Mass General Brigham
Spaulding Rehabilitation

Dr. J. Robert Shaughnessy PM&R Research & Education

Department of Physical Medicine and Rehabilitation
Spaulding Rehabilitation Hospital

Friday, June 7, 2024

Agenda

8:00am Welcome
Ross Zafonte, DO
President, Spaulding Rehabilitation Network

8:10am AI for Healthcare
Regina Barzilay, PhD
Distinguished Professor of AI and Health
Massachusetts Institute of Technology, School of Engineering

9:10am Break

9:20am Risk Factors Associated with Achilles Tendon Rupture Following Fluoroquinolone Exposure: A Nested Case-Control Study
Hye Chang Rhim, MD, MPH
PGY-3 Resident, Harvard Medical School/Physical Medicine & Rehabilitation Residency Program

9:40am Post-Operative Rehabilitation for Ossification of the Posterior Longitudinal Ligament: A Systematic Review
Tracey Hunter, MD
PGY-3 Resident, Harvard Medical School/Physical Medicine & Rehabilitation Residency Program

10:00am Chronic Use of Prescription Pain Medication and Outcomes in Patients with Burn Injury
Kevin Vu, MD
PGY-4 Resident, Harvard Medical School/Physical Medicine & Rehabilitation Residency Program

10:20am Break

10:30am Prevention of Concussion and Long-Term Effects of Repetitive Traumatic Brain Injury (RTBI)
Robert Cantu, MA, MD, FACS, FACSM
Chief, Neurosurgery Service
Medical Director, Dr. Robert C. Cantu Concussion Center
Emerson Health

11:30am Presentation of Awards & Closing Remarks

12:00pm PM&R Research Poster Session

Guest Lecturers

Regina Barzilay, PhD

Distinguished Professor of AI and Health
Massachusetts Institute of Technology, School of Engineering

Regina Barzilay is a School of Engineering Distinguished Professor of AI & Health in the Department of Computer Science and the AI Faculty Lead at MIT Jameel Clinic. She develops machine learning methods for drug discovery and clinical AI. In the past, she worked on natural language processing. Her research has been recognized with the MacArthur Fellowship, an NSF Career Award, and the AAAI Squirrel AI Award for Artificial Intelligence for the Benefit of Humanity. Regina is a member of the National Academy of Engineering, National Academy of Medicine, and the American Academy of Arts and Sciences.

Robert Cantu, MA, MD, FACS, FACSM

Chief, Neurosurgery Service
Medical Director, Dr. Robert C. Cantu Concussion Center
Emerson Health
Clinical Professor of Neurology and Co-Founder CTE Center,
Boston University School of Medicine
Vice President and Chair of Scientific Advisory Committee NOCSAE
Senior Advisor to NFL Head Neck and Spine Committee

Currently Dr. Cantu's professional responsibilities include Medical Director and Director of Clinical Research, Dr. Robert C. Cantu Concussion Center, Chief of Neurosurgery Service and Director of Sports Medicine at Emerson Health in Concord, MA; Clinical Professor of Neurology and Neurosurgery, Clinical Therapeutics Leader AD-CTE Center Boston University Medical Center, Boston, MA; Founding member and Medical Director Concussion Legacy Foundation, Boston, MA; Medical Director National Center for Catastrophic Sports Injury Research, Chapel Hill, NC; Vice President and Chairman of Scientific Advisory Committee, National Operating Committee on Standards for Athletic Equipment (NOCSAE); Senior Advisor NFL Head, Neck and Spine Committee; Member NFLPA Mackey-White Health and Safety Committee and Co-chair of the equipment committee; NCAA Concussion Safety Advisory Group Member and NCAA Student-Athletic Concussion Injury Litigation Committee (Medical Science Committee); Member of the World Rugby Concussion Working Group.

He has authored over 552 scientific publications, including 34 books on neurology and sports medicine. A past president and spokesperson for the American College of Sports Medicine, he has participated in numerous nationally televised sports programs. He has served as associate editor of Medicine and Science in Sports and Exercise and Exercise and Sports Science Review, and on the editorial boards of The Physician and Sports Medicine, Clinical Journal of Sports Medicine, Journal of Athletic Training, Neurosurgery, and World Neurosurgery.

Title

Tracey Hunter, MD

PGY-3 Resident, Harvard Medical School/Physical Medicine & Rehabilitation Residency Program

Dr. Tracey Hunter, MD is a third-year physician resident in Physical Medicine & Rehabilitation at Spaulding Rehabilitation Hospital. She graduated from David Geffen School of Medicine at UCLA and earned a Bachelor of Arts in Sociology from The George Washington University. In Washington DC, Dr. Hunter served as a health advocate for marginalized communities including HIV and sickle-cell anemia patients. Her role working with underserved groups ignited her interest in medical research with a focus on health disparities. As a National Institutes of Health grant recipient and two-time awarded academic scholar, she has been dedicated to medical research for over a decade. She co-authored nearly 20 peer-reviewed journal articles, including several publications about the role of prehabilitation for vulnerable patient populations. As a recreational athlete with a special interest in musculoskeletal medicine and interventional pain, Dr. Hunter aims to assist patients in optimizing individualized goals for physical mobility and psychosocial health, striving to enhance their quality of life. Dr. Hunter is committed to extend her leadership in academic medicine and contribute to the vital mission of health equity.

Hye Chang Rhim, MD, MPH

PGY-3 Resident, Harvard Medical School/Physical Medicine & Rehabilitation Residency Program

HC Rhim is a PGY-3 resident physician at Spaulding Rehabilitation Hospital. He majored in human biology and minored in exercise science from Cornell University where he graduated with high distinction. For medical education, he returned to his home country, South Korea, and graduated from Korea University College of Medicine. Before starting his residency training, HC also earned a Master of Public Health degree at Harvard School of Public Health. His current research interest includes epidemiology of sports medicine injuries and outcome research following nonoperative interventions in sports medicine injuries. His passion in research has led to over 50 peer-reviewed publications, some of which at high-impact journals such as British Journal of Sports Medicine, and over 30 presentations nationally and internationally. He hopes to continue his research career in identifying effective ultrasound-guided interventions for tendinopathies and chronic musculoskeletal disorders.

Kevin Vu, MD

PGY-4 Resident, Harvard Medical School/Physical Medicine & Rehabilitation Residency Program

Kevin Vu, MD is a PGY-4 Spaulding Rehab PM&R resident who specializes in rehabilitation and pain medicine. His primary research interests include functional outcomes related to pain, virtual delivery of pain care and education, and neuromodulation. Originally from Texas, his next step in his academic career is a pain fellowship at Brigham and Women's Hospital.

Research Poster Session Information

The following includes a list of the poster location numbers, the name of the research poster lead, a map of poster locations, and the complete list of authors with the abstract included.

Research Poster List

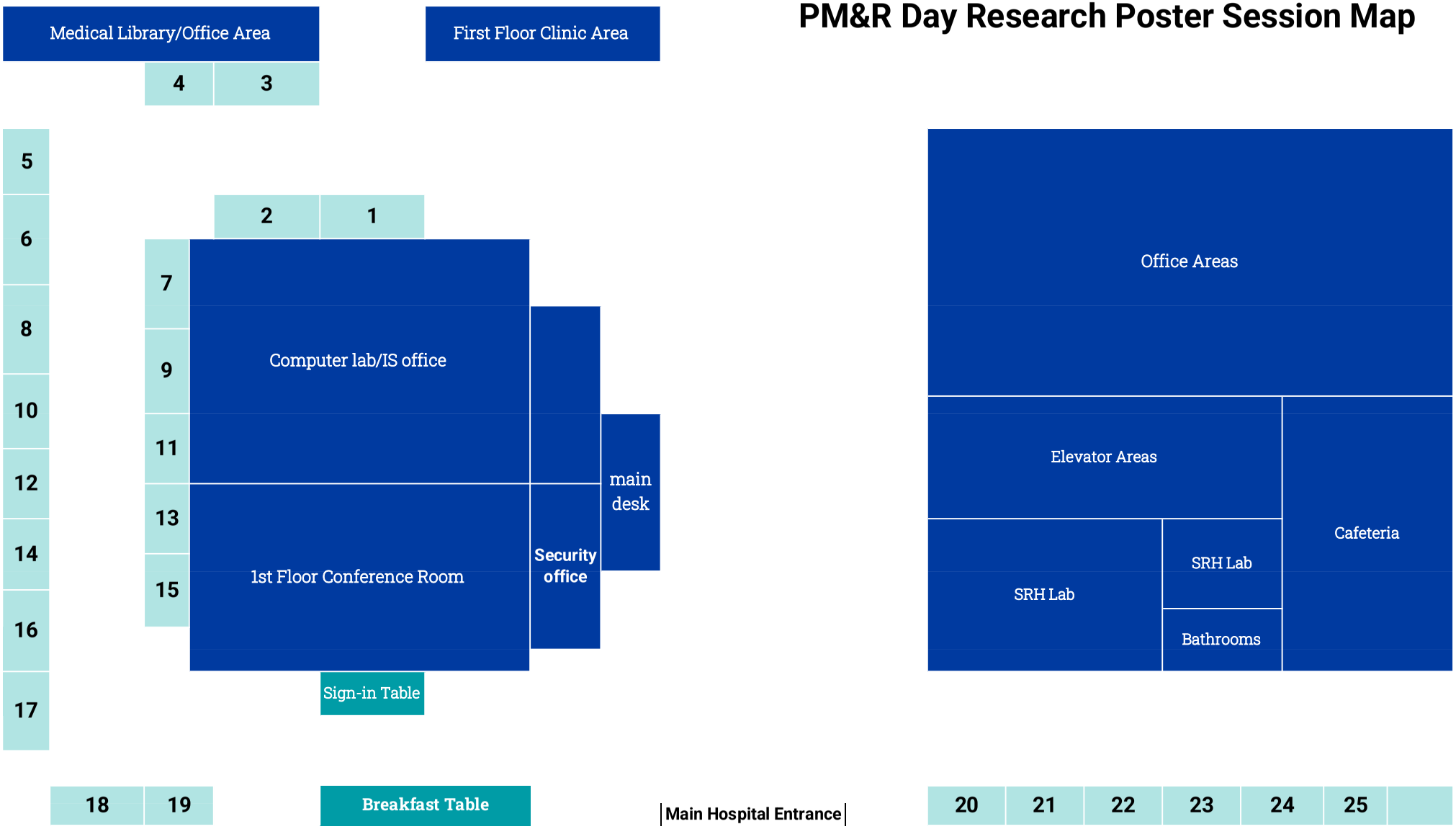
Number	Name	Title
1	Hirotaka Iijima	Network medicine-based mechanistic dissection of chondroprotective effects of rehabilitation program via extracellular vesicles
2	Matheus Arana	A quantum-based model of muscle progenitor cell motility
3	Nafiseh Shahshahan	Combining mitochondrial transplantation and magnetic field stimulation to improve aged skeletal muscle regeneration
4	Edward Santos	Balance Impairments in the Burn Population: A Burn Model System National Database Study
5	Madison Costa	First in Human Application of Trans-spinal Direct Current Stimulation in Patients with Amyotrophic Lateral Sclerosis (ALS)
6	Lauren Hall	Promoting Reproductive Health Equity After Spinal Cord Injury: Identifying Needs in Physiatry Training and Continuing Education
7	Ashley Gureck	Implementation of an interdisciplinary neuroimaging course to augment clinical therapeutic assessment of patients in acute inpatient rehabilitation
8	Emily Evans	Practice to Data: Assessing Data Quality
9	Nicole Katz	Gender Differences: Representation of Women in Lateral Ankle Sprain Research
10	Julianna Santangelo	Measuring Social Vulnerability, Area Deprivation, and Childhood Opportunity in Sport Concussion Specialty Clinic Research
11	Brendan Cormier	Peer Health Coach Perspectives on Coaching Adolescents with Physical Disabilities about Physical Activity
12	Connie Hsu	Generalized Joint Hypermobility and Injury Patterns in Elite Division I Swimmers
13	Alexandra Beling	Outcomes Using Focused Shockwave for Treatment of Bone Stress Injury in Runners
14	Logan Gaudette	Biomechanical Variables Associated with History of Bone Stress Injury in Female Runners
15	Michelle Bruneau	Factors Associated with Functional Outcomes in Former American Style Football Players with Knee and Hip Osteoarthritis
16	Hannah Houston	Can progesterone maintain muscle contractility in post-menopausal mice?

Number	Name	Title
17	Kai Wang	Nanotopographical cues tune the therapeutic potential of extracellular vesicles for the treatment of aged skeletal muscle injuries
18	Gabrielle Gilmer	Menopause drives cartilage degeneration via chondrocyte senescence and extracellular matrix disassembly
19	Michael Chiang	Dynamic Instability is Underestimated on Standing Flexion-Extension films when compared to Prone CT Imaging
20	Lorna Brown	Chronic Pain Education Delivered with a Virtual Reality Headset in Outpatient Physical Therapy Clinics: A Multi-site Observational Trial
21	Arvina Grahl	Riding The Waves of Pain: The Neural Correlates and Impact of Day-to-Day Pain Fluctuations on Clinical Outcomes after Cognitive Behavioral Therapy
22	Lara Gardiner	Designing a study to reveal neural mechanisms supporting the role of social interaction in MDMA-assisted therapy for chronic pain in Fibromyalgia
23	Michael Datko	Elevated Insula Glutamate in Migraine is Linked with Longer Headache Duration: A 7T H-MRS Study
24	Sarasa Tohyama	Structure-function associations of the trigeminal system in episodic migraine - a combined DTI, fMRI and PET study
25	Seneca Ellis	Peak alpha frequency as a predictive biomarker for treatment outcomes in chronic pain patients

Map of Poster Locations

Mass General Brigham
Spaulding Rehabilitation

PM&R Day Research Poster Session Map



Poster Abstract Information

Poster Location # 1

Poster Title

Network medicine-based mechanistic dissection of chondroprotective effects of rehabilitation program via extracellular vesicles

Author List

Hirotaka Iijima, Kai Wang, Ella D'Amico, Wan-Yee Tang, Renee J. Rogers, John M Jakicic, Fabrisia Ambrosio

Abstract

Extracellular vesicles (EVs) have emerged as a potent mechanism through which the beneficial effects of rehabilitative exercise are transmitted throughout the body. Yet, the mechanisms by which beneficial information is transmitted from EVs to recipient cells are poorly understood, precluding a holistic understanding of how exercise promotes cellular and tissue health. As a first step to address this critical knowledge gap, using articular cartilage as a model, this study introduced a network medicine paradigm to simulate how exercise facilitates communication between circulating EVs and chondrocytes, the cells resident in articular cartilage. METHODS: First, through a systematic review and subsequent bioinformatics, we identified 16 EV miRNAs significantly changed after an acute bout of aerobic exercise in elderly participants (GSE144627). Next, to assess the biological impacts of the 16 EV miRNAs on articular cartilage, we implemented a network propagation approach to the miRNA regulatory cartilage-specific functional gene network. Finally, follow up experimental studies were designed to interrogate the direct influence of exercise-primed circulating EV on chondrocyte function. Circulating EVs isolated from older adults ages 65-85 years old (n=10) before and after a 12-week aerobic exercise were then co-cultured with aged human chondrocytes seeded onto a substrate that mimics the microenvironment of aged human cartilage (100kPa). RESULTS: Network medicine-based inference revealed that circulating EVs activated by aerobic exercise perturb chondrocyte-matrix interactions and downstream cellular aging processes, including "PI3K/Akt signaling" and "TGF-beta signaling". Follow up experimental studies supported the findings from the computational analyses and found that pathogenic matrix signaling in chondrocytes was abrogated in the presence of exercise-primed EVs, restoring a more youthful cellular phenotype, as determined by chondrocyte morphological profiling and evaluation of chondrogenicity. Epigenetic reprogramming of the gene encoding the longevity protein, α-Klotho, mediated these effects, as evidenced by decreased Klotho promoter methylation level. DISCUSSION/CONCLUSION: This study introduces a network medicine approach to elucidate the functional targets of exercise-primed EVs in aged chondrocytes, demonstrating the rejuvenating effects of exercise on cellular health. By integrating computational analysis with experimental verification, this study provides mechanistic insights into the link between exercise-primed EVs and cellular aging.

Poster Location # 2

Poster Title

A quantum-based model of muscle progenitor cell motility

Author List

Matheus Araña, Gabrielle Gilmer, Kai Wang, Hirotaka Iijima, Juliana Bergmann, Zachary Hettinger, Antonio Woollard, Meghan McGraw, David Waldeck, Brian Zoltowski, David Pekker, Sunil Saxena, Seth Lloyd, Fabrisia Ambrosio

Abstract

Although quantum effects in biological systems have been implicated in avian navigation and photosynthesis, it is unclear whether and how quantum processes can influence mammalian cell behavior and tissue regeneration. Applying quantum biology concepts to living cells/tissues can drive a new level of understanding in cell biology and help establish novel interventions to effectively enhance tissue regeneration. Therefore, in this work, we aimed to investigate the potential of the radical pair mechanism (RPM), a process rooted in quantum mechanics, to guide muscle progenitor cell (MPC) motility and wound closure. The RPM involves the formation of short-lived radical pairs within a molecule upon absorbing a photon. Ambient magnetic fields can influence the state of these radical pairs, impacting the likelihood of a covalent bond breaking and initiating a cellular response. In the first set of experiments, we found that an acute myoblast injury provokes blue photon (430-470 nm) emission. In a gain-of-function experiment design, we found that MPCs exposed to blue photons exhibit enhanced migration and wound closure compared to those in the dark and exposed to red (630-670 nm) or green (530-570 nm) photons. This effect was most pronounced within a specific intensity range (21.4 mW/m2), consistent with the optimal conditions for radical pair formation. Furthermore, in silico multi-omics analyses support the activation of calmodulin and upregulation of actomyosin proteins by blue photons, potentially downstream of the RPM. In a second set of experiments, we observed that magnetic field stimulation promotes MPC motility, potentially by amplifying the effects of the light-induced radical pair formation. Our in vitro studies revealed that exposure to 400 μT static magnetic field perpendicular to the injury site significantly improves wound closure. This effect was not observed for fields parallel to the injury site, and increasing/decreasing the field strength diminished the observed enhancement. These observations align with current theories on magnetoreception and suggest a novel approach for promoting tissue healing through non-invasive light and magnetic field therapies. Our work provides evidence for a quantum-based mechanism underlying MPC migration and paves the way for further investigation into the therapeutic potential of biophotonics and biomagnetism, particularly when combined.

Poster Location # 3

Poster Title

Combining mitochondrial transplantation and magnetic field stimulation to improve aged skeletal muscle regeneration

Author List

Nafiseh Shahshahan, Fabrisia Ambrosio, Kai Wang

Abstract

Age-related mitochondrial dysfunction compromises the regenerative capacity of skeletal muscle stem cells (MuSCs), leading to impaired muscle regeneration. While mitochondrial transplantation therapy (MTT) shows promise in improving mitochondrial function and tissue repair, the efficacy of MTT in promoting skeletal muscle recovery after injuries is limited, especially in the context of aging. Here, we tested a synergistic approach to enhance aged muscle regeneration by augmenting MTT with magnetic field stimulation. We chose magnetic field stimulation given previous work demonstrating the ability of magnetic fields to enhance mitochondrial function, including mitochondrial biogenesis and respiration. For this work, we employed our aging muscle construct model that not only recapitulates the effects of aging on muscle (i.e., muscle atrophy, weakness, and regenerative impairment) but also enables the evaluation of muscle responses to interventions in a high throughput and cost-effective way. Aged muscle constructs were injured using cardiotoxin, followed by treatment with young muscle progenitor cells-derived mitochondria, magnetic fields, or a combination of both. Our results showed that mitochondria treatment promoted aged muscle construct regeneration and recovery of contractile function, and the beneficial effects were further augmented by magnetic field stimulation. Mechanistic investigations revealed that combining MTT and magnetic field stimulation significantly increased MuSC proliferation and myogenic differentiation compared to either approach in isolation. Overall, our data demonstrate the feasibility of combining MTT and magnetic field stimulation as a regenerative rehabilitation approach to synergistically improve aged muscle repair.

Poster Location # 4

Poster Title

Balance Impairments in the Burn Population: A Burn Model System National Database Study

Author List

Edward Santos, BS, Kaitlyn L. Chacon, BA, Lauren J. Shepler, MPH, Kara A. McMullen, MPH, Mary D. Slavin, PT, PhD, Marc van de Rijn, MD, Karen J. Kowalske, MD, Colleen M. Ryan, MD, Jeffrey C. Schneider, MD

Abstract

Objective: Examine the frequency of long-term balance impairments and associated factors after burn injury. Design: August 2015 to January 2023 data from the Burn Model System National Database was analyzed. Trouble with balance was self-reported at discharge, 6, 12, 24 and 60-months after injury. Regression analyses examined associations between demographic and clinical characteristics and balance impairments at 12-months. Results: Of 572 participants, balance impairments were most reported at discharge (40.3%) and continued over 60-months (26.8 to 36.0%), with 153 participants reporting balance impairments at 12-months. Those with self-reported balance impairments were more likely to be older, unemployed, have Medicaid or Medicare, inpatient rehabilitation, outpatient physical or occupational therapy, vision problems, leg or feet burns and swelling, and foot numbness compared to those without balance impairments ($p \leq 0.001$). Regression analysis demonstrated 4% increased odds of self-reported balance impairment for every increase in year of age ($p<0.001$), 71% lower odds for those employed at time of injury ($p<0.001$) and 140% higher odds for those that received outpatient physical or occupational therapy at 12-months ($p=0.008$). Conclusions: Balance impairments are commonly reported at discharge and persist for up to 60-months after injury. Long-term, routine balance screening measures should be used to identify individuals living with burn injury who may benefit from targeted interventions.

Poster Location # 5

Poster Title

First in Human Application of Trans-spinal Direct Current Stimulation in Patients with Amyotrophic Lateral Sclerosis (ALS)

Author List

Madison Costa, OTD, OTR/L, Anayali Estudillo-Guerra MD, MPH, Lna Ali, MSc , Leon Morales-Quezada MD, MSc, PhD, MPH

Abstract

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) is a progressive neurodegenerative disease that affects the motor neurons in the spinal cord and brain. There are about 20,000-30,000 ALS patients in the United States and about 6,000 new diagnoses yearly. This study investigated the effect of multi-site direct current stimulation (DCS) treatment to suppress neuronal hyperexcitability along the neural axis in patients with ALS. Specifically, this approach combines trans-spinal DCS (tsDCS) with peripheral DCS (pDCS). Objectives: To assess the safety and feasibility of non-invasive multi-site direct current stimulation in people with amyotrophic lateral sclerosis (ALS). In addition, the study aims to provide preliminary evidence of the potential impact of this treatment approach on daily function for patients with ALS. Methods: This is an early feasibility, single-center, single-arm, open-label, non-blinded study. Study volunteers participated in 16 visits over 10 weeks that consisted of three treatment intervention during treatment weeks and one day in between treatments. Results: Four participants were enrolled and able to successfully complete each treatment session without presenting any serious adverse events. Patients' perceived level of functioning remained relatively stable over the course of treatment as shown by the lack of statistically significant change on the ALS Functional Rating Scale Revised (ALSFRS-R) ($F(4, 15) = [0.0457]$, $p = 0.9956$). In this validated instrument, a decline in scores would reflect a progression of the disease and decline in function. Conclusions: This is the first in human application of multi-site direct current stimulation combining tsDCS with pDCS for patients with ALS. This report illustrates that this treatment approach is a safe and feasible treatment for ALS patients. It suggests that further investigation into its effect on the functional impact on patients with ALS is warranted.

Poster Location # 6

Poster Title

Promoting Reproductive Health Equity After Spinal Cord Injury: Identifying Needs in Physiatry Training and Continuing Education

Author List

Lauren Hall, Christa Nnoromele, Amber Lalla, Chloe Slocum

Abstract

Counseling and education on women's health, specifically contraception, following spinal cord injury (SCI) is an important component of care for women with SCI. While a plethora of available contraceptive options exists, research in this area is scarce. This systematic review assesses the quality and quantity of research on contraception for individuals with spinal cord injury. Methods: Literature searches of three medical databases were performed to identify articles that addressed contraception and family planning for women with spinal cord injury. Articles were then screened in a two-stage selection process and evaluated for content. Results: Of 165 articles, 21 were identified that fit the inclusion criteria. The majority (66%) of articles were literature reviews or professional practice guidelines. 14 (66%) included information on short-acting hormonal oral contraception, 11 (52%) included information on long-acting reversible contraception, 15 (71%) included information on barrier methods, 6 (29%) included information on fertility awareness, 9 (43%) included information on permanent contraception, and one (5%) included information on emergency contraception. Discussion: This systematic review demonstrates a paucity of evidence-based information on contraception tailored to women with SCI. It highlights a need for research and comprehensive guidelines on primary and emergency contraception in this population.

Poster Location # 7

Poster Title

Implementation of an interdisciplinary neuroimaging course to augment clinical therapeutic assessment of patients in acute inpatient rehabilitation

Author List

Ashley Gureck, Emily Cook, Craig Rovito

Abstract

This introductory neuroimaging course was created as an educational tool for physical (PT), occupational (OT), and speech therapists (SLP) to aid in the comprehensive evaluation and interdisciplinary management of patients admitted to a standalone inpatient rehabilitation facility. Design: PT, OT, and SLP's attended a physician-led three-session lecture series which taught key concepts in neuroradiology foundations, normal and pathologic neuroimaging studies, and clinical implications of neuroimaging findings. Therapists were asked to rate their comfortability in 6 domains related to accessing and understanding patients' neuroimaging data before and after the course on a 5-point Likert scale. Individual items were scored as 1 (not at all confident), 2 (slightly confident), 3 (somewhat confident), 4 (fairly confident), and 5 (completely confident). Paired responses following a non-normal distribution were compared using Wilcoxon signed rank test. Results: Nineteen therapists with complete pre- and post-course data were included in analysis. Following the course, therapists felt more confident in understanding indications for CT vs. MRI (overall median response improved from a 3 pre-course to 4 post-course, $p<0.001$), accessing the radiology section of the electronic medical record (improved from 2 to 5, $p<0.001$), examining imaging without a radiology report available (improved from 1 to 3, $p<0.001$), identifying neuroanatomical structures on normal imaging (improved from 3 to 4, $p<0.001$), identifying areas of pathology (improved from 1 to 3, $p<0.001$), and using imaging to support clinical recommendations (improved from 2 to 4, $p<0.001$). Narrative feedback suggested overall satisfaction with the course. Conclusions: This interdisciplinary neuroimaging education series improved therapists' understanding and clinical application of neuroimaging in the inpatient neurorehabilitation setting. Future directions include ongoing education of additional therapists, and understanding how this education translates to patient outcome measures.

Poster Location # 8

Poster Title

Practice to Data: Assessing Data Quality

Author List

Emily Evans, Stacey Zalanowski, James Green, Angela Link, Catriona Modoono, Deborah Clooney, Kathryn Quaglia, Abigail Spaulding, Mary Slavin

Abstract

Standardized outcome measures are a primary means of collecting data about rehabilitation practice and serve as a foundation for generating knowledge. For five years, the physical therapy department at Spaulding Rehabilitation Hospital (SRH), Boston, has collected outcome measures recommended by the American Academy of Neurologic Physical Therapy in a Core Outcome Measure (COM) Clinical Practice Guideline. The measures include the Six-minute walk test (6MWT), Berg Balance Test (Berg), Functional Gait Assessment (FGA), 10 Meter walk (10MWT), and 5 times Sit-to-stand (5STS). Objective: The objective of this proposal is to evaluate the conformance, plausibility, and completeness of the data to assess data quality before additional analysis. Design: This retrospective descriptive analysis includes data extracted from EPIC flowsheets and the Inpatient Rehabilitation Facility-Patient Assessment Instrument (IRF-PAI) obtained from the facility's electronic health record (EHR) during 2022 and 2023. Analysis: We evaluated the outcome measures in terms of conformance with the expected format and plausibility of the data distribution. We used descriptive statistics to characterize the proportion of outcome measure completion across each measure at three time points: "any time," at "admission," and both "admission and discharge." We then compared patient characteristics between those with completed versus incomplete assessments using t-test, $\chi 2$ tests, and logistic regression. Results: Across 4400 admissions, we observed that the data was in the expected form, i.e., reflected distances and times when expected, and fell within the anticipated distributions. However, incomplete rates ranged from 17% to 78%, depending on the measure and time frame. Data did not appear to be missing at random as the diagnosis group, floor, cognitive status, and walking ability at admission were associated with outcome assessment completion across measures. Conclusion/Discussion: The core outcome measure data is valuable for evaluating practice and patient outcomes at SRH. Analysis revealed that the data was in the expected form and included plausible values. However, a significant portion of data was missing, which did not appear to be missing at random. Future analyses must adjust for potential selection bias when drawing inferences that may be used to inform practice.

Poster Location # 9

Poster Title

Gender Differences: Representation of Women in Lateral Ankle Sprain Research

Author List

Nicole B. Katz, Julie K. Silver, Kelly C. McInnis

Abstract

Lateral ankle sprains (LAS) are a common injury for women and men athletes. Historically, there has been low representation of women as participants and authors in sports medicine research. We aimed to assess the representation of women participants and authors in LAS research. Methods: This is an observational study of original research included in systematic reviews on LAS in adults published between May 2013 and May 2023. We assessed the proportion of women participants and in author roles (primary, senior, and overall). Gender was determined by online information mostly using pronouns. When unavailable, photographs or Gender API (online gender tool) were used to infer gender. Results: Eleven reviews with 77 unique studies (10,080 participants, 335 authors) were identified. Participant gender was not reported for 8 studies, and author gender was undetermined for more than 25% of authors for 4 studies; these studies were excluded from the analyses. No participant or author was identified as non-binary. Studies had a mean publication year of 2006 +/- 8, 5 +/- 2 authors, and 146 +/- 176 participants. Of the study populations, 55% were general, 43% athlete, and 3% military. The overall proportion of women participants was 41%; less than in the European Union and United States population ($p < 0.001$). The proportion of women participants in general population (40%) and athlete studies (42%) were similar ($p = 0.1$). Women were the minority of primary (32%), senior (29%), and overall authors (26%). There were weak positive correlations between women participants and women authors overall, publication year and women participants, and publication year and women authors overall (all $r < 0.2$, all $p > 0.1$). Conclusions: We found underrepresentation of women as research participants, and a minority of women as study authors. Despite the high prevalence of LAS in women athletes, the research guiding clinical care disproportionately included men, which may have limited knowledge about LAS in women. It is not known how this low representation may impact clinical care for patients or career advancement for women physicians and scientists. Greater efforts are needed to increase the proportion of women included in this research and conducting this work.

Poster Location # 10

Poster Title

Measuring Social Vulnerability, Area Deprivation, and Childhood Opportunity in Sport Concussion Specialty Clinic Research

Author List

Julianna Santangelo, Julia E. Maietta, Nathan E. Cook, Grant L. Iverson

Abstract

Social determinants of health, including socioeconomic status (SES) and neighborhood characteristics, are underrepresented in concussion research. We examined three measures of neighborhood advantage and opportunity among patients accessing a multidisciplinary sports concussion clinic in Greater Boston. Methods: We collected the Child Opportunity Index (COI), Area Deprivation Index (ADI), and Social Vulnerability Index (SVI) scores for new patients who presented to our clinic in 2023. The COI, an index of neighborhood conditions that impact childhood development, is grouped into three domains: education, health and environment, and SES. The ADI characterizes an area's socioeconomic conditions (e.g., income, housing quality, employment, education), with higher scores representing more neighborhood disadvantage. The SVI was developed to help public officials identify communities at higher risk for events such as natural or human-caused disasters, or disease outbreaks. The SVI rates vulnerability on four themes: SES, housing and transportation, minority status, and household composition. It is scored from 0 to 1, where closer to 0 indicates lower vulnerability. Results: There were 247 new patients who visited the specialty clinic in 2023 (Mage=17.5, SDage=5.2, 47.8% Girls/Women, 81.4% White, 4.0% Black, 6.5% Asian, and 4.9% Hispanic). The majority lived in an area with a high or very high state COI (74%) and high or very high national COI (88%). The median ADI state decile was 2.0 (interquartile range [IQR]=1.0-4.0) and the median national percentile was 10.0 (IQR=5.0-18.0) (representing the highest 10% of neighborhood advantage). The median state SVI was 0.27 and national SVI was 0.20, indicating a low level of social vulnerability. The state decile scores for the COI and ADI were correlated (Spearman rho=0.72), but not redundant. The correlations between the SVI and the COI (r=0.55) and ADI (r=0.37) were moderate and weak, respectively. Conclusions: The COI, ADI, and SVI are important, nonredundant, accessible measures of neighborhood advantage and social vulnerability that can be included in future concussion studies. Patients from low SES households were underrepresented in our specialty clinic compared to the population of our metropolitan area. Patients were predominantly from higher SES, consistent with prior studies suggesting socioeconomic disparities in accessing specialty concussion care.

Poster Location # 11

Poster Title

Peer Health Coach Perspectives on Coaching Adolescents with Physical Disabilities about Physical Activity

Author List

Brendan Cormier, Cheri Blauwet, Mary Dubon

Abstract

Although quantum effects in biological systems have been implicated in avian navigation and photosynthesis, it is unclear whether and how quantum processes can influence mammalian cell behavior and tissue regeneration. Applying quantum biology concepts to living cells/tissues can drive a new level of understanding in cell biology and help establish novel interventions to effectively enhance tissue regeneration. Therefore, in this work, we aimed to investigate the potential of the radical pair mechanism (RPM), a process rooted in quantum mechanics, to guide muscle progenitor cell (MPC) motility and wound closure. The RPM involves the formation of short-lived radical pairs within a molecule upon absorbing a photon. Ambient magnetic fields can influence the state of these radical pairs, impacting the likelihood of a covalent bond breaking and initiating a cellular response. In the first set of experiments, we found that an acute myoblast injury provokes blue photon (430-470 nm) emission. In a gain-of-function experiment design, we found that MPCs exposed to blue photons exhibit enhanced migration and wound closure compared to those in the dark and exposed to red (630-670 nm) or green (530-570 nm) photons. This effect was most pronounced within a specific intensity range (21.4 mW/m2), consistent with the optimal conditions for radical pair formation. Furthermore, in silico multi-omics analyses support the activation of calmodulin and upregulation of actomyosin proteins by blue photons, potentially downstream of the RPM. In a second set of experiments, we observed that magnetic field stimulation promotes MPC motility, potentially by amplifying the effects of the light-induced radical pair formation. Our in vitro studies revealed that exposure to 400 μT static magnetic field perpendicular to the injury site significantly improves wound closure. This effect was not observed for fields parallel to the injury site, and increasing/decreasing the field strength diminished the observed enhancement. These observations align with current theories on magnetoreception and suggest a novel approach for promoting tissue healing through non-invasive light and magnetic field therapies. Our work provides evidence for a quantum-based mechanism underlying MPC migration and paves the way for further investigation into the therapeutic potential of biophotonics and biomagnetism, particularly when combined.

Poster Location # 12

Poster Title

Generalized Joint Hypermobility and Injury Patterns in Elite Division I Swimmers

Author List

Connie Hsu, Jason Schon, Daniel Daneshvar, Kelly McInnis

Abstract

The objective of this study is to compare the prevalence of hypermobility between swimmers and non-swimming athletes and investigate patterns between hypermobility, stroke specialties, and injury rates in swimmers. Design: Cross-sectional study Setting: Division I College Participants: 41 collegiate Division I athletes (23 swimmers and 18 runners) Assessment of Risk Factors: Participants were assessed for hypermobility using the 9-point Beighton scale (threshold, 5 points or above) at the end of the 2022-2023 athletic season. Swimmers reported stroke specialty and injury history. Main Outcome Measures: Hypermobility, injury patterns in hypermobile swimmers Results: The prevalence of hypermobility in swimmers was 60.9%, compared to 22.2% in runner controls (OR: 5.444, 95% CI 2.035, 14.563, $p < .001$). Dolphin kick specialists (backstroke and butterfliers) and non-sprinters were more likely to be hypermobile (OR: 6.300, 95% CI 1.627, 24.390; OR: 7.333, 95% CI 1.935, 27.792). Hypermobility was associated with increased rates of shoulder injury and trunk injury in swimmers (OR: 6.000, 95% CI 1.153, 31.228; OR: 1.167, 95% CI 1.003, 1.357). Conclusion: This study demonstrates a high prevalence of hypermobility in elite swimmers. Different rates of hypermobility are seen in different stroke specialties, specifically higher frequencies in backstroke, butterfly, and distance swimmers, which suggests a training-related association or self-selection for hypermobile strokes. Hypermobility is associated with an increased frequency of shoulder and trunk injuries. The implementation of a preseason screening using the Beighton scale to identify areas of weakness associated with joint hypermobility may help develop an injury prevention rehabilitation program for swimmers.

Poster Location # 13

Poster Title

Outcomes Using Focused Shockwave for Treatment of Bone Stress Injury in Runners

Author List

Alexandra Beling, Amol Saxena, Karsten Hollander, Adam Tenforde

Abstract

Bone stress injury (BSI) is a common overuse injury that can result in prolonged time away from sport. Limited studies have characterized the use of extracorporeal shockwave therapy (ESWT) for the treatment of BSI. The purpose of this study was to describe the use of ESWT for the management of BSI in runners. A retrospective chart review was performed to identify eligible patients in a single physician's clinic from 1 August 2018 to 30 September 2022. BSI was identified in 40 runners with 41 injuries (28 females; average age and standard deviation: 30 +/- 13 years; average pre-injury training 72 +/- 40 km per week). Overall, 63% (n = 26) met the criteria for moderate- or high-risk Female or Male Athlete Triad categories. Runners started ESWT at a median of 36 days (IQR 11 to 95 days; range 3 days to 8 years) from BSI diagnosis. On average, each received 5 +/- 2 total focused ESWT treatments. Those with acute BSI (ESWT started <3 months from BSI diagnosis) had an average return to run at 12.0 +/- 7.5 weeks, while patients with delayed union (>3 months, n=3) or non-union (>6 months, n=9) had longer time for return to running at 19.8 +/- 14.8 weeks (p = 0.032). All runners returned to pain-free running after ESWT except one runner with non-union of grade 4 navicular BSI who opted for surgery. No complications were observed with ESWT. These findings suggest that focused ESWT may be a safe treatment for the management of BSI in runners.

Poster Location # 14

Poster Title

Biomechanical Variables Associated with History of Bone Stress Injury in Female Runners

Author List

Logan Gaudette, Michelle Bruneau, Kristin Popp, Adam Tenforde

Abstract

Bone Stress Injury (BSI) is a common overuse injury in female athletes. Anatomical location of BSI has been associated with different risk factors for injury. Terminology of "high-risk" anatomy (defined as femoral neck or pelvis), or "low-risk" sites (including the metatarsals, tibia and fibula) have been proposed based on different risk factors for injury. In addition, for runners, aspects of fatigue may influence biomechanical risk factors for BSI. Purpose: To evaluate biomechanical variables associated with history of BSI, history of only low-risk BSI, and history of high-risk BSI in pre-menopausal women runners. Methods: 44 women between the ages of 18 and 40 ran on an instrumented treadmill (AMTI, Watertown MA) wearing 68 retroreflective markers recorded using a motion capture system (Vicon, Oxford UK). Participants ran at a self-selected speed and 5 km race pace while data was collected. Next, participants ran at the race speed until they reach an RPE of 17 and data was collected at 5 km speed and self-selected speed (exerted condition). Biomechanical variables of interest include cadence and Center of Mass (COM) vertical excursion. Student's t-tests and one-way ANOVAs were used to test for between group differences. Results: Participants with a history of BSI ran with significantly lower cadences at their self-selected speeds in the fresh (165±10 vs 172±10, $p = 0.011$) and exerted (164±8 vs 170±7, $p = 0.012$) states. Differences in cadence were also detected at 5k race speed in the fresh (173±11 vs 182±12, $p = 0.02$) and exerted (171±11 vs 179±8, $p < 0.01$) condition. Participants in the history of high-risk BSI group ran with higher COM vertical excursion compared to those with no history of BSI at self-selected speed in the fresh (8.9cm±1.2 vs 10.4cm±1.6, $p = 0.018$) and exerted state (8.9cm ±0.9 vs 10.3cm±1.6, $p = 0.019$) as well as at race speed in the fresh (8.4cm±1.0 vs 10.3cm±1.7, $p < 0.01$) and exerted state (8.5cm±0.9 vs 10.2cm±1.7, $p < 0.01$). Clinical Application & Conclusion: Biomechanical variables including lower cadence and higher COM vertical excursion are associated with BSI and may be modifiable factors for injury.

Poster Location # 15

Poster Title

Factors Associated with Functional Outcomes in Former American Style Football Players with Knee and Hip Osteoarthritis

Author List

Michelle Bruneau, Logan Gaudette, Rachel Grashow, Joanne Borg-Stein, Alexandra Fogarty, Ross Zafonte, Aaron Baggish, Meagan Wasfy, Adam Tenforde

Abstract

Knee and hip osteoarthritis (OA) are common conditions with estimated global prevalence of 300 million. Previous work in former American-style football (ASF) players has characterized factors that may contribute to higher burden of knee and hip OA; however, diagnostic and management strategies for OA in this population remain poorly understood. Purpose: To explore association of current health, sports exposure, and prior injuries to joint function using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Hip Disability and Osteoarthritis Outcome Score (HOOS) in former ASF players. Methods: The Football Player Health Study (FPHS) at Harvard University is an ongoing study evaluating health outcomes in former ASF players. Living former ASF players who participated from 1960 to present were eligible to complete surveys and attend a three day In-Person Assessment (IPA), that included completion of surveys on health and function, KOOS and HOOS, and X-rays of both knees and hips. All variables were entered into a backward stepwise linear regression for each subscale for the KOOS and HOOS to identify key variables. Results: Data were collected from 99 former ASF players. Most former players were in their fourth decade of life (age = 48.0 + 7.9), overweight or obese (BMI =32.6 + 5.9), had an average career duration of just over five years (5.6 + 3.5), with half identifying as Black (n=55, 56%) and as a lineman (n=52, 53%). Nearly all former players had radiographic evidence of hip (n=95, 96%) or knee (n=89, 90%) OA. Backward stepwise regression identified lower HOOS scores most strongly associated with higher BMI and presence of pain status (R2 range= 0.079, 0.134). Lower KOOS scores were also associated with higher BMI and presence of pain status, along with lineman status, prior ACL surgery, and greater radiographic severity (R2range=0.079, 0.251). Clinical Application & Conclusion: While this study is limited by cross-sectional design, our findings suggest that modifiable factors, weight and pain may be associated with knee and hip function in former ASF players. Radiographs may better represent severity of knee OA in this population.

Poster Location # 16

Poster Title

Can progesterone maintain muscle contractility in post-menopausal mice?

Author List

Hannah Houston, Z Hettinger, G Gilmer, K Wang, N Shahshahan, J Bergmann, E Creed, T Mkandawire, S Sinkar, R Kopchak, F Ambrosio

Abstract

Postmenopausal women disproportionately experience mobility limitations correlated with muscle weakness. Prior research suggests declining estrogen during menopause exacerbates muscle weakness, yet the results of estrogen replacement therapies designed to maintain muscle size and strength have been inconsistent. This inconsistency may be due to rodent models' inadequacy in developing therapies because aged rodents do not maintain a menopausal phenotype. In this study, we used two different models, chemically-induced menopause in female mice and three-dimensional (3D) muscle organoids, to investigate the impacts of menopause on muscle strength. For the mouse model, we injected an ovarian toxin, 4-vinylcyclohexene diepoxide (VCD), into middle-aged female mice for ten consecutive days to simulate menopause-sesame oil (SO)-injected mice served as controls. Prior to euthanasia, tibialis anterior muscle force was measured in both groups. The VCD-injected mice demonstrated a decrease in muscle contractile force. However, there was no change in cross-sectional area between VCD-injected and SO-injected mice. Next, we measured muscle force production in 3D muscle constructs, allowing us to evaluate the effects of individual sex hormones without interference from other systems or cell types. Muscle constructs were cultured in hormone-free media and randomized to one of the following groups: Pre-menopausal conditions (high 17-β estradiol (E2) and progesterone (P4, postmenopausal conditions (high follicle stimulating hormone (FSH) and luteinizing hormone (LH)), individually with FSH, LH, E2, or P4, or hormone free. Single hormone culture revealed constructs treated with P4 had an increase in force relative to hormone-free. FSH, LH, or E2 exposure alone did not affect force production. To validate this finding in vivo, VCD-injected mice received E2, P4, E2 + P4, or sham Nutella. Via tetanic force measurement, we found that E2+P4, E2 alone, and P4 alone restored muscle force in menopause. Together, these data suggest that the loss of progesterone associated with menopause may lead to muscle force deficits via mechanisms acting directly on the muscle and that E2 may improve muscle contractile force in vivo but not by directly acting on muscle. These findings highlight a previously unappreciated role of progesterone loss, in addition to estrogen loss, in menopause in contributing to skeletal muscle weakness.

Poster Location # 17

Poster Title

Nanotopographical cues tune the therapeutic potential of extracellular vesicles for the treatment of aged skeletal muscle injuries

Author List

Kai Wang, Nolan Frey, Andres Garcia, Kun Man, Yong Yang, Alice Gualerzi, Zachary Clemens, Marzia Bedoni, Philip LeDuc, Fabrisia Ambrosio

Abstract

Skeletal muscle regeneration relies on the tightly temporally regulated lineage progression of muscle stem/progenitor cells (MPCs) from activation to proliferation and, finally, differentiation. However, with aging, MPC lineage progression is disrupted and delayed, ultimately causing impaired muscle regeneration. Extracellular vesicles (EVs) have attracted broad attention as next-generation therapeutics for promoting tissue regeneration. As a next step toward clinical translation, strategies to manipulate EV effects on downstream cellular targets are needed. Here, we developed an engineering strategy to tune the therapeutic potential of EVs using nanotopographical cues. We found that EVs released by young MPCs cultured on flat substrates (fEVs) promoted the proliferation of aged MPCs while EVs released by MPCs cultured on nanogratings (nEVs) promoted myogenic differentiation. We then employed a bioengineered 3D muscle aging model to optimize the administration protocol and test the therapeutic potential of fEVs and nEVs in a high-throughput manner. We found that the sequential administration first of fEVs during the phase of MPC proliferative expansion (i.e., one day after injury) followed by nEV administration at the stage of MPC differentiation (i.e., three days after injury) enhanced aged muscle regeneration to a significantly greater extent than fEVs and nEVs delivered either in isolation or mixed. The beneficial effects of the sequential EV treatment strategy were further validated in vivo, as evidenced by increased myofiber size and improved functional recovery. Collectively, our study demonstrates the ability of topographical cues to tune EV therapeutic potential and highlights the importance of optimizing the EV administration strategy to accelerate aged skeletal muscle regeneration.

Poster Location # 18

Poster Title

Menopause drives cartilage degeneration via chondrocyte senescence and extracellular matrix disassembly

Author List

Gabrielle Gilmer, Hirotaka Iijima, Zachary Hettinger, Natalie Jackson, Juliana Bergmann, Allison C. Bean, Nafiseh Shahshahan, Ekaterina Creed, Rylee Kopchak, Hannah Houston, Michael Calderon, Claudette St Croix, Rebecca C. Thurston, Christopher Evans, Fabrisia Ambrosio

Abstract

Knee osteoarthritis (KOA) is twice as likely to occur in post-menopausal women than in men. However, few preclinical studies appropriately model menopause, as female rodents rejuvenate their ovarian follicles in middle-age. This gap in knowledge likely contributes to the lack of disease modifying therapies for KOA. The purpose of this study was to implement a chemically-induced menopause model in middle-aged female mice, characterize the trajectory of cartilage degeneration, and systematically test potential treatment modalities. Middle-aged female C57/BL6N mice were randomized to receive intraperitoneal injections of either an ovarian-specific toxin (4-vinylcyclohexene diepoxide, VCD; "menopause group") or sesame oil ("non-menopause group"). Knees were collected from menopause and non-menopause groups across the perimenopause and menopause transition and were prepared in paraffin blocks, sectioned, and stained with Safranin-O/Fast green. A validated, semi-quantitative scoring system was used to assess the degree of cartilage degeneration by a blinded scorer. The menopause group had significantly more cartilage degeneration compared to the non-menopause group. Next, using mass spectrometry proteomics on cartilage across groups, we found that menopause triggers cellular senescence and extracellular matrix disassembly. These cascades were predicted to be driven by a loss estradiol and progesterone. To validate these findings in vivo, we randomized menopausal mice to one of the following treatment groups: non-hormonal control, estradiol (E2), progesterone (P4), or combined estradiol+progesterone (E2+P4)). We found E2 and E2+P4 decreased cartilage degeneration. To evaluate the translational potential of this murine finding, we isolated post-menopausal human chondrocytes and exposed them to sex hormone conditions in vitro. Here, E2+P4 decreased markers of senescence and increased markers of chondrogenicity. These findings demonstrate that (1) a loss of E2 and P4 with menopause propagates cartilage degeneration by increasing chondrocyte senescence and extracellular matrix disassembly and (2) supplementation of these hormones protects cartilage against the deleterious effects of menopause-induced KOA.

Poster Location # 19

Poster Title

Dynamic Instability is Underestimated on Standing Flexion-Extension films when compared to Prone CT Imaging

Author List

Michael C. Chiang, Albert Jiao, Melvin C. Makhni, Jacob C. Mandell, Zacharia Isaac

Abstract

We performed a retrospective study evaluating the incidence and degree of L4-5 anterior spondylolisthesis in patients with standard supine MRI, standing radiographs, and prone CT. We hypothesize that prone CT imaging will provide greater sensitivity for instability compared to standing or supine positions. Summary of Background Data: Dynamic lumbar instability evaluated by flexion-extension radiographs may underestimate the degree of lumbar spondylolisthesis. Despite efforts to characterize dynamic instability, significant variability remains in current guidelines regarding the most appropriate imaging modalities to adequately evaluate instability. Methods: We assessed single-level (L4-5) anterolisthesis between 2014 - 2022 with standing radiographs (CR), prone CT images (CT), or supine MRI images (MRI). Results: We identified 102 patients with L4-5 anterolisthesis. The average translation (± SD) measured were 4.9 ± 2.2 mm (CR), 2.5 ± 2.6 mm (CT), and 3.7 ± 2.6 mm (MRI) ($p < 0.001$). The mean difference in anterolisthesis among imaging modalities were 2.7 ± 1.8 mm between CR and CT ($p < 0.001$), 1.8 ± 1.4 mm between CR and MRI ($p < 0.001$), and 1.6 ± 1.4 mm between CT and MRI ($p = 0.252$). Ninety two of 102 patients (90.2%) showed greater anterolisthesis on CR compared to CT, 72 of 102 (70.6%) comparing CR to MRI, and 27 of 102 (26.5%) comparing CT to MRI. We found that 17.6% of patients exhibited ≥ 3 mm anterior translation comparing CR with MRI, whereas 38.2% patients were identified comparing CR with CT imaging ($\chi 2$ test $p = 0.0009$, post-hoc Fisher's exact test $p = 0.0006$ between CR and CT). Only 5.9% of patients had comparable degrees of instability between flexion-standing. Conclusion: Prone CT imaging revealed the greatest degree of single L4-5 segmental instability compared to flexion-extension radiographs.

Poster Location # 20

Poster Title

Chronic Pain Education Delivered with a Virtual Reality Headset in Outpatient Physical Therapy Clinics: A Multi-site Observational Trial

Author List

David Binder, Lorna Brown, Tina DiCenso-Fleming, Trevor Ensign, Alexander J Boyd, Gail Monaghan

Abstract

Chronic pain is multidimensional, requiring expanded interventions for optimal management. Pain education, mindfulness training, and virtual reality (VR) are showing promise, but barriers remain for implementation in outpatient rehabilitation settings. This study aimed to explore the experiences of chronic low back pain patients and physical therapists with a pain education and mindfulness intervention. Methods: Patients were identified and consented by study staff. Baseline and follow-up questionnaires and surveys were collected with quantitative and qualitative data. Patients viewed five videos explaining key pain concepts and guided imagery nature videos using a VR headset. Results: Twenty patients were consented, and 15 patients completed the intervention. Patients and physical therapists rated their experiences with the program as excellent, however, concerns were raised related to logistical challenges around use of the VR headset in busy clinic settings. Changes in pain knowledge occurred in the desired direction in 8 out of 9 key concepts. Conclusions: Delivering standardized educational and mindfulness training with a VR headset to patients with chronic low back pain was feasible and acceptable to patients and physical therapists. Concerns remain regarding the increased time burden with use of this technology in a busy clinic setting weighed against potential benefits. Alternative delivery methods are needed to reduce logistical challenges and increase patient access to content outside of the clinic setting. Impact Statement: Outpatient rehabilitation clinic-friendly interventions are needed to address the complex, multi-dimensional nature of chronic pain. Content that patients can consume in the clinic ensures compliance and can be used as an adjunct to reinforce additional interventions typically used in this population.

Poster Location # 21

Poster Title

Riding The Waves of Pain: The Neural Correlates and Impact of Day-to-Day Pain Fluctuations on Clinical Outcomes after Cognitive Behavioral Therapy

Author List

Arvina Grahl, Maya Barton-Zuckerman, Jeungchan Lee, Asimina Lazaridou, Myrella Paschali, Lara Gardiner, Seneca Ellis, Kylie Isenburg, Alessandra Anzolin, Robert R. Edwards, Vitaly Napadow

Abstract

Pain is a subjective, multifaceted experience characterized by somatosensory, affective, and cognitive components. Its manifestation and severity vary between and within patients. Recent guidelines suggest that patients with high day-to-day baseline pain fluctuations could be excluded from randomized controlled trials (RCTs) using enrichment protocols to enhance homogeneity in a study sample (US FDA, 2019). However, the current literature is inconclusive reporting clinical benefits for high day-to-day fluctuations ("hope for change") as well as consistent pain experiences ("know what to expect"). In this longitudinal MRI study involving an 8-week intervention of cognitive behavioral therapy (CBT) in Fibromyalgia patients (N=70, all female, age ±SD 41.27 ±12.54), the impact of daily reported pain fluctuations, i.e. standard deviation, on brain responses to nociceptive stimuli and clinical outcomes were investigated. Patients either received CBT or a duration-matched education-control (EDU). Preceding the intervention, patients underwent an evoked pressure pain paradigm during whole-brain fMRI (Siemens 3T MRI, TR/TE=1250/33ms, voxel size 2mm3 isotropic, SMS MB acc. factor 5). This included six cuff stimulations of either non- or moderately painful pressures (calibrated to individual's threshold). Clinical outcomes were assessed using the Pain Catastrophizing Scale (PCS), a specific target of CBT. Greater day-to-day clinical pain fluctuations at baseline were related to greater post-therapy improvement in pain catastrophizing in the CBT but not the EDU group. Furthermore, greater day-to-day clinical pain fluctuations were negatively correlated with BOLD fMRI responses during pain anticipation observed in nociceptive processing areas (i.e., primary-sensory-cortex and superior-parietal-lobe). The results suggest that greater clinical baseline pain fluctuations may boost CBT treatment effects for chronic pain by influencing the anticipation of pain. Specifically, entering a CBT intervention with the prior experience of "dynamic pain" instead of "static pain" may reflect beneficial anticipatory flexibility and potential for change concerning future cognitive pain interventions. Importantly, this study highlights the importance of a stronger emphasis on the effects of pain variability in research studies involving chronic pain populations.

Poster Location # 22

Poster Title

Designing a study to reveal neural mechanisms supporting the role of social interaction in MDMA-assisted therapy for chronic pain in Fibromyalgia

Author List

Ellis, S., Grahl, A., Anzolin, A., Gardiner, L., Edwards, R., Kaptchuk, T., King IV, F., Napadow, V.

Abstract

3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy) is a psychedelic drug demonstrated to boost empathy and prosocial behavior, potentially leading to enhanced therapeutic alliance in clinical settings. However, the underlying mechanisms are not well understood. Importantly, MDMA is considered a tool to augment psychotherapy rather than a pain medication. Given recent evidence suggesting the promise of MDMA-assisted therapy (MDMA-AT) for PTSD, anxiety, and depression, exploring applications for chronic pain conditions seem warranted, particularly given the central role of the patient-clinician relationship in the experience of pain. Further, there is significant overlap between the rumination and anxiety encountered in PTSD and those same facets of negative emotion experienced by fibromyalgia patients. Hence, it can be suggested that individuals with fibromyalgia are likely to experience similar benefits from MDMA-assisted therapy. Understanding the neural mechanisms through which MDMA-AT enhances therapeutic alliance and reduces pain-related negative affect and interference is of increasing importance. Consequently, this open-label pilot study using hyperscanning, a brain imaging method simultaneously collecting EEG or fMRI data in patient and clinician while they interact (target N=15 dyads) has been developed to target this knowledge gap. An adapted hyperscanning protocol will allow for imaging during the MDMA sessions. Clinical outcomes will include evaluating pain interference and severity using the Brief Pain Inventory and assessing brain-to-brain concordance through EEG and fMRI hyperscanning. Participants will complete baseline fMRI and EEG scans before participating in three preparatory therapy sessions with clinicians trained in administering MDMA-AT. Patients will then complete two experimental sessions where they receive 100-150mg of MDMA. Shortly after peak drug effect, participants will undergo either EEG or fMRI hyperscanning. Experimental sessions will be followed by two integration therapy visits and a three-month follow-up. The protocol has been approved by the Multidisciplinary Association for Psychedelic Studies (MAPS), the FDA, and the MGB IRB, and will hopefully be initiated by the Summer of 2024. This is the first MAPS-approved study of MDMA-AT for fibromyalgia. The unique hyperscanning methods utilized in this protocol will allow for a novel assessment of potential benefits determined by the social and neural underpinnings of MDMA-AT in chronic pain patients.

Poster Location # 23

Poster Title

Elevated Insula Glutamate in Migraine is Linked with Longer Headache Duration: A 7T H-MRS Study

Author List

Michael Datko, Sarasa Tohyama, Jack H. Schnieders, Ludovica Brusaferri, Lillian D. Kinder, Kassandra Round, Alison Goldstein, Melaina Gilbert, Mackenzie Hyman, Frances Marin, Hannah Goodman, Danielle Giachos, Ronald G. Garcia, Randy L. Gollub, Hsinlin T. Cheng, Nouchine Hadjikhani, Marco L. Loggia, Zev Schuman-Olivier, Bruce R. Rosen, Robert R. Edwards, Eva Ratai, Vitaly Napadow

Abstract

Migraine is a prevalent and highly disabling disorder, with complex neurobiological underpinnings including increased cortical excitability. This hyperexcitability may be mediated by the excitatory neurotransmitter glutamate, and recent magnetic resonance spectroscopy (H-MRS) studies have found evidence for increased glutamate in posterior insula in chronic pain patients. We hypothesized that compared to healthy volunteers (HV), participants with episodic migraine (MIG) would show increased glutamate concentration in the posterior insula using ultrahigh-field H-MRS. We further hypothesized that elevated insula glutamate would be associated with greater frequency, intensity, and duration of migraine attacks. We scanned 55 MIG (51 F, 4 M, mean age=35.1 years) and 20 HV (19 F, 1 M, mean age=35.6 years) participants in a Siemens Terra 7-Tesla MRI scanner. We compared glutamate concentration in the left posterior insula between MIG and HV participants using two-tailed t-tests. Participants completed daily headache diaries electronically for ≥30 days prior to scan, reporting pain intensity and duration of any headaches, and occurrence of migraine symptoms such as nausea, laterality, and aura. We examined associations between insula glutamate concentration and migraine frequency, intensity, and duration with Spearman correlation tests (α=0.05). The mean duration of migraine attacks for MIG participants was 9.9±6.9 hours (range: 2.4-33 hours). Mean migraine frequency (average migraines per month throughout enrollment period) was 4.2±2.4 migraines/month (range: 0.6-10.5). Mean pain intensity (1-10, 1 being lowest and 10 being highest pain) was 5.4±1.4 (range: 3.3-8.6). Participants with migraine had significantly higher glutamate concentration in the posterior insula compared to healthy controls (MIG mean=17.1±1.1 mmol/l, HV mean=16.3±1.0 mmol/l, d=0.65, $p<0.05$). There was a significant association between insula glutamate concentration and the mean duration of migraine attacks ($r=0.41$, $p<0.01$), but not with migraine frequency or pain intensity. This study found elevated glutamate concentration in the posterior insula among individuals with episodic migraine using ultrahigh-field H-MRS. The association between elevated insula glutamate and migraine attack duration suggests that glutamate in this region may contribute to longer duration of migraine attacks. Furthermore, interventions targeting insular glutamate levels and cortical hyperexcitability via glutamatergic mechanisms may be able to improve patient outcomes by reducing migraine duration.

Poster Location # 24

Poster Title

Structure-function associations of the trigeminal system in episodic migraine - a combined DTI, fMRI and PET study

Author List

Sarasa Tohyama, Michael Datko, Ludovica Brusaferri, Mackenzie Hyman, Alison M. Goldstein, Kassandra Round, Lillian D. Kinder, Ronald G. Garcia, Randy L. Gollub, Robert R. Edwards, Bruce R. Rosen, Nouchine Hadjikhani, Hsinlin T. Cheng, Zev Schuman-Olivier, Marco L. Loggia, Vitaly Napadow

Abstract

Migraine, a highly prevalent neurological disorder, involves sensitization of the trigeminal system. The trigeminal system has been historically difficult to image using advanced magnetic resonance imaging (MRI) techniques because of the small-scale structure of the nerve and brainstem nuclei. Thus, the white matter microstructural properties of the trigeminal nerve using Diffusion Tensor Imaging (DTI) in migraine patients has not yet been adequately explored. Furthermore, no studies have examined the structure-function associations of the trigeminal system by combining structural MRI (i.e. DTI) with functional MRI (i.e. fMRI and positron emission tomography (PET)). Thus, we used 7 Tesla DTI/fMRI and 3 Tesla PET/MRI, to investigate the structure-function associations of the trigeminal system in patients with episodic migraine. 58 patients with episodic migraine and 18 sex/age-matched healthy controls underwent MRI sessions to acquire DTI, fMRI, and PET images. For the PET acquisition, we used the radioligand [11C]-PBR28, which binds to the translocator protein, a marker of glial activation. DTI metrics and the [11C]-PBR28 PET signal were extracted from the root entry zone of both trigeminal nerves. For the fMRI acquisition, non-painful electrical stimulation was applied to the trigeminal nerve territory of the right forehead using a block design. Migraine patients showed significantly reduced fractional anisotropy (FA), and increased radial and mean diffusivity, in the trigeminal nerve compared to healthy controls, revealing altered white matter microstructure. The fMRI group averaged map of migraine patients demonstrated significant activation in the spinal trigeminal nucleus (SpV), a key nucleus of the trigeminal system that mediates cranial pain sensation. Furthermore, a positive association between the white matter integrity of the nerve (as measured by FA) and functional response in SpV (as measured by fMRI) was observed. Additionally, a negative association between FA and neuroinflammation (as measured by PET) in the trigeminal nerve was observed, suggesting interesting structure-function associations. Identification of the mechanisms that contribute to migraine sensory hypersensitivity, symptom frequency, and severity provides insight into the PNS and CNS changes that characterize episodic migraine, and the potential importance of these structures for therapeutic targeting. Trigeminal system remodeling may be an important aspect of the dynamics underlying migraine pathophysiology.

Poster Location # 25

Poster Title

Peak alpha frequency as a predictive biomarker for treatment outcomes in chronic pain patients

Author List

Seneca Ellis, Alessandra Anzolin, Arvina Grahl, Lara Gardiner, Dan-Mikael Ellingsen, Jeungchan Lee, Ted Kaptchuk, Vitaly Napadow

Abstract

The experience of chronic pain can be debilitating and highly variable. For that reason, patients also show very different responses to clinical interventions. The mechanisms behind this variability in treatment outcomes remain largely unknown. Understanding these mechanisms, along with the social and contextual variables that contribute, is crucial to identify patients that are at high risk for developing chronic pain. Recent research has identified resting brain alpha rhythm (8-12 Hz on electroencephalography, EEG) in the sensorimotor cortex as differentiating chronic pain patients, who show abnormally slow peak alpha frequency (PAF), from healthy adults. Additionally, as excellent stability and limited pre-processing characterize PAF assessment this metric may be a promising biomarker for clinical pain assessment. While PAF has been identified as a valuable biomarker for pain sensitivity in healthy subjects using an evoked pain model, limited research has been done to assess PAF activity in chronic pain populations. The aim of the present study was to investigate the role of PAF as a predictor of clinical treatment outcomes in chronic pain patients. EEG was acquired from chronic pain patients during a resting state session performed after initial clinical encounter with an acupuncturist, but just prior to acupuncture treatment. We hypothesized that faster PAF would be correlated with better treatment outcome. Brain signals were acquired from 34 dyads composed of chronic low back pain (cLBP) patients and acupuncturists via two synchronized 64-channel EEG nets. LBP significantly decreased after the treatment -POST, compared to the beginning of the visit -PRE. Almost all participants experienced pain relief following acupuncture treatment. The EEG analysis revealed predominant alpha oscillatory activity in sensorimotor areas, confirming robust sensorimotor PAF. We found a significant correlation between PAF, recorded prior to acupuncture treatment, and subsequent treatment efficacy. Faster PAF was associated with more pain relief following acupuncture treatment. While previous research exploring PAF as a biomarker for pain outcomes used healthy subjects undergoing experimental pain, our study extends the applicability of PAF as a potential predictive biomarker for pain clinical outcomes following non-pharmacological therapy.