Division of Neurotoxicology

Presented by:

Sherry Ferguson, Ph.D.

Division Director

U.S. Food and Drug Administration

Division Staff

- Government Positions (# FTEs)
  - Research Scientists, Staff Fellows & Visiting Scientists: 19 and one open position (for a Neuropathologist)
  - Support Scientists: 11
  - Administrative: 2
  - FDA Commissioner Fellows (program ended in 2019): 0
- ORISE Post-Docs, Graduate Students, etc: 2 current post-docs, 1 part-time undergraduate student, and 3 open post-doc positions
- Total = 35

Outreach

- **Collaborations**
  - NCTR Divisions: Systems Biology, Microbiology, Bioinformatics & Biostatistics
  - FDA Regulatory Centers: CDER, CDRH, CFSAN
  - Government agencies: CDC/NIOSH, EPA, NTP, HESI, Critical Path for Parkinson's of Coalition Against Major Diseases (CAMD)

- **Global Leadership Outreach**
  - UAMS & Arkansas Children's Hospital; Univ. of Arkansas at Fayetteville; Univ. of Texas Health Sciences Center, San Antonio; Icahn School of Medicine, Mount Sinai, NY; Albert Einstein College of Medicine; University of Birmingham, UK
  - Mayo Clinic (MASK study)
  - Steering Committee of SmartTots – a collaborative effort of the FDA, the International Anesthesia Research Society and others
  - National Institute of Perinatology, Mexico, National Institute of Public Health, Mexico
  - European Cooperation on Science and Technology (COST) - Committee for Nano4Neuro project

Division Mission/Vision

- Mission: to identify and quantify the neurotoxicity associated with FDA-regulated products, to develop and validate quantitative biomarkers of neurotoxicity, and identify biological pathways associated with the expression of neurotoxicity while meeting and supporting the evolving needs of other FDA regulatory centers

- Goals: to provide the data and expertise necessary for crucial regulatory decisions made by other Centers and to advance regulatory science research in neurotoxicology for FDA

- Strategies: development of translationally valid imaging approaches, alternative preclinical models, and cross-species metrics of brain function to identify novel markers of neurotoxicity

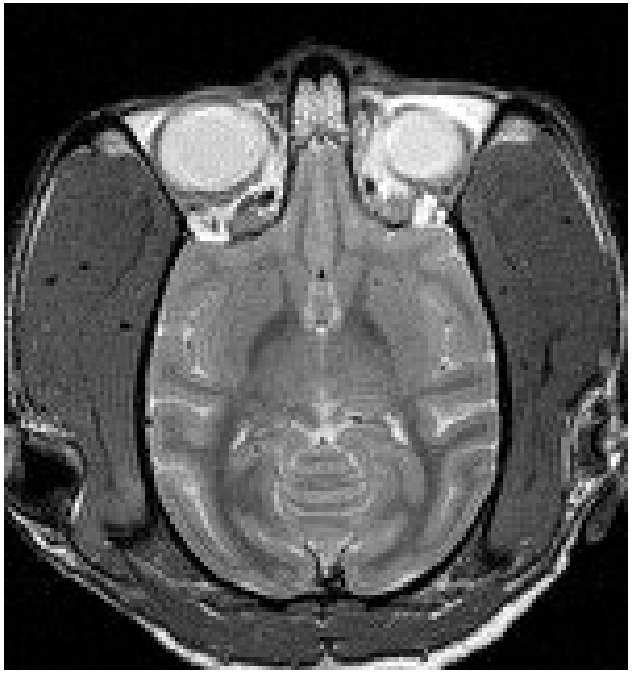
Top Three Accomplishments during 2019

- MRI of nonhuman primates previously exposed to methylphenidate
- Expansion of in vitro work
- Increased responsiveness to Agency-specific needs

Examples of Current Projects

- MRI of nonhuman primates exposed to methylphenidate
- Expansion of in vitro work
- Increased response to Agency-specific needs

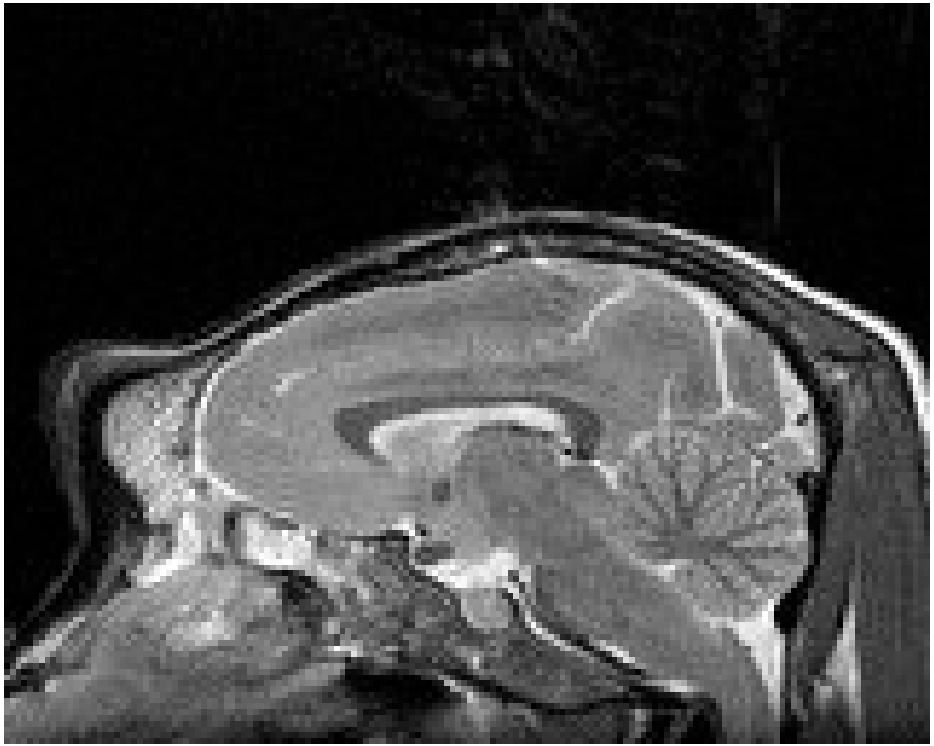
Details of Selected Projects

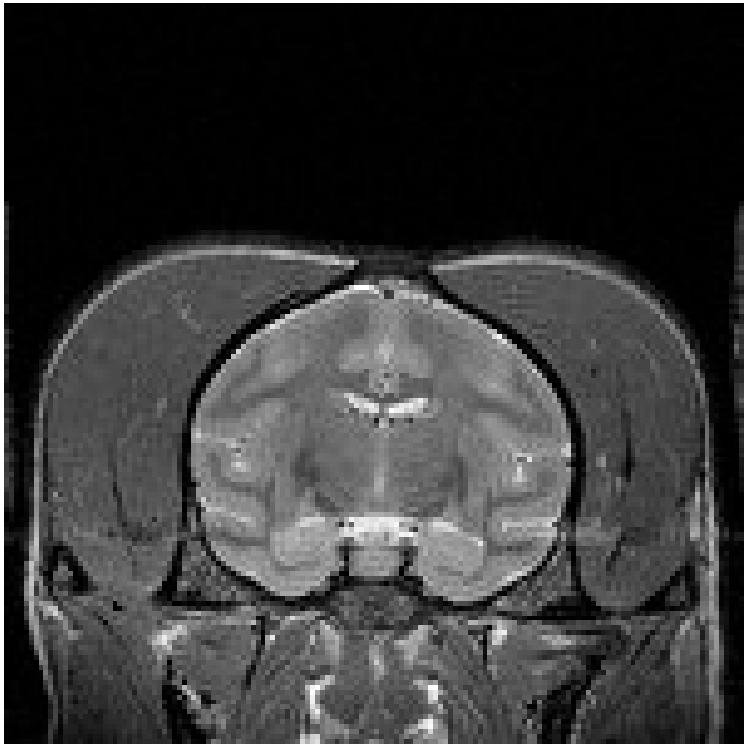


4.7 T 40 cm bore MRI
Anatomy + quantitative T2 map
Final resolution 0.65 x 0.65 x 0.65 mm
Total scan time 32 minutes

(preliminary data)

Details of Selected Projects





Examples of Current Projects

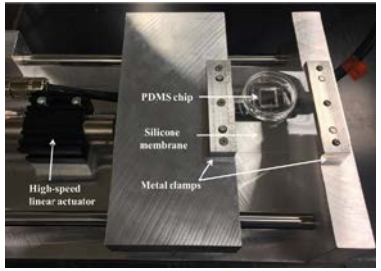
- MRI of non-human primates exposed to methylphenidate
- Expansion of in vitro work
- Increased response to Agency-specific needs

Details of Selected Projects

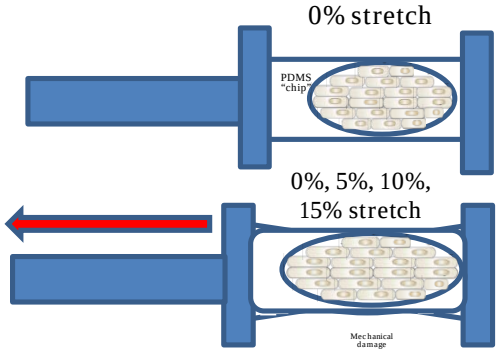
- Stretch system to model TBI
- Multielectrode assay (MEA)
- MPS system

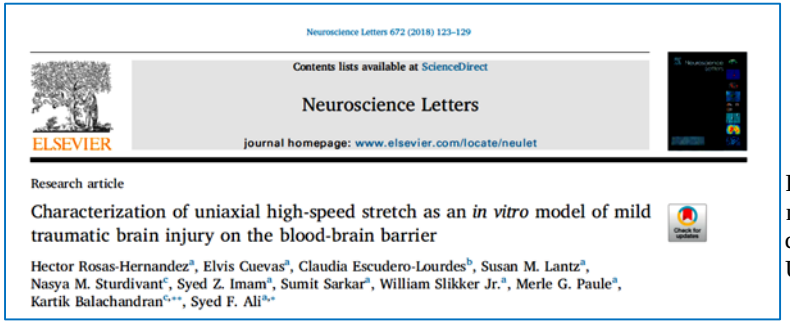
Stretch Model of TBI

Uniaxial high-speed stretch model of TBI



- Custom-made high-speed stretcher (Univ Arkansas)
- Movement of mechanical arm induces stretch
- Cells are cultured in stretchable PDMS chips
- Stretch up-to 15% is achievable
- Stretch induced in 40 ms





Neuroscience Letters 672 (2018) 123–129

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

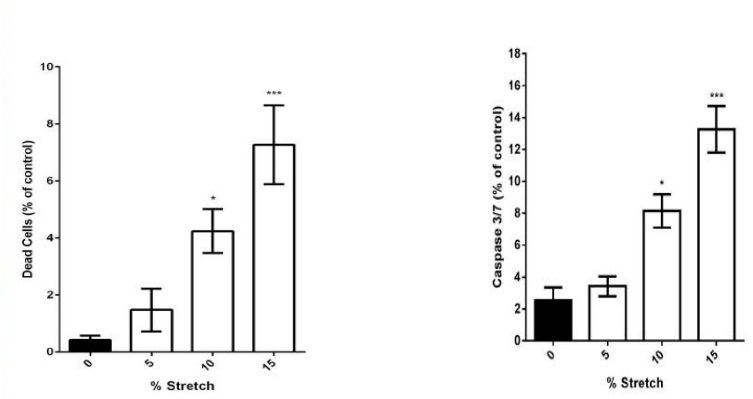
Research article

Characterization of uniaxial high-speed stretch as an *in vitro* model of mild traumatic brain injury on the blood-brain barrier

Hector Rosas-Hernandez[a], Elvis Cuevas[a], Claudia Escudero-Lourdes[b], Susan M. Lantz[a], Nasya M. Sturdivant[c], Syed Z. Imam[a], Sumit Sarkar[a], William Slikker Jr.[a], Merle G. Paule[a], Kartik Balachandran[c,**], Syed F. Ali[a,*]

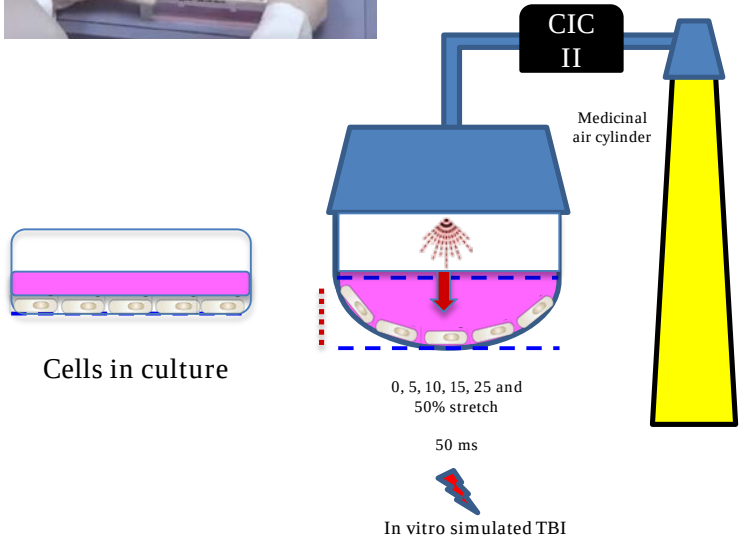
Primary isolated rat brain microvascular endothelial cells: 0%, 5%, 10%, 15% Uniaxial high-speed stretch

Low levels of uniaxial high-speed stretch induces cell death



Biaxial stretch model of TBI

- Cell Injury Controller II (Custom Design and Fabrication)
- Infuses pressurized medicinal air into the cultured cells
- Cells cultured in flexible-bottom stretchable plates
- Up to 50% stretch
- Stretch induced in 50-100 ms



Primary isolated rat brain microvascular endothelial cells
0%, 5%, 10%, 15%, 25% and 50% biaxial stretch

Mol Neurobiol
DOI 10.1007/s12035-017-0738-5

CrossMark

Characterization of Biaxial Stretch as an In Vitro Model of Traumatic Brain Injury to the Blood-Brain Barrier

Hector Rosas-Hernandez[1] · Elvis Cuevas[1] · Claudia Escudero-Lourdes[2] · Susan M. Lantz[1] · Nancy P. Gomez-Crisostomo[3] · Nasya M. Sturdivant[4] · Kartik Balachandran[4] · Syed Z. Imam[1] · William Slikker Jr[1] · Merle G. Paule[1] · Syed F. Ali[1]

Neurochemical Research 2019
https://doi.org/10.1007/s11064-019-02872-8

ORIGINAL PAPER

Stretch-Induced Deformation as a Model to Study Dopaminergic Dysfunction in Traumatic Brain Injury

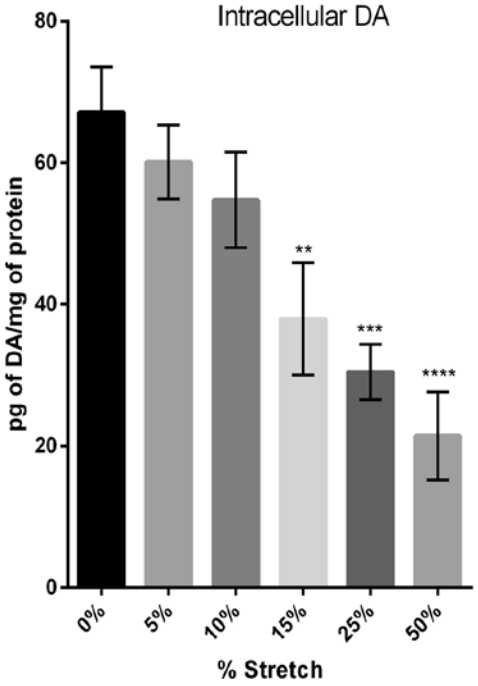
Hector Rosas-Hernandez[1] · Susan M. Burks[1] · Elvis Cuevas[1] · Syed F. Ali[1]

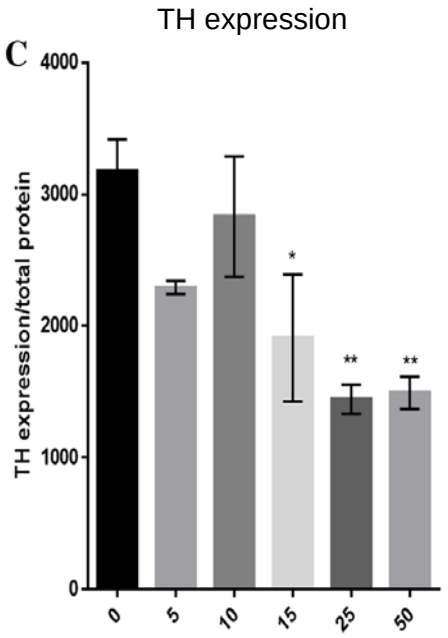
Human primary dopaminergic cells
0%, 5%, 10%, 15%, 25% and 50% biaxial stretch

Biaxial Stretch Model of TBI

High biaxial stretch levels induce necrosis (50%) and apoptosis (25 and 50%)

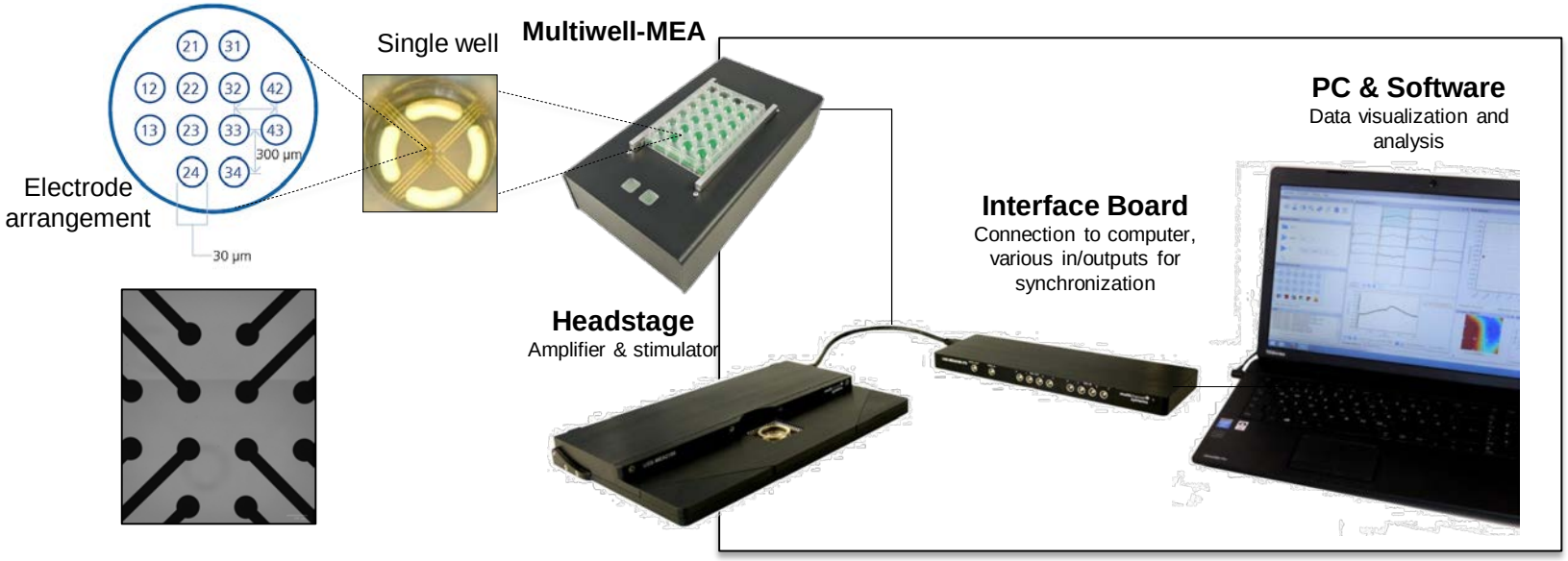
Mid to high levels of biaxial stretch decrease intracellular DA and TH expression (extracellular DA and DAT expression unaffected)





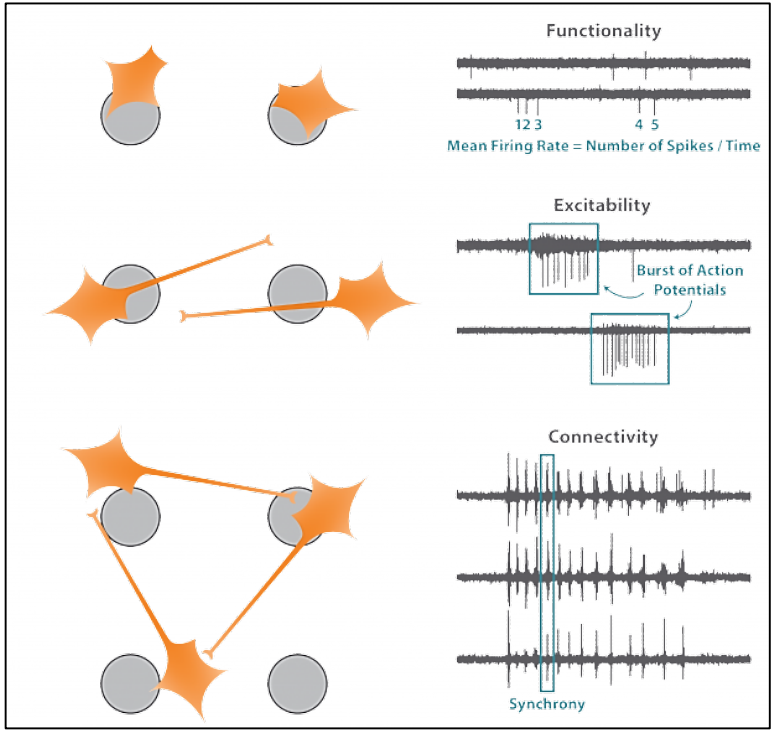
Microelectrode Array (MEA)

[also termed *multielectrode arrays*]



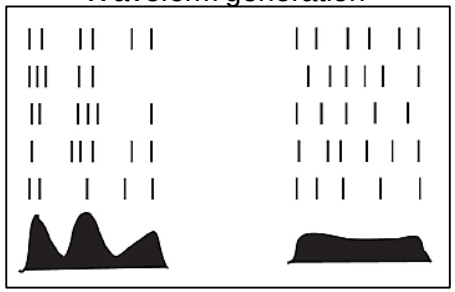
The Multiwell-MEA-System measures in vitro electrophysiology. The assay features a 24-well plate set-up with 12 electrodes [or channels] per well. The system [Multi Channel Systems, Reutlingen, Germany] can record electrophysiological activity from cultured cells and brain slices for neurotoxicity screenings.

MEA assay



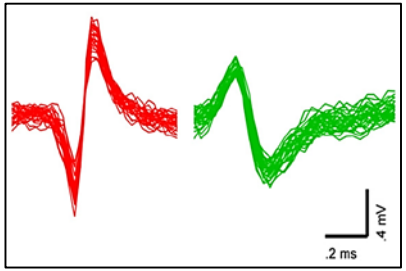
Axion Biosystems (San Francisco, CA, USA).

Waveform generation



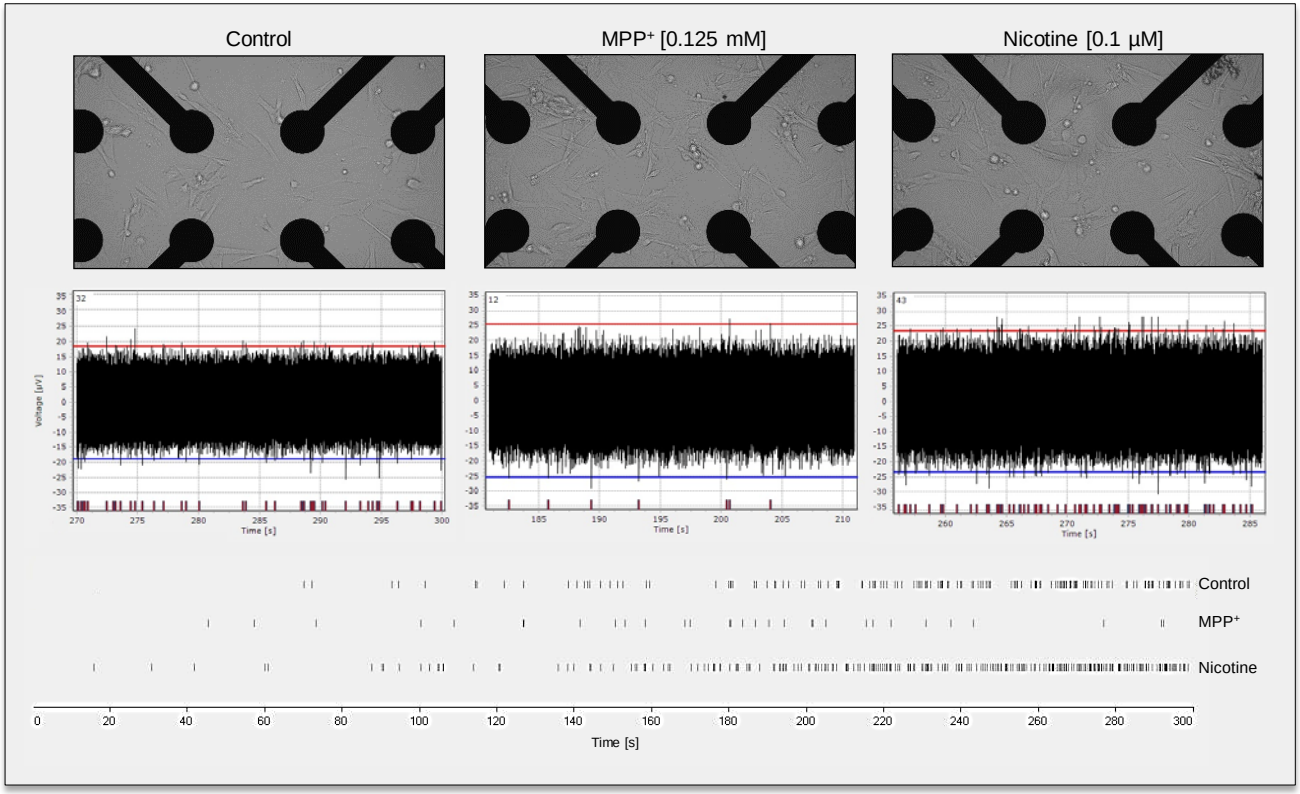
Front Syst Neurosci. 2015 Nov 10;9:151.

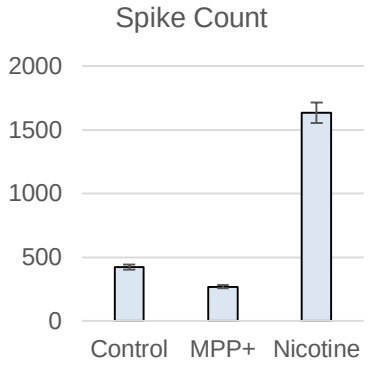
Neuron characterization

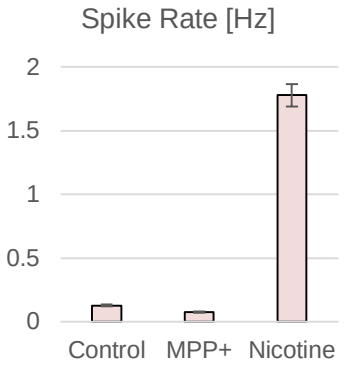


J Neurosci. 2012 Apr 18;32(16):5534-48.

Effect of MPP+ and nicotine on electrophysiological activity of human dopaminergic neurons





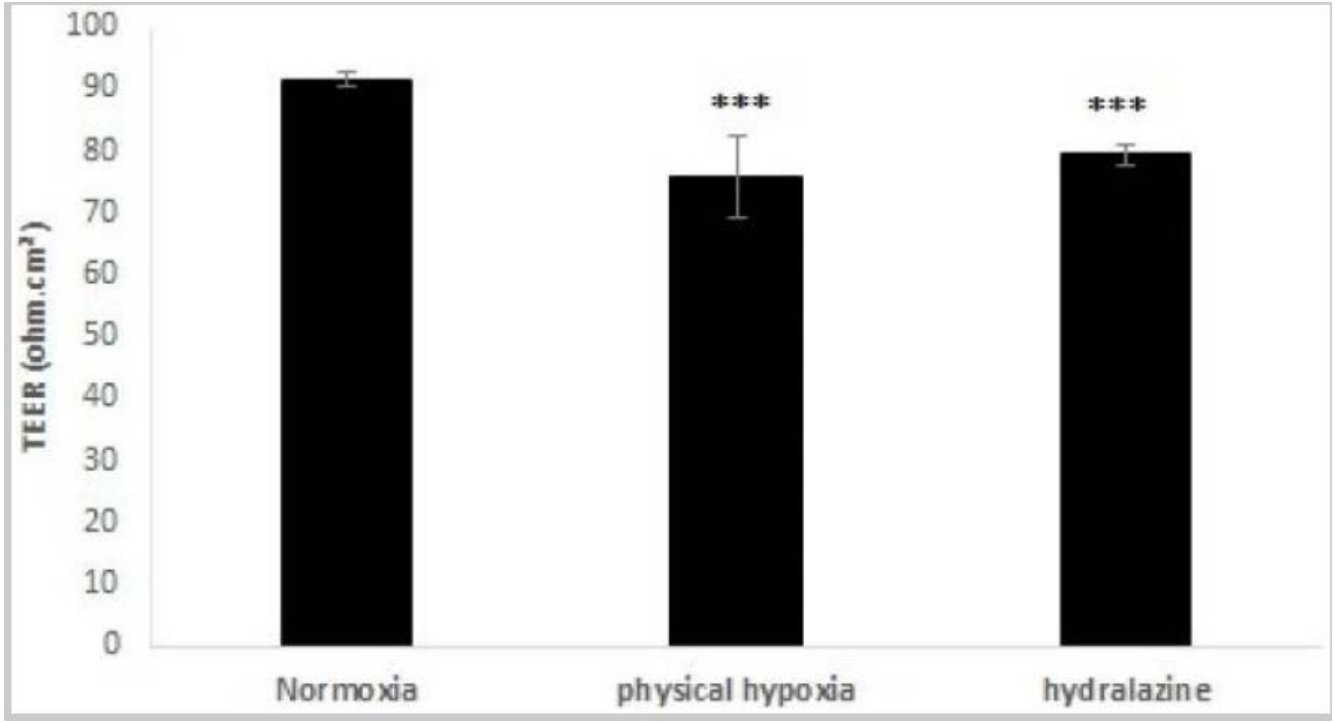


(unpublished data)

MPS for Blood-Brain-Barrier

- E7698: Blood-brain-barrier on-a-chip technology as a toxicological screen (PI Syed Ali, approved July 2019)
  - Compare BBB properties (TEER, paracellular permeability and expression of TJ proteins) with those in a static trans-well BBB model
  - Analyze BBB changes after treatment with known BBB disruptors (methamphetamine, TNF-α, LPS) and compare to static trans-well BBB model

MPS for Blood-Brain-Barrier



Chatard et al., 2016

Examples of Current Projects

- MRI of non-human primates exposed to methylphenidate
- Expansion of in vitro work
- Increased responsiveness to Agency-specific needs

Details of Selected Projects

- CDER
  - Entire portfolio of the pediatric anesthesia work (2004 to present)
  - Gadolinium deposition in rat brain (2016)
  - Adolescent exposure to methylphenidate (2017 to present)
  - Adolescent exposure to ketamine (2019)
  - Analysis of sex differences in amyloid β transporters of the cerebral vasculature in Alzheimer's disease (under review)
  - Use of acetaminophen during pregnancy (under review)

Details of Selected Projects

- CFSAN
  - Developmental exposure to Bisphenol A (2009)
  - Developmental exposure to inorganic arsenic (2017 to present)
- OWH
  - Gender differences in nicotine using MRS (2012)

Details of Selected Projects

- Multiple Centers
  - Developmental exposure to cannabidiol (CBD) (under review)

Details of Acetaminophen (APAP) Project

- APAP marketed for pain/fever relief since 1950 and is the treatment of choice for pain/fever during pregnancy
- Comprehensive datasets for safety during pregnancy do not exist (drug label does not contain warning for use during pregnancy)

Details of Acetaminophen (APAP) Project

- Agency issued a safety announcement in 2015 which noted recent clinical findings of in utero APAP exposure and adverse developmental outcomes

FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy

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[1-9-2015]

Safety Announcement

- Acetaminophen in both OTC and prescription products and the risk of attention deficit hyperactivity disorder (ADHD) in children born to women who took this medicine at any time during pregnancy.[9] Acetaminophen is a common pain reducer and fever reducer found in hundreds of medicines including those used for colds, flu, allergies, and sleep.

NEWS RELEASES

Media Advisory Wednesday, October 30, 2019

NIH-funded study suggests acetaminophen exposure in pregnancy linked to higher risk of ADHD, autism

What

Exposure to acetaminophen in the womb may increase a child's risk for attention deficit/hyperactivity disorder and autism spectrum disorder, suggests a study funded by the National Institutes of Health and the Agency for Health Care Research and Quality. The study was conducted by Xiaobing Wang, M.D., of the Johns Hopkins University Bloomberg School of Public Health, Baltimore, and colleagues. It appears in *JAMA Psychiatry*.

Details of Acetaminophen (APAP) Project

- CDER Medical Policy and Program Review Council recommended that NCTR conduct a nonclinical study to characterize the potential risks of APAP
- Discussions with CDER to determine exactly what data would be needed
- Concept paper approved June 2019 (C19045)
- Full protocol currently under review by CDER colleagues prior to formal submission

Future Directions

- Collaboration with Division of Systems Biology for lipidomic analyses of the AD Tg rat using MALDI-IMS (PI Sumit Sarkar, E763101)
- Collaboration with Division of Microbiology for analysis of intestinal and neuronal pathology in AD Tg rats and human post-mortem tissue (PI Sumit Sarkar, E770201, approved July 2019)
- Collaboration with Division of Systems Biology for assays of Parkinson's disease lipidome and peripheral biomarkers of PD via 3D-MALDI MS imaging and SeleXION Lipidyzer (PI Syed Imam, E770701, approved August 2019)

Future Directions

- Continued collaborations with the Mayo Anesthesia Safety in Kids (MASK) studies

Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia

The Mayo Anesthesia Safety in Kids (MASK) Study

David O. Warner, M.D., Michael J. Zaccariello, Ph.D., L.P., Slavica K. Katusic, M.D., Darrell R. Schroeder, M.S., Andrew C. Hanson, B.S., Phillip J. Schulte, Ph.D., Shonie L. Buenvenida, R.N., Stephen J. Gleich, M.D., Robert T. Wilder, M.D., Juraj Sprung, M.D., Danqing Hu, M.D., Robert G. Voigt, M.D., Merle G. Paule, Ph.D., John J. Chelonis, Ph.D., Randall P. Flick, M.D., M.P.H.

Anesthesiology, 2018

Contemporary Clinical Trials, 2015

Neurodevelopment of children exposed to anesthesia: Design of the Mayo Anesthesia Safety in Kids (MASK) study

Stephen J. Gleich [a], Randall Flick [a], Danqing Hu [b], Michael J. Zaccariello [c], Robert C. Colligan [c], Slavica K. Katusic [d], Darrell R. Schroeder [d], Andrew Hanson [d], Shonie Buenvenida [a], Robert T. Wilder [a], Juraj Sprung [a], Robert G. Voigt [e], Merle G. Paule [f], John J. Chelonis [f], David O. Warner [a,*]

British Journal of Anaesthesia, 2019

Performance on the Operant Test Battery in young children exposed to procedures requiring general anaesthesia: the MASK study

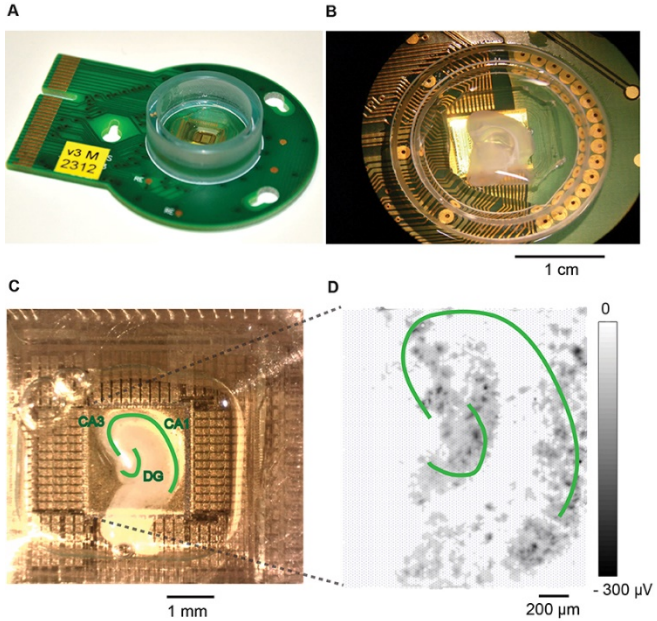
David O. Warner[1,*], John J. Chelonis[4], Merle G. Paule[4], Ryan D. Frank[2], Minji Lee[2], Michael J. Zaccariello[3], Slavica K. Katusic[2], Darrell R. Schroeder[2], Andrew C. Hanson[2], Phillip J. Schulte[2], Robert T. Wilder[1], Juraj Sprung[1] and Randall P. Flick[1]

Future Directions

- Improved cerebrovascular analysis to increase translational value of rodent models
  - Isolated capillaries for functional assays and protein analysis
- Increased use of the 4.7 T MRI in NHPs
- Validation of the T2 MRI biomarker of neurotoxicity (C18052 under review)

Future Directions

- Training and use of new instruments/assays
  - Cytation 5
  - – Combination plate reader and high content imaging system (live imaging, fixed samples, cells, zebrafish, slides)
  - Hippocampal slice capabilities of the MEA system
  - – LTP induction, synaptic excitability



Division Challenges

- Best way(s) to fund expensive maintenance contracts for high-tech instruments (e.g., MRIs, microPET)
- Better hiring techniques
  - Recruiting difficulties
- Enhanced interactions with other Centers

Feedback Requested

- What pressing neurotoxicological issues should we pursue?
- What emerging technologies should we examine?
- How can we best verify those newer technologies?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