Functional Neurorehabilitation Research Opportunities for UAB Medical Students

Victor Mark, MD

and the faculty of the UAB Department of Physical Medicine and Rehabilitation

Research Advisory Committee

Members:

Victor Mark, MD (chair)

Yu-Ying Chen, MD PhD

Candace Floyd, PhD

Amy Knight, PhD

Danielle Powell, MD

Ceren Yarar-Fisher, PhD

Sherricka Embery, Administrative Associate

Committee meets on an as-needed basis

- **FNR Scholars Program**

  Rationale:

  - Increase awareness of the field of PM&R and physiatrists among UAB Medical Students.
  - Support School of Medicine educational mission (i.e., scholarly activity and student research)
  - Mentor next-generation of leaders in the field, including physician-scientists.

Approach

- Provide stipend and research fund for UAB 1st year Medical Students to conduct a summer research project mentored by PM&R faculty: **($4,000 stipend + $1,000 travel funds for conference presentation = $5,000/ medical student).**
- Students will apply to FNR Scholars Program, and PM&R faculty will evaluate applications, awarding most meritorious.
- Up to two awards will be made for summer 2017

Timeline

- December 2016: Orientation to FNR project
- Late December 2016: Post notice of FNR project at UAB Scholarly Activity office: distribute on-line and e-mail to all 1st year medical students
- List potential mentors and areas of research in mailing
- Prospective applicants contact mentors to develop project
- March 6 2017: Deadline to submit application to the office of the UAB Medical Summer Research program
- Applications to be then forwarded to Dr Mark for redistribution to PM&R faculty for reviewing applications, removed of students' names
- Faculty vote on submissions by blinded ballot
- March 20 2017: Announcement of summertime scholars

Timeline

- Summer 2017: awardee conducts ~8-10 weeks of research under mentorship
- October 2017: awardee presents a poster or oral presentation at the annual Med Student Research Day
- Late 2017-2018: Encourage research submission to national conference and/ or publication
- All medical students are required to conduct formal Scholarly Activity starting summer of 2nd year
- The FNR project can create a feeder source for students to meet needs of the Scholarly Activity, and thus extend the scope or duration of their research

RREMS option

- Rehabilitation Research Experience for Medical Students
- National program, similar mechanism to UAB PM&R
- UAB PM&R Dept participates annually
- 8-week summertime research
- $4000 stipend
- Deadline for submissions February 1, 2017
- Present findings at annual meeting Feb 2018
- http://www.physiatry.org/?page=RREMS_students

Potential kinds of research projects

- Join on-going research by mentor
- Student-initiated research (must be approved by mentor)
- Database or chart review
- Clinical study proposed by clinical faculty member, with secondary mentorship by research faculty member, OR
- Research study proposed by research faculty member, with secondary mentorship by clinical faculty member
- The following do not qualify: literature review, case report

Additional aspects

- PhD faculty may serve as mentors
- Mentorship counts toward faculty member's annual productivity report
- Students must perform all critical aspects of research analysis and interpretation, and not delegate to staff research assistants or students

Additional aspects

- Statistical analysis should be under the supervision of a statistician or research-experienced mentor
- Mentor needs to keep the Research Committee informed of progress, complications, revisions to research topic

Research Support Services Office

- Sherricka Embery, Administrative Associate
- 5th floor, room R529 Spain Rehab Center; 934-3283

  sembery@uab.edu
- Literature searches
- PowerPoint tutorial
- Research conference identification
- Budget development
- Grant sources

Current faculty research topics for Scholarly Projects

Yuying Chen, MD, PhD
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- Secondary data analysis
  - National SCI Database
- Wheelchair cushion monitor
- Weight matters after SCI
  - *EatRight SCI* weight management program
  - Underweight issue
  - Low cost solutions for weight estimation
- Cardiovascular risk profile in women with SCI

Candace Floyd, PhD

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Pre-Clinical Research Opportunities in TBI and SCI

- **CNS Protection**
  - Catalytic oxioreductants as protective agents in TBI or SCI animal models
  - Role of innate immunity in SCI
  - Combinations of clinically-approved drugs for use as protective agents in TBI
- **Mechanisms of neuropathic pain after SCI**
  - Evaluation of clinically-approved drugs to inhibit/ decrease neuropathic pain in rat SCI model
  - Interaction of stress and injury on mechanisms of neuropathic pain after SCI in rat model
- **Bioengineering approaches to nerve regeneration**
  - Carbon nanotubes to promote recovery
  - Nanospun matrixes to promote axonal growth
- **Effect of antidepressants on recovery after SCI in a rat model**

- **Bring your unanswered question from the clinic about TBI or SCI, and we will design your project!**

Keneshia Kirksey, M.D.
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- Falls in Adults with Lumbar Stenosis
- Effectiveness of Gabapentin vs Amitryptiline in Chronic Radiculopathy

Amy Knight, PhD
ajk@uab.edu

- Neurobiological stress response in acute medical trauma: behavioral and imaging relationships

Neurobiological Stress Response in Acute Medical Trauma

Knight, A.J., Harnett, N.G., Wood, K.H., Wheelock, M.D., Bishop, J.A, Ference, E., Setliff, M.R., Melton, S., Novack, T., Pitts, A.C., Knight, D.C.
University of Alabama at Birmingham

BACKGROUND

The present study investigated the human neurobiological response to stress in humans who have had recent in vivo exposure to an acute medical trauma (<30 days post event).

Little is known about the neural activity during the acute phase of a stress reaction following trauma. In this study, neuroimaging methods were used to determine the neural correlates of the stress response to acute medical trauma.

METHODS

Subjects: Trauma-exposed individuals (n = 8, 2 female) participated in a stress-inducing Pavlovian conditioning study. These individuals were recruited from UAB Hospital Trauma and Burn Intensive Care Unit within 30 days of trauma event, independent of a stress disorder diagnosis.

Procedure: Participants completed a stress-inducing conditioning paradigm during functional magnetic resonance imaging (fMRI) designed by Dr. David Knight that has been previously validated in healthy controls. This paradigm evaluated the effects of stressor predictability. The influence of stressor predictability was assessed by presenting loud (105dB) white noise stressors under predictable and unpredictable conditions.

BEHAVIORAL DATA

Posttraumatic Stress Diagnostic Scale (PDS): The PDS is a 17 item self-report instrument designed to aid in the diagnosis of PTSD using DSM-IV diagnostic criteria for PTSD.

The Psychosocial Risk Factor Survey (PRFS): The PRSF is a 70 item self-report assessment tool to measure primary psychosocial risk factors. 5 scales measure degree of: Depression, Anxiety, Anger/Hostility, Social Isolation and Emotional Guardedness.

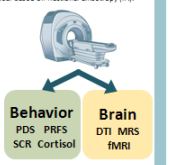
BRAIN DATA

Diffusion Tensor Imaging

- Whole brain DTI acquired in 60 directions (TR=4600ms, TE=79ms, b-value=1000, FOV=24cm, slice thickness=2.3mm. DTI data were preprocessed and analyzed using ExploreDTI.
- White matter integrity was determined for each individual based on fractional anisotropy (FA).

Magnetic Resonance Spectroscopy

- MRS data processed using jMRUI (v5.0)
- Residual water peak was removed using HLSVD filter.
- Spectra were quantified in the time domain by the AMARES algorithm.
- The model consisted of peaks for NAA, choline (Cho), creatine (Cr), 3 peaks for glutamate + glutamine (Glx)
- NAA, Cho, and Glx were quantified with respect to H_2O and ratio of gray and white matter within voxel.
- CRLB ratios greater than 30% were excluded from the group level analyses.



Functional MRI Data

- 3T Siemens Allegra Scanner.
- **fMRI EPI:** (TR=2000ms, TE=30ms, FOV=24cm, matrix=64x64, slice thickness=4mm, no gap)
- **MPRAGE:** (T1, TR=2300ms, TE=3.9ms, FOV=25.6cm, 256x256, slice thickness=1mm, 0.5mm gap).
- Standard preprocessing using AFNI.
- Skin conductance response (SCR), startle response and UCS expectancy also monitored.

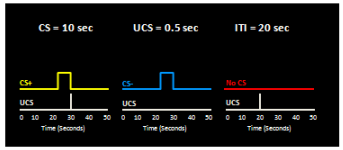
RESULTS

Neuroimaging analysis is still in progress for publication, but preliminary findings revealed structural, functional, and biochemical differences that varied with PTSD symptoms following an acute medical trauma.

Pavlovian Conditioning Task

Conditioning Task

- fMRI paradigm measured reactivity to a loud (105dB) white noise in predictable and unpredictable conditions
- Participants rate d their expectancy the noise (0-100)
- Skin conductance response & startle electromyography - validate imaging data.
- Cortisol levels collected before & after imaging session



Spectroscopy

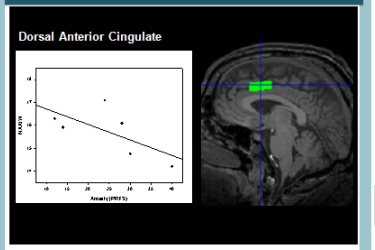


Figure 1. NAA peak was quantified with respect to H_2O and ratio of gray and white matter within the MRS voxel. A relationship between NAA level in the dorsal anterior cingulate and trait anxiety measured on the PRFS was noted.

BOLD Response

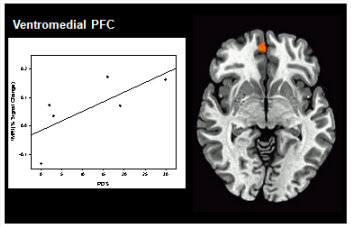


Figure 2. Participants completing a Pavlovian conditioning study showed a blood oxygen level dependent (BOLD) relationship to scores on the Posttraumatic Diagnostic Scale (PDS). Participants with higher scores on the PDS showed greater BOLD signal activation in the ventromedial prefrontal cortex (vmPFC)

Fractional Anisotropy

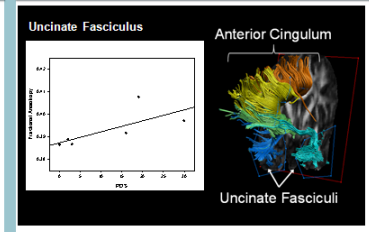


Figure 3. White matter integrity was determined for each individual based on fractional anisotropy (FA) in the uncinate fasciculi. FA values of the uncinate fasciculus were obtained using deterministic tractography. FA values in this region showed a relationship to scores on the Posttraumatic Diagnostic Scale (PDS).

CONCLUSIONS

Brain & Behavior

Metabolic

Dorsal anterior cingulate (ACC) N-acetyl-aspartate (NAA) levels, an index of neuronal health, varied with symptoms of anxiety, such that as anxiety symptoms increased NAA levels decreased.

Structural

Fractional anisotropy, and index of neuronal connectivity, within the uncinate fasciculus, varied with scores on the PTSD Diagnostic Scale (PDS), such that as PTSD scores increased fractional anisotropy increased.

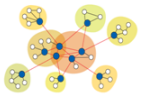
Functional

The fMRI signal response to threat within the dorsal ACC showed a negative relationship with social isolation symptoms of PTSD, such that as dorsal ACC activity increased, social isolation decreased.

FUTURE DIRECTIONS

- Utility of these mechanisms in predicting progression or resolution of acute stress symptoms at follow-up will be explored.
- Goals for this research are biomarkers to identify who is most likely to be resilient to the development of PTSD following trauma.
- Analyze skin conductance and cortisol behavioral data
- Assess the impact of other behavioral variables on brain measures.
- Investigate network connectivity related to the stress response

Viewing the brain as a network may help tackle the complexity and individual variability of the stress response.



ACKNOWLEDGEMENTS

This research is supported by

- UAB Faculty Development Grant Program
- UAB Functional Neurorecovery Pilot Grant

Acute stress reactivity following acute medical trauma

Ference, E., Harnett, N., Bishop, J.A, Setliff, M.R., Wood, K.H., Wheelock, M.D., Melton, S., Novack, T., Pitts, A.C., Knight, D.C. & Knight, A.J.

University of Alabama at Birmingham

BACKGROUND

This prospective study examined the relationship of the stress reaction to emotional, cognitive, and demographic variables following acute medical trauma (<30 days post event).

Little is known about the neural activity during the acute phase of a stress reaction following trauma. The central hypothesis of this research is that trauma exposure will be associated with elevated self-reported psychological symptoms and decreased performance on attention, and will potentially be modulated by demographic factors.

METHODS

Procedure: Over a 9 week period, the trauma intake history of present illness (HPI) for every new patient in the Acute Trauma and Burn Unit at UAB Hospital was screened for study eligibility, including demographic information and prior comorbidity. A secondary in-person screen was conducted on the unit. Consenting participants completed self reported surveys of psycosocial risk factors and posttraumatic stress, as well as a sustained attention task. Correlational analysis was conducted on variables of interest, including demographic factors of gender, race, education, and estimated IQ.

Subjects: Trauma-exposed individuals (n = 24) were recruited from UAB Hospital Trauma and Burn Intensive Care Unit within 30 days of trauma event, independent of a stress disorder diagnosis. Exclusion criteria for the study included prior head injury, substance abuse, and significant psychiatric illness.

Required Tasks

Posttraumatic Stress Diagnostic Scale (PDS): The PDS is a 17 item self-report instrument designed to aid in the diagnosis of PTSD using DSM-IV diagnostic criteria for PTSD.

The Psychosocial Risk Factor Survey (PRFS): The PRSF is a 70 item self-report assessment tool to measure primary psychosocial risk factors. 5 scales measure degree of Depression, Anxiety, Anger/Hostility, Social Isolation and Emotional Guardedness.

Continuous Performance Test II (CPT): The CPT is a 15 minute test of sustained and selective attention. Participants are told to click the mouse when any letter but "X" flashes on the screen. The participant must refrain from clicking if they see the letter "X".

The Wechsler Test of Adult Reading (WTAR): The WTAR is a 50 word reading test that is used to estimate premorbid intelligence.

RESULTS

Neuroimaging analysis is still in progress for publication, but preliminary findings revealed psychosocial differences that varied with PTSD symptoms following an acute medical trauma.

PTSD-Psychosocial Correlates

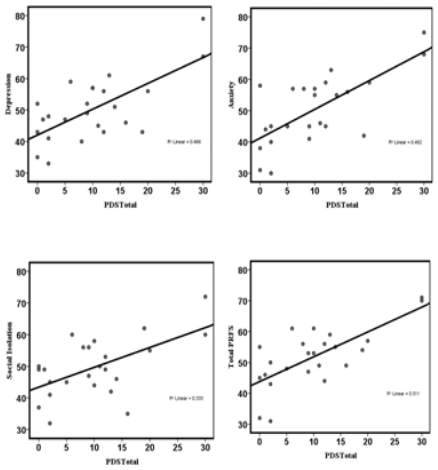


Figure 1. Endorsement of PTSD symptoms was correlated with depression, anxiety, and social isolation. The Total PRFS score, which is the summation of the individual depression, anxiety, anger/hostility, social isolation, and emotional guardedness scores, was even more tightly correlated.

Symptom Severity and Attention

Mood and PTSD scores were not consistently correlated with attention measures of omission, commission, hit reaction time, or reaction time between interstimulus intervals.

Differences in Reporting by Ethnicity

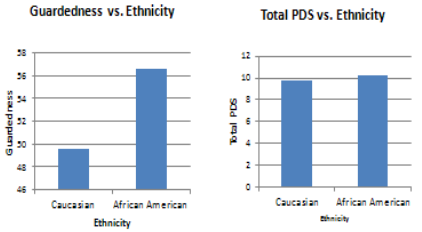


Figure 2. African Americans had higher emotional guardedness scores (an individual's willingness to divulge personal information) than Caucasians (p=.044), highlighting cultural differences or potentially suggesting bias in oral survey administration. Guardedness was not found to influence a willingness to disclose PTSD symptoms, while it lowered the severity of other mood symptoms endorsed.

Social Isolation and Estimated IQ

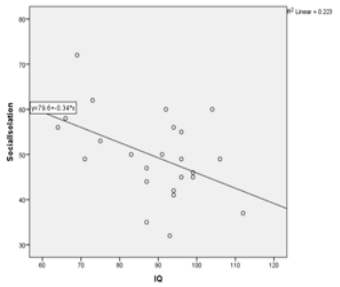


Figure 3. PRFS Social isolation scores had a negative correlation with estimated IQ derived from WTAR scores. This is an area for future investigation.

CONCLUSIONS

Responses to Medical Trauma

PTSD Symptom Score and Emotional Reactivity

Strong correlations exist between feelings of depression, anxiety, and social isolation and the severity of PTSD symptoms endorsed.

Ethnicity and Guardedness

Although a significant difference was evident between ethnic groups in terms of emotional guardedness scores, no statistical difference was shown for self-reported PTSD symptom reporting

Social Isolation and IQ

Self-reported symptoms of social isolation showed a negative relationship with estimated IQ scores, such that as estimated IQ increased, social isolation decreased.

Mood/Symptom Scores and Attention

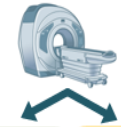
No significant differences were found between mood/symptom scores and measures of attention.

FUTURE DIRECTIONS

- The overarching goal of this research is to identify biomarkers to determine who is most likely to be resilient to the development of PTSD following trauma.

Magnetic Resonance Spectroscopy

- This work is part of larger imaging study that relates behavior responses to acute trauma to neural activity. Participants completed a stress-inducing conditioning paradigm during functional magnetic resonance imaging (fMRI) designed by Dr. David Knight that has been previously validated in healthy controls/



Behavior
PDS PRFS
SCR Cortisol

Brain
DTI MRS
fMRI

ACKNOWLEDGEMENTS

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- UAB Medical Student Summer Research Program
- UAB Functional Neuro-Recovery Award Program
- UAB Faculty Development Grant Program

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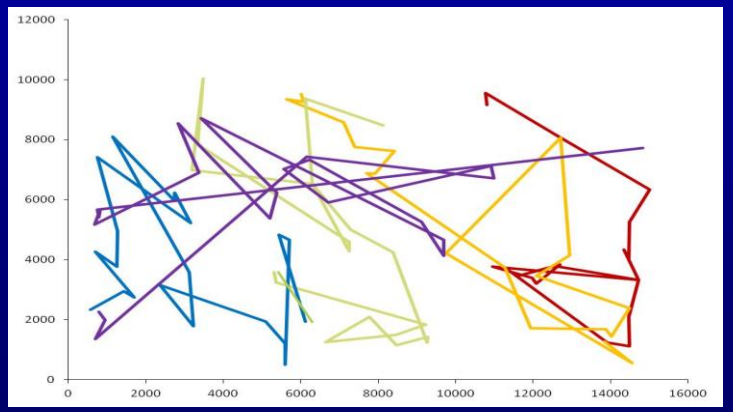
Topics

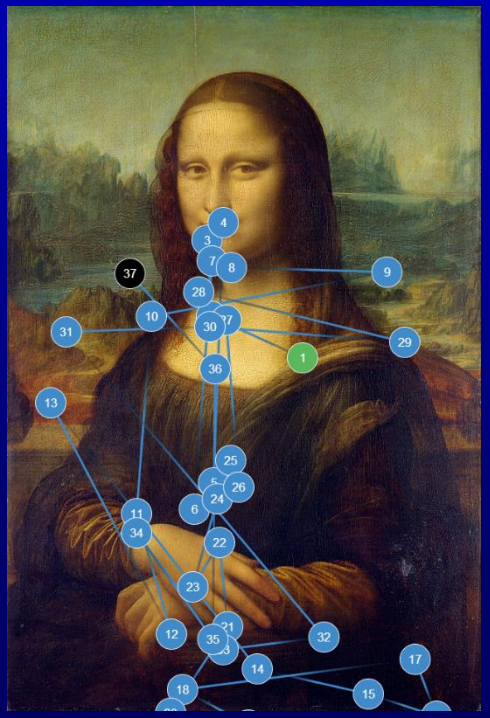
1) Visuomotor attention in severe aphasia compared to other kinds of patients using computerized kinematics measurement: is there a difference? Relation to rehab?



Victor Mark, M.D.

Topics

2) In-hospital eye tracking on spatial problem-solving exercises in rehabilitation patients—related to rehabilitation outcomes?



Victor Mark, MD

- 3) Evaluate arm apraxia in acute stroke rehabilitation patients and relationship to functional recovery

Amie McLain, M.D.
mclaina@uab.edu

- Women with SCI
  - Reproduction and Gynecological Issues

Danielle Powell, MD
daniellepowell@uabmc.edu

- Obesity in spinal cord injury
- Other topics in spinal cord injury
- Obesity and weight management in adults with spina bifida
- Issues with transitioning young adults with spina bifida into the adult healthcare system

CEREN YARAR, PT PhD
cyarar@uab.edu

Research Interests

- Investigate the potential mechanisms behind skeletal muscle's influence on metabolic disease in individuals with spinal cord injury (SCI).
- Develop exercise/rehab and diet interventions to improve neuro-recovery, metabolic health and function in the acute and chronic stages of SCI.

Ongoing Projects in the Yarar-Fisher Laboratory

- **Ketogenic diet and neuro-recovery**
  - Aims:
    - Determine the effects of ketogenic diet on sensory and motor function, functional independence, and metabolism in patients with SCI.
    - Identify serum neurochemical biomarkers and how their concentrations relate to the neurological and functional outcomes following SCI using proteomics.
    - Survey potential intracellular molecular pathways that are responsible for promoting neuro-recovery in patients with SCI.

- **Neuromuscular electrical stimulation (NMES) and skeletal muscle metabolism**
  - Aims:
    - Determine the effects of NMES on skeletal muscle intracellular signaling for glucose utilization, atrophy/hypertrophy, and mitochondria function.
    - Identify muscle biomarkers and how their concentrations relate to the metabolic outcomes using proteomics.

Xiaohua Zhou, M.D.
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- Adherence to dysphagia restrictions after Stroke discharge: Some dysphagic patients show aspiration on formal swallowing evaluation, do not complain about recommended diet, never have aspiration pneumonia. What are best dysphagia recommendations for discharged patients?
- Microcyn® Technology for wound care

Xiaohua Zhou, M.D.

- Bladder training on stroke patients. Currently protocol is the same as for SCI patients. Apparently bladder issues are different with stroke patient from SCI.

Questions?

- Contact Dr Mark, FNR coordinator:

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  vwmark@uabmc.edu

- 934-3499