in patients with cerebral edema and raised ICP. Further studies to determine whether PE ratio may serve as an easily-obtained and clinically useful surrogate marker for the extent of brain edema are warranted.

532. Analysis of Shunted Hydrocephalus Follow-up: What do Routine Clinic Visits Yield? What Factors Affect Revision Surgery Presentation and Outcomes?

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Introduction: Frequency and duration of outpatient clinic follow-up for patients with shunted hydrocephalus varies among clinicians and assessment of follow-up regimens is lacking. The aim of this study is to investigate whether routine clinic visits alter care and whether they identify patients requiring shunt revision surgery, as well as, to better understand how patients utilize the outpatient clinic and present for shunt revision evaluation.
Methods: This is a single-centered retrospective study of 154 patients requiring shunt revision surgery from 2009 to 2018 who had at least one prior clinic evaluation. The primary exclusion criterion was if patients had no clinic records prior to the revision.
Results: The median age for shunt placement and revision were 3 months and 11 years old, respectively. Routine clinic visits led to a change in care for 16 patients (10.4%); including additional imaging, follow-up, or a combination of the two. With regards to revision surgery, days from prior shunt surgery, Chiari II/myelomeningocele pathology, and shunt type ($p < 0.01$) did affect time to presentation. Four patients (2.6%) requiring revision surgery were identified at routine clinic follow-up, while 92 (59.7%) and 47 (30.5%) presented to the emergency department and clinic sick visit, respectively. Presentation to clinic resulted in a statistically significant decrease in shunt revision surgery length-of-stay compared to presentation to the emergency department or inpatient admission for another condition.
Conclusion: Even with increased emergency room utilization, increased clinic connectivity, and improved patient education, routine clinic visits remain an important component in the follow-up of patients with shunted hydrocephalus by helping to guide clinical care and identify patients requiring shunt revision surgery.

533. Multiple Independent Current Controlled and Directional DBS Lead Implantation for Pediatric Dystonia

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Introduction: Deep brain stimulation (DBS) therapy is well-established for movement disorders in children and adults. However, there are challenges to using DBS for pediatric dystonia patients secondary to heterogenous etiology, ongoing neurodevelopment, and individual neuroanatomy. Recently developed multiple independent current control (MICC) and directional DBS leads permit control of stimulation fields to enhance therapy but use of these devices in children is not described. Here, we report our initial experience using these leads in medication-refractory pediatric dystonia.

Methods: Analysis was performed on patients with dystonia implanted with DBS systems including MICC and directional DBS leads from 2018-2020 at a single pediatric center. Leads were targeted to the internal globus pallidus. One patient received an additional lead targeted to the ventralis oralis anterior/posterior. Age at surgery, target, stimulation settings, and clinical changes were analyzed.

Results: A total of 6 patients underwent DBS. 83.3% of patients received bilateral leads. Etiology of dystonia included primary (n=1) and secondary (n=5). Average age at surgery was 14.0 (± 4.5) years. Initial current ranged from 2.0-5.1mA and optimized settings were 2.5-7.6mA with an average increase of 1.4mA over 38.4 (± 24.5) months. Patients initially received high-frequency stimulation (130-159Hz) with optimized frequency settings ranging from 60-159Hz. The majority of patients (n=5) responded well to high-frequency and one patient required low-frequency stimulation to mitigate dyskinesias and impaired gait. Initial pulse width was 60-100μs with an optimized range from 60-120μs requiring a mean adjustment of 12.5μs. 33% of patients received directional stimulation to maximize therapeutic window and reduce capsular side effects. All patients demonstrated clinical improvement in multiple domains including hand function, speech, feeding, and gait.

Conclusion: The use of DBS systems with constant current-controlled and directional leads offers greater programming flexibility and, in our experience, is safe and feasible in pediatric dystonia. We observed favorable outcomes using these systems in primary and secondary dystonia.

534. NEUROsurgical PReoperative Evoked Potentials (NEUROPREP); A Single Centre Retrospective Review of Paediatric Presurgical Evoked Potentials

Welege S.B Wimalachandra (Ingol, United Kingdom); Ioannis Mavridis; Laura Quinn; William Lo; Andrew Lawley; Desiderio Rodrigues; Guirish Solanki; Richard Walsh; Will McDevitt

Introduction: Intraoperative neuromonitoring (IONM) is integral in complex neurosurgical procedures for somatosensory and motor pathway lesions. Studies on presurgical evoked potentials (EP) are lacking and not routinely performed. The purpose of this study was to find utility ofpresurgical somatosensory evoked potentials (SSEP) and transcranial magnetic motor evoked potentials (TMS-MEP) for IONM.

Methods: Children who had outpatient SSEP/TMS-MEPs and their IONM baseline EPs were reviewed.Abnormalities were identified as prolonged latency and decreased amplitude outside normative data. Monitorability was categorised into standard alert criteria, modified alert criteria (presence/absence) or not possible groups. Patient characteristics were summarized, and associations with monitorability were measured using McNemar test, paired t-test, and logistic regression models.

Results: Sixty-two had presurgical EPs and IONM baseline with both modalities. Median age was 10 years (IQR 6-13;56% females), consisting of spinal (52/62,84%) and intracranial motor pathway associated lesions (10/62,16%). Forty-five (73%) had impairment of sensory-motor function. Thirty-one (50%) had abnormal presurgical SSEP and 29/62 (47%) with abnormal intraoperative baseline SSEPs. Abnormal TMS-MEPs were seen in 17/62 (27%) and baseline intraoperative MEPs were abnormal in 25/62 (40%). This resulted in 27/62 (44%) with at least one modality monitored under modified alert criteria. Presurgical SSEPs/TMS-MEPs were associated with baseline sensory-motor function and monitorability (p<0.001). Having an intraoperative EP abnormality was associated with abnormal presurgical SSEP (OR:5.46,95%CI:1.80-16.59) and TMS-MEP (OR:4.31,95%CI:1.10-16.93). Monitorability was not associated with baseline sensory-motor function, lesion location or pathology.

Conclusion: We found a high prevalence of abnormal presurgical EPs which was the only parameter associated with the adoption of modified IONM alert criteria. Prior knowledge of monitorability is important for the neurophysiologist, the surgeon, and to counsel patients and families. Therefore, we recommend presurgical EPs in complex neurosurgical patients.

535. Sex Differences in the Incidence, Severity, and Recovery of Concussion in Adolescent Student-Athletes from 2009-2019

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Introduction: Biological sex is thought to modulate concussion incidence, however the effects of sex on concussion severity and recovery are less clear. This study evaluates sex differences on concussion severity and recovery using a large, heterogeneous sample of young student-athletes.

Methods: The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) results of 11563 baseline tests were used to calculate the incidence of concussion among student-athletes. The post-injury tests of 3465 males and 1751 females presenting after a head injury were used to assess differences in severity and recovery. Chi-squared tests and t-tests were used to compare demographic, incidence, and severity differences between the two cohorts. Multivariable linear, logistic, and Cox hazard regressions were used to control for differences between cohorts in analyses of incidence, severity, and recovery.

Results: When controlling for demographic differences, females had higher odds of concussion (OR=1.62, 95% CI: 1.40-1.86, p<.0001) and higher severity concussions (β=.67, 95% CI: .02-1.32, p=.04). This discrepancy in severity was a result of differences in Symptom (1.27 vs. 1.76, p<.02) and Processing Speed (.68 vs 1.12, p=.001) composite scores between males and females. There was no effect of sex on time to recovery when controlling for initial concussion severity (HR=.94, 95% CI: .78-1.12, p=.48).

Conclusions: Using large, multisport cohorts, this study provides evidence that females are at higher risk for more concussions and these concussions are more severe. As more females begin playing high concussion risk sports such as football, these disparities are likely to increase without targeted interventions.

536. Complications Associated with Gastrostomy and Ventriculoperitoneal Shunt Placement

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Introduction: Pediatric patients requiring ventriculoperitoneal (VP) shunts often require gastrostomy tubes (G-tube) as well. G-tube placement during the same hospitalization is associated with increased VP shunt complications and failure. The influence of G-tube placement method on shunt complications is unknown.

Methods: The Nationwide Readmissions Database was queried from 2010-2014 for patients ≤18 years who underwent G-tube and VP shunt placement during index admission. Patients were stratified by method of G-tube placement; laparoscopic, open, or Percutaneous Endoscopic Gastrostomy (PEG). Outcomes were compared with standard statistical methods.

Results: 626 patients were identified (47% newborns, 49% male). The most common approach for G-tube was open (49%) followed by PEG (34%) and laparoscopic (26%). G-tube complications were seen in 13%, most commonly localized infection (4%). Suspected shunt infection requiring tap occurred in 21%, of which 74% required removal at index hospitalization. The readmission rate was 26% at 30 days and 48% within the year. Readmission rate was lower for patients undergoing laparoscopic G-tube (15% vs. 23% open vs. 35% PEG, p<0.001). Overall VP shunt revision rate was 35%; 16% required VP shunt revision at readmission. The median time to VP shunt revision was 15 [11-43] days from discharge. There was a trend towards lower VP shunt revision rates in the laparoscopic cohort (10% vs. 15% open vs. 20% PEG, p=0.060). Newborns were more likely than older children to require VP shunt revision at readmission (22% vs. 11%, p<0.001). Newborns undergoing laparoscopic G-tubes were less likely to require VP shunt revision at readmission (13% vs. 15% open vs. 44% PEG, p<0.001).

Conclusion: VP shunt complications are common with placement of G-tubes during the same hospitalization. Readmission for shunt revision is more common in newborns and after open procedures or PEG. Special consideration should be given to use of laparoscopy due to improved outcomes and less complications.

537. Tractography Analysis of Deep Brain Stimulation for Obsessive-Compulsive Disorder

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Introduction: DBS of the anterior limb of the internal capsule (ALIC-DBS) is an effective treatment for refractory obsessive-compulsive disorder (OCD). Current evidence suggest that the ALIC target impacts brain circuits for reward, affect and inhibitory control, including projections from different parts of the prefrontal cortex. The recent development of directional segmented DBS leads may allow for selective stimulation of these ALIC-projections.

Methods: We generated structural connectivity maps of therapeutic stimulation using probabilistic tractography in OCD patients treated with ALIC-DBS. Response was defined as ≥ 35% improvement in YBOCS after routine clinical parameter optimization. We also generated the volume of tissue activation (VTA) based on the stimulation parameters at the last follow-up. We estimated probability of connections between the VTA and each projection to the prefrontal regions [orbitofrontal (OFC) and ventromedial (vmPFC) cortex, ventrolateral cortex (vlPFC), dorsal anterior cingulate cortex (dACC), dorsal medial cortex (dmPFC) and dorsolateral prefrontal cortex (dlPFC)] in responders and non-responders. To further explore how connectivity would explain clinical improvement, we correlated connectivity values from stimulation sites to cortical regions to the percentage of change in YBOCS using Spearman correlation. Finally, we developed directional tractography activation models and explored personalized circuit-specific targeting and stimulation for patients with directional DBS-leads.

Results: All patients with ALIC DBS displayed stimulation of OFC/vmPFC and dmPFC connections. However, non-responders had incomplete stimulation of vlPFC, dACC and dlPFC compared to responders. Correlation analysis revealed that fibers from the dorsolateral ALIC to vlPFC were positively associated with improvement in Y-BOCS scores, while connections from ventral ALIC to vmPFC were negatively associated. We were able to successfully construct a stimulation tractography model of directional segmented lead configurations along the medial-lateral axis, which we used for personalized DBS targeting and programming in our most recent patients.

Conclusion: Our findings suggest that the therapeutic benefit of ALIC DBS for OCD is associated with stimulation of a subset of specific ALIC WM pathways, which can be selectively targeted using directional DBS-systems.

538. Frameless MLC-based Radiosurgical Thalamotomies on the Modern Linear Accelerator Platform - Prospective Phase I/II Clinical Trial Results

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Introduction: Stereotactic radiosurgery (SRS) to the ventral intermediate nucleus (VIM) of the thalamus has been used with success to manage tremor in select patients. Because of the high doses, small target, & required precision, Gamma Knife (GK) has been the historical choice platform. Our institution recently developed a technique to replicate functional SRS GK dose distributions on a multi-leaf collimator (MLC)-equipped linear accelerator (LINAC) without cumbersome, inefficient cones. We deployed this technique & tested it in a prospective clinical trial of safety & efficacy of SRS thalamotomy for non-DBS candidate patients with medically refractory essential or Parkinsonian tremor.

Methods: We quantified pre-treatment tremor according to FTM/PROMIS scores. We generated MPRAGE, FGATIR, diffusion-weighted tractographic, & resting-state fMRI sequences with Phillips 3T Prisma MRI. We identified the VIM via both thalamic parcellation & classical stereotactic reference location, & targeted it to 130Gy dmax in a fashion dosimetrically equivalent to 4.5mm GK shot. We adjusted each target such that the 26Gy isodose line did not overlap the posterior limb of the capsule. We immobilized patients in a highly rigid thermoplastic mask (Qfix Encompass). We delivered treatment with Varian Edge LINAC with high-definition HDMLC & intrafraction optical surface monitoring (OSMS) to ensure patient immobility. We surveilled post-treatment imaging and tremor scores.

Results: We accrued 32 patients over 30 months. One withdrew, & one elected to pursue previously declined DBS. At submission, 24 of the 32 patients had ≥6 month follow-up. 23/24 (96%) exhibited clinically meaningful tremor reduction. Median maximum pre- & post-tremor reduction was 59.8% (range: 11 - 100%). Time to patient-reported tremor improvement ranged from 0.3 to 15 months. One patient experienced Grade 2, and none experienced Grade 3 or higher toxicity.

Conclusion: Frameless, coneless MLC-based SRS thalamotomy on the LINAC is a safe, effective treatment for tremor. Proper implementation requires attentive involvement by an experienced movement disorder

539. Spiking Sequences as a General Organizational Principle for Neural Activity in the Human Cortex

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Introduction: The temporal dynamics of spiking activity in cortical networks are of great importance in understanding behavior, cognition, and disease states. An organizational motif, the spiking sequence, has recently been shown to be associated with memory formation and retrieval in the human cortex. However, it remains unknown how sequences may manifest in other behavioral scenarios and if spiking sequences are a general organizational principle for network level activity in the human brain.
Methods: We recorded intracranial micro-LFP and single unit data in 6 participants with medically refractory epilepsy during monitoring for potential resective surgery. To accomplish this, we implanted Utah micro-electrode arrays under the subdural macro-iEEG contacts in the anterior temporal lobe of each patient. In order to examine the presence of spiking sequences across many behavioral states, we examined spiking activity from the participants during rest, memory formation and retrieval, and during distractor periods.
Results: We found that spiking sequences are present across all epochs of our data. In fact, we were able to extract an average 'backbone' sequence that was loosely adhered to across all behavioral states, and individual time periods exhibited variation around this sequence. To explicitly demonstrate the temporal and behavioral invariance of this pattern of activity, we show that the average sequence from the 5 minute resting period persists through memory tasks, distractor periods, and subsequent rest periods for up to an hour later.
Conclusion: Our findings demonstrate that spiking sequences are a general motif for the organization of spiking activity in the human cortex. In broader terms, the existence of an average 'backbone' spiking sequence likely indicates a constrained set of neural dynamics that arise inherently from the network level synaptic structure of a given cortical column.

540. Predicting Verbal Fluency Changes Following Deep Brain Stimulation Using Machine Learning

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Introduction: Deep brain stimulation (DBS) is an effective treatment for the motor aspects of Parkinson's Disease (PD). However, DBS can concurrently lead to detrimental effects on cognition, especially a decline in verbal fluency. Nonetheless, the mechanism underlying the decline remains poorly understood and the ability to predict its occurrence remains elusive. Therefore, we have employed a machine learning approach to predict postoperative verbal fluency following DBS in a large prospective cohort.
Methods: We prospectively recruited 90 patients at Vanderbilt University Medical Center undergoing both STN (n=47, Bilateral=44) and GPi (n=43, Bilateral=39) stimulation. We assessed the participants using a host of neuropsychological tests preoperatively and at 6 months following DBS surgery. We assessed verbal fluency using the (D-KEFS) for phonemic (P), semantic (S) and action (A) fluency. Next, we used the patients' demographics, neuropsychological test scores and type of surgery as features to develop a model for predicting postoperative change in verbal fluency. We used a leave-one-out scheme to split the data iteratively into test and training groups. We assessed the performance of the models by calculating the Pearson correlation and the median absolute error (MAE) between the actual postoperative scores and the predicted scores.
Results: The prediction models showed a small MAE (A: 1.07, P: 1.16 and S: 1.45) from the actual scores and a high correlation between actual and predicted scores (A:0.77, P:0.85, S:0.76, p-value <0.001) when assessed on an independent test group. Preoperative fluency, depression, executive function and MMSE scores largely contributed to the models. The DBS target did not contribute to the prediction models.
Conclusion: We are able to predict postoperative fluency change following DBS surgery with high accuracy using preoperative neuropsychological test performance to identify high risk patients.

541. Outcomes and Complications following Treatment for Sacral Chordoma: A Comparison between the United States Experience and Carbon Ion Radiation Therapy at the National Institutes for Quantum and Radiological Science & Technology

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Introduction: Chordomas are rare tumors that arise from notochordal remnants. Although maximal safe resection is preferred for initial management, radiotherapy can also provide a treatment option when surgical resection is not possible. Carbon ion treatment, as an alternative to conventional radiotherapy modalities, has shown promising results to date.

Methods: Following IRB approval from both institutions, baseline and tumor-related characteristics were collected for two institutional cohorts of patients diagnosed with sacral chordomas. Multivariable logistic regression was performed to assess the association between treatment type and each outcome. Overall survival and progression free survival was compared using Cox proportional hazards models Kaplan-Meier curves. The National Cancer Database (NCDB) was also queried for sacral chordoma patients and included in survival analyses as an additional comparison.

Results: A total of 919 patients were included in the study. Comparison of the institutional cohort (en-bloc resection) to carbon ion treatment showed similar outcomes for two groups, with the exception of peripheral neuropathy where carbon ion treatment group showed lower rates of peripheral neuropathy (OR: 0.13 [0.04-0.40], $p<0.001$). In a comparison of national experience to carbon ion treatment, significantly higher overall survival was found for carbon ion treatment when compared to subtotal resection without adjuvant radiotherapy ($p=0.029$) and undergoing radiotherapy alone ($p<0.001$).

Conclusion: These findings suggest that carbon ion treatment might be a useful tool in providing an alternative to surgical resection for older patients with high performance status. Moreover, the use of carbon ion as an adjuvant radiotherapy might provide additional benefit for patients who undergo subtotal resection.

542. Biomimetic Laser-Etched Titanium Promotes Gene Expression of Early Bone Markers

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Introduction: Surface properties are a key factor in bone-implant interactions. Subtractive laser etching is a technique that can be used to create intentionally designed surface pores that mimic features found in that of native bone, specifically osteoclast resorption pits. Surfaces with   microscale surface roughness and biomimetic features may promote an osteogenic cellular response. This study sought to evaluate the osteogenic potential of smooth titanium (TS), polyether-ether-ketone (PEEK), and laser-etched titanium (TL) by comparing the capabilities of each substrate to promote bone-relevant gene expression.

Methods: Discs of TS, PEEK, and TL along with tissue culture polystyrene (TCPS) were used to culture murine bone marrow mesenchymal stem cells at a density of ~56 x10 3 cells/cm 2. Cell count was measured using a cell viability assay at day 1 and 7 for all materials. Gene expression was analyzed at day 1 and 7 using two-step RT-qPCR for the following markers of bone formation: Alkaline Phosphatase (ALP), Vascular Endothelial Growth Factor (VEGF), and RUNX2.

Results: TL exhibited higher cell count than TS and PEEK over 7 days, though significantly less than the TCPS at all time points. By D7, TCPS, TL, PEEK, and TS cultures resulted in the proliferation of (383±16, 162±7, 122±22, 47±45) x10 3 cells, respectively. The TL cell count was significantly ($p<0.05$) higher than both PEEK and TS at D7 (162±7 x10 3, 122±22 x10 3, and 47±45 x10 3 respectively). Cells seeded on TL also exhibited enhanced bone-relevant gene expression compared to TS and PEEK over the 7 day experiment (Fig 1).

Conclusion: This study suggests that biomimetic patterning of titanium enhances the cellular response compared to titanium. Biomimetic, laser-etched titanium exhibited significantly higher cell counts and early bone markers than both smooth titanium and PEEK over 7 days. Further research using an animal model is required to assess the osseointegration potential of laser-etched titanium interbody spacers in vivo.

543. Early (<24 hrs) versus Late (≥24 hrs) Surgical Decompression for Central Cord Syndrome: A Propensity Score-Matched Analysis

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Introduction: The optimal clinical management of central cord syndrome (CCS) remains unclear. This study provides a head-to-head comparison of the outcomes of early (< 24 hrs) versus late (≥ 24 hrs) surgical decompression for CCS.
Methods: Patients who underwent surgery for CCS (LEMS–UEMS≥5) were identified from three prospective, multi-center spinal cord injury (SCI) datasets (NACTN; STASCIS; NASCIS III). Propensity scores were calculated adjusting for data source, age, injury mechanism, baseline ASIA motor score (AMS), AIS grade, and neurological level. Propensity score matching was performed in a one-to-one ratio by an 'optimal matching' technique. The primary endpoint was motor recovery (upper extremity motor score [UEMS]; lower extremity motor score [LEMS]; AMS) at 1 year. Secondary endpoints were Functional Independence Measure (FIM) motor score and complete independence in each FIM motor domain at 1 year. Effect sizes for outcomes were summarized by mean differences (MDs) or odds ratios (ORs).
Results: The study cohort consisted of 186 patients. Baseline characteristics were balanced between early (N =93) and late (N =93) surgery groups. Early surgical decompression resulted in significantly improved recovery in upper limb (MD 2.3, P=0.047), but not lower limb (MD 1.1, P=0.256), motor function, as compared with late surgery. On subgroup analysis, outcomes were comparable with early or late decompressive surgery in AIS grade D patients. However, in patients with AIS grade C injury, early surgery resulted in significantly greater recovery in overall motor score (MD 9.5, P=0.038), owing to gains in both upper and lower limb motor function.
Conclusion: This study found early (< 24 hrs) compared to late (≥ 24 hrs) surgical decompression to result in improved recovery in upper limb motor function at 1 year in patients with central cord syndrome. The benefit of early surgery was especially realized in patients with AIS grade C injury.

544. Reliable Prediction of Extended Length of Stay Following Non-fusion Spine Procedures using Machine Learning Validated on Nearly One Million Cases in the United States

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Introduction: Significant clinical risks and economic costs to both hospitals and patients are associated with excessively prolonged hospitalizations. Adverse health outcomes may include hospital-acquired infections, disuse atrophy and deep vein thrombosis. Reliable preoperative decision-support algorithms have the potential to predict excessive length of stay (LOS), thereby facilitating targeted interventions to minimize clinical harm and reduce economic burden. The purpose of this study is to develop a machine learning algorithm to predict prolonged LOS after non-fusion spine surgery across both single-center and national cohorts and elucidate markers for prediction.
Methods: Retrospective electronic medical records were obtained from the Mount Sinai Data Warehouse (MSDW) and reviewed to identify patients undergoing non-fusion spine surgeries between 2008 and 2016 to develop and validate a machine learning algorithm. The National Inpatient Sample (NIS) dataset was reviewed for thoracolumbar spine surgeries between 2009 and 2017 to externally validate algorithm performance. Extended LOS was calculated as the 75th percentile of LOS in the MSDW cohort, or LOS of three or more days after surgery. Gradient-boosted decision trees were trained to predict prolonged LOS and evaluated using the area under the receiver operating characteristic curve (AUROC). Shapley scores were used to elucidate drivers of prediction.
Results: 2,667 non-fusion spine surgeries were identified in the MSDW dataset and 942,426 cases were obtained from NIS. Gradient-boosted trees achieved an AUROC of 0.74 (SD=0.01) on the MSDW test set and AUROC of 0.77 (SD=0.008) on the national NIS dataset, thereby demonstrating reliable prediction of prolonged LOS across cohorts. All payer refined diagnosis related group (APRDRG), age, non-elective admission status, female sex and lack of private insurance were the top five most predictive features of excessive LOS.
Conclusion: Machine learning algorithms reliably predict prolonged LOS after non-fusion spine procedures across nearly one million cases and highlight features that guide algorithm decisions.

545. Awake Twist Drill Craniostomy with Middle Meningeal Artery Embolization for Chronic Subdural Hematoma: Case Series

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Introduction: Optimal treatment for chronic subdural hematomas (cSDH) in the elderly remains unclear given comorbidities and perioperative risks. Minimally invasive procedures are emerging as alternatives to the standard operative techniques to address these concerns. We evaluate our experience with minimally invasive middle meningeal artery (MMA) embolization combined with Subdural Evacuating Port System (SEPS) placement as a first line treatment protocol for patients with cSDH.

Methods: A retrospective review was performed of all patients comparing clinical, radiographic, and outcome data. Analysis of baseline characteristics and outcomes was performed by procedure: 17 patients were treated with MMA embolization and SEPS placement (MMA/SEPS), 22 with MMA embolization and surgery (MMA/OR), 18 with SEPS placement only (SEPS), and 185 with surgery only (OR).One-way ANOVA was used to assess continuous variables and Chi-square tests were applied to categorical variables between the groups.

Results: In comparing the MMA/SEPS group to the combination of the other three treatment groups, the patients treated with MMA/SEPS were significantly older (79.0 v. 69.8 years, p=0.0022), more likely to be on anticoagulation medication (41.2% vs 15.1%, p=0.0127), more likely to have heart failure or atrial fibrillation (41.2% vs 15.6%, p=0.0146), and abnormal liver function tests (35.3% vs 12.4%, p=0.0194). In terms of outcomes, MMA/SEPS patients had a shorter length of stay (7.1 vs 11.6 days, p=0.0071) and when compared across all four groups, they were also less likely to have symptomatic recurrence within 60 days (5.9% MMA/SEPS vs 27.3% MMA/OR vs 33.3% SEPS vs 12.4% OR, p=0.0126).There were no differences in disposition, readmission, mortality, or postoperative complications.

Conclusion: MMA embolization combined with SEPS placement is a safe and effective first-line treatment of cSDH. This minimally invasive treatment paradigm provides a treatment option for older patients with significant comorbidities that may otherwise be poor surgical candidates and has the additional benefits of reducing the length of stay and the rate of cSDH recurrence.

Natus Resident/Fellow Award for Neurocritical Care
546. Oscillations in Cerebral Blood Flow Protect the Pericontusional Penumbra in Traumatic Brain Injury

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Introduction: The traumatic pericontusional penumbra represents a crucial target for therapeutic interventions after traumatic brain injury (TBI). Current resuscitative approaches do not adequately alleviate impaired cerebral microcirculation in these pericontusional areas. Computational models suggest that low-frequency oscillations in cerebral blood flow (CBF) can improve cerebral microcirculation and oxygen delivery. We sought to determine if CBF oscillations at 0.1Hz induced by trigeminal nerve stimulation (TNS) have this beneficial effect.

Methods: In 109 male Sprague-Dawley rats, a controlled cortical impact (CCI) model was used to induce severe TBI immediately followed by pressure-controlled blood withdrawal to induce hemorrhagic shock (HS). Animals were randomly assigned to four groups: (1) Sham; (2) Delayed fluid resuscitation (DR); (3) Immediate fluid resuscitation (IR); (4) Low frequency oscillation (LFO): these animals received CBF oscillations induced by electrical trigeminal nerve stimulation (TNS) and followed by fluid resuscitation. Hypoxic stress and neuroinflammation in the pericontusional area, lesion volume, and neurological function were measured.

Results: TNS is capable of generating CBF oscillations in the targeted low frequency range, as well as producing gradual improvement in CBF. TNS-induced CBF oscillations (0.1 Hz) did not significantly increase CBF as compared with the immediate and delayed resuscitation animals. However, it did result in significant preservation of peri-contusional brain tissues by reducing hypoxic brain injury (HIF-1α positive cells/field: 69 vs. 74 vs. 6; IR vs. DR vs. LFO) and neuroinflammation (IL6: 735 vs. 897 vs. 552 pg/mg protein) in the pericontusional area, leading to reduced lesion volume (14.7% vs. 13.1% vs. 9.7%) and improved neurological recovery (mNSS: 9.5 vs. 11.6 vs. 5.6).

Conclusion: Our findings suggest that CBF oscillations enhance cerebral microcirculation and oxygenation in the peri-contusional brain tissue and may be more effective as a resuscitative strategy role than traditional cerebral perfusion or volume expansion alone.

547. Dural Venous Sinus Injury in Patients with Blunt Traumatic Brain Injury

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Introduction: Dural venous sinus injury (DVSI) is an uncommon but potentially devastating consequence of traumatic brain injury (TBI). Given its rarity, risk factors and outcomes have not been adequately described. We sought to investigate these with a national database.
Methods: The National Trauma Data Bank from 2013 to 2017 was used to identify adults with blunt traumatic brain injury (TBI). Outcomes included mortality, discharge disposition, in-hospital stroke, total length of stay (LOS), intensive care unit (ICU) LOS, and duration of mechanical ventilation. Binary logistic and multiple linear regressions were used to identify variables associated with categorical or continuous variables, respectively, while adjusting for confounders.
Results: Among 619,659 patients with blunt TBI, a total of 1,792 (0.3%) patients experienced DVSI. Patients with mixed intracranial injury types were three times as likely to have DVSI (OR 2.99, 95% CI 2.47 – 3.62), while skull fracture   (OR 1.73, 95% CI 1.56 – 1.92), epidural hematoma (OR 1.53, 95% CI 1.06 – 2.21), and GCS 3 – 8 (OR 1.38, 95% CI 1.15 – 1.65) were also associated. Among skull fractures, comminuted types had the strongest association with DVSI (OR 1.54, 95% CI 1.32 – 1.80). DVSI carried increased odds of mortality (OR 1.32, 95% CI 1.13 – 1.54), non-routine discharge (OR 1.24, 95% CI 1.11 – 1.38), and stroke (OR 1.93, 95% 1.31 – 2.84). DVSI was also independently associated with longer LOS (p < 0.001), ICU LOS (p < 0.001), and duration of mechanical ventilation (p = 0.038).   In patients with DVSI, superior sagittal sinus was the location with the greatest odds of mortality (OR 2.46, 95% CI 1.36 – 4.44).
Conclusion: This study illustrates the morbidity and mortality associated with traumatic DVSI. The variables associated with DVSI may help inform clinical suspicion for this uncommon entity.

Charles Tator Spinal Cord Injury Resident Research Award
548. The Effects of Connexin Inhibitors on the Behavioral, Cellular and Molecular Outcomes in a Porcine Spinal Cord Injury Model

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Introduction: Connexin inhibition has demonstrated promising results in rodents spinal cord injury models (SCI) as a neuroprotective strategy that improves SCI outcomes. However, it has not been tested in a larger animal yet, a necessary step before conducting a human clinical trial. We aim to assess the efficacy of intrathecal connexins inhibitors in a porcine SCI model on four different levels: Locomotion/behavior, Histology, Immunofluorescence, and systemic biomarker behavior using enzyme immunoassay.
Methods: SCI was induced using a compression/contusion weight drop model in three groups of pigs with 2 animals per group. Group A: sham, Group B: Nonselective gap junctions blocker (Carbenoxolone) treated, Group C: Connexin-43 memetic peptide (Gap26) treated. The medication was delivered intrathecally at the time of injury. The locomotor development of the animals was assessed over 11 weeks. After which the animals were euthanized and their spinal cords were harvested for histological and immunofluorescence assessment.
Results: In terms of locomotion recovery, Groups B and C regained the stepping ability in their hind limbs, whereas the control group did not. Second, the histological damage was limited in Gap 26-treated group (C). Third, groups B and C exhibited a decreased level of astrocytes activation at the injury site. Finally, PGE 2 serum levels remained low in the two treated groups.
Conclusion: We translated the positive neuroprotective effect of a connexin-43 memetic peptide and gap junction blockers in a porcine SCI model. This study provides further evidence supporting the potential role of these agents in improving SCI outcome.

549. Proximal Junctional Kyphosis After Pedicle Subtraction Osteotomy: Is There An Association With Roussouly Type?

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Introduction: The pelvic incidence-lumbar lordosis (PI-LL) mismatch has been used to plan pedicle subtraction osteotomies (PSO). Proximal junctional kyphosis (PJK) may result from overcorrection in low sacral slope (SS) patients. We evaluated if there was a correlation between Roussouly type and PJK after PSO in adult spinal deformity (ASD) patients.
Methods: A retrospective study of ASD patients treated by 4 surgeons at UCSF was performed. Degenerative ASD patients treated with open PSOs and minimum 2-year follow-up were studied. Osteoporotic and non-degenerative cases were excluded. Patients were classified by Roussouly type based upon SS and PI. Sub-analysis of types 1 and 2 were combined into low sacral slope (LSS) Roussouly types. Radiographic parameters, PJK, and Roussouly type were analyzed.
Results: Ninety six patients met inclusion criteria. Mean follow up was 32.19 months (24 to 97). Classified by SS, PJK occurred in 24 LSS, 1 type 3, and 0 type 4 patients (p =0.0182). L3 PSOs had more PJK than L4 PSOs in LSS types (p =0.0398). Classified by PI, PJK occurred in 15 LSS types, 8 type 3, and 2 type 4 (p =0.0277). L3 PSOs had more PJK than L4 PSOs in LSS patients (p =0.0279). L3 PSOs had more PJK than L4 PSOs (p =0.0238). Average post-operative PI-LL mismatch, SVA, and PT were not different between PJK and non-PJK patients (p =0.97, p =0.33, p =0.14).
Conclusion: PSO in LSS Roussouly had higher PJK rates than type 3 or 4. L3 PSO in LSS patients had higher PJK rates than L4 PSO. Proximal PSOs in low SS Roussouly types appear to be associated with higher PJK rates.

550. A Connectomic Approach to Reduce Transient Supplementary Motor Area Syndrome in Frontal Lobe Glioma Surgery

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Introduction: Connectomics is the use of big data to map the brain's neural infrastructure; employing such technology to improve surgical planning may improve neuro-oncological outcomes. Supplementary motor area (SMA) syndrome is a well-known complication of medial frontal lobe surgery. The 'localizationist' view posits that damage to the posteromedial bank of the superior frontal gyrus (SFG) is the basis of SMA syndrome. However, surgical experience within the frontal lobe suggests that this is not entirely true and a more accurate cortical model of SMA syndrome may be produced utilizing a network-based 'connectomic' modeling approach.
Methods: In a study on n=45 patients undergoing frontal lobe glioma surgery, we sought to determine if a network-based 'connectomic' approach can decrease the likelihood of SMA syndrome. The control group (n = 23) underwent surgery avoiding the posterior bank of the SFG while the treatment group (n = 22) underwent mapping of the SMA network and Frontal Aslant Tract (FAT) using network analysis and DTI tractography. Patient outcomes were assessed post operatively and in subsequent follow-ups.
Results: Control and treatment groups were similar in age and gender as well as in tumor location, volume, grade, laterality, and extent of resection (p > 0.05 for all measures). When preserving the FAT in the treatment group, fewer patients (8.3%) experienced transient SMA syndrome compared to the control group (47%) (p = 0.003). Furthermore, while not significantly different, 13% of the control group experienced permanent SMA syndrome while no patients (0%) experienced permanent SMA syndrome in the treatment group (p = 0.49).
Conclusion: We demonstrate how utilizing tractography and a network-based approach decreases the likelihood of transient SMA syndrome during medial frontal glioma surgery. We found that not transecting the FAT and the SMA system improved outcomes which may be important for functional outcomes and patient quality of life. With emerging surgically-relevant connectomic platforms on the rise, this work adds support towards 'connectomic surgery' in ultimately improving neuro-oncological outcomes.

551. Effects of Stimulant-based Therapy on the Incidence of Concussion and the Recovery of Neurocognitive Dysfunction Post-Injury among Young Athletes with ADHD

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Introduction: With an estimated 1.6-3.8 million annual injuries, concussions are the leading cause of injury among youth athletes in the United States. We sought to evaluate the effects of stimulant-use among youth with ADHD on the incidence of concussion and the recovery of symptoms and neurocognitive dysfunction post-injury.

Methods: Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) was administered to 7,453 adolescent athletes at the start of the season. Throughout the season concussions were diagnosed by physicians. ImPACT was readministered at two post-diagnostic follow-ups, the first a median of 2 days post-concussion (FU1) and the second a median of 7 days post-concussion (FU2). Subjects were divided into three categories: those with ADHD on stimulant-based therapy (ADHD+meds; n=167), those with ADHD not on stimulant-based therapy (ADHD-only; n=354), and those with no ADHD (non-ADHD; n=6932). Concussion incidence was calculated as the total number of diagnosed concussions per total number of patient-years. The recovery of neurocognitive dysfunction post-injury was calculated as standardized deviations from baseline to FU1 and then FU2 in the five ImPACT composite scores. Univariate results were confirmed with multivariate analysis.

Results: The ADHD+meds cohort had a reduced risk for concussions as compared to the ADHD-only (OR 0.51[0.37-0.71], p<0.0001) and non-ADHD groups (OR 0.50[0.37-0.67], p<0.0001). At FU1 ImPACT scores were elevated from baseline to a similar extent in the ADHD+meds cohort as compared to the other two groups. However, by FU2 deviations from baseline were lower among the ADHD+meds group as compared to the non-ADHD group in verbal memory (OR 0.46[0.28-0.76], p=0.002), visual memory (OR 0.27[0.10-0.66], p=0.005), and visual motor skills (OR 0.58[0.33-0.99], p=0.048). The deviation at FU2 was also lower among the ADHD+meds group as compared to the ADHD-meds group in visual memory (OR 0.56[0.33-0.96], p=0.04) and visual motor skills (OR 0.42[0.22-0.81], p=0.01).

Conclusion: Stimulant-use among ADHD youth is associated with 1) reduced risk for concussion and 2) reduced deviations from baseline in verbal memory, visual memory, and visual motor skills at seven days post-diagnosis, suggesting improved neurocognitive recovery on ImPACT.