UC Congressional Briefing:
Navigating and Comprehending the Human Brain

January 29, 2015
Dr. Cameron Carter
Director, Center for Neuroscience and the Imaging Research Center
UC Davis
Serious Mental Illness in youth: Schizophrenia and Bipolar Disorder

- 2-4% of the population
- Onset during adolescence to young adulthood
- Psychosis frequently leads to hospitalization
- School failure, unemployment, substance abuse, incarceration
- Suicide and aggression
Shortened productive lives

Source: Mental Health Report of the Surgeon General
Impacting Serious Mental Illness in Youth to Improve Outcomes

• Early Identification and intervention (EDAPT programs, EDIPPP, Ginger-IO)
• Clinical Neuroscience to identify disrupted brain circuitry to guide interventions (cognitive training, brain stimulation)
• Basic and Translational Research to reveal underlying causes, identify novel treatment targets and develop diagnostic biomarkers
Early Diagnosis and Preventive Treatment at UC Davis

EDAPT & SacEDAPT

http://earlypsychosis.ucdavis.edu
Early Detection and Intervention for the Prevention of Psychosis

- Effectiveness Trial at six sites:
  - Portland, Maine / Maine Medical Center (McFarlaine)
  - Glen Oaks, New York / Albert Einstein College of Medicine (Cornblatt)
  - Ann Arbor, Michigan / University of Michigan (Taylor)
  - Salem, Oregon / Oregon Health Sciences University (Sales)
  - Sacramento, California / University of California at Davis (Carter)
  - Albuquerque, New Mexico / University of New Mexico (Adelshein)

- Large and diverse nationally representative sample
- Community-wide outreach and identification systems
- Sponsored by RWJF
Using Smartphone Apps in Early Psychosis Care

Investigators: Tara Niendam, Ph.D (PI) & Laura Tully, Ph.D
Funding: Robert Wood Johnson Foundation

STUDY DESCRIPTION:
- Test smartphone app “Ginger.io” as add on tool in early psychosis care
- App gathers “passive” communication data and “active” self report surveys via patients’ smartphones
- Patients complete monthly gold-standard clinical assessments with research staff (BPRS, GFS/GFR)
- Clinicians view app data through secure web portal and incorporate into treatment

STUDY AIMS
- Test validity of assessing symptoms/functioning via app
- Improve relapse prediction & prevention
- Examine impact of app on treatment outcomes & costs
Reducing Duration of Untreated Psychosis Through Rapid Identification and Engagement

1RO1 MH104235-01 NIMH
Clinical Neuroscience Research Reveals Disrupted Brain Circuitry in Schizophrenia

NIMH 2R01MH059883-11
Brain Training to Enhance Cognition in Schizophrenia
Change in cognitive performance in subjects with recent onset schizophrenia after computerized auditory training (AT) or computer games (CG).

Fisher M et al. Schizophr Bull 2014;schbul.sbt232

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Decoding and Enhancing Neural Mechanisms for Episodic Memory

Objectives

- To determine how neural oscillations in the theta band (4-8Hz) contribute to memory retrieval
- **Manipulate** theta activity using 3 different empirically motivated methods
  - Audiovisual entrainment
  - Transcranial Alternating Current Stimulation (tACS)
  - Reward Motivation
- **Measure** effects on memory and corresponding changes in cortico-hippocampal activity using EEG and FMRI
Neuroimmune mechanisms underlying impaired functional circuitry in schizophrenia?

- MHC and cytokines play a critical role in normal brain development and adult synaptic function and I/E balance.
- Maternal infections during gestation increase risk for schizophrenia.
- Schizophrenia patients show evidence of altered immune molecules in plasma and CSF as well as in post mortem tissue.
- Studies using PET targeting TSPO suggest the presence of microglial activation in patients with schizophrenia.
- Genetic studies have revealed a surprisingly robust association between MHC and related genes and schizophrenia.
- Animal model systems involving maternal immune activation and other intrauterine perturbations produce behavioral and neuroanatomical phenotypes suggesting construct validity as a schizophrenia related model system.
- Several small clinical trials suggest clinical benefits from anti-inflammatory agents in schizophrenia.
Novel Approach of Conte Center: Test neuroimmune mechanism hypothesis across scales

- Human
- Non-Human Primate
- Mouse

Carter Lab
Amaral/Bauman Labs
McAllister Lab

Neuroimmune Mechanisms of Psychiatric Disorders
1P50MH106438-01
Improved Outcomes for Psychotic Disorders of Youth

- Multi-pronged approach
- Prevention and Early Intervention: Evidence Based Therapies timed for greatest impact
- Novel technology based tools to enhance early identification and engagement in treatment
- Clinical neuroscience investigations to understand altered brain circuitry and target for novel interventions
- Basic and translational research that integrates across scales to reveal disease mechanisms and develop the treatments and diagnostic tools of the future.
Traumatic Brain Injury

The Most Complex Injury to the Most Complex Organ

Christopher C. Giza, M.D.
Professor, Pediatric Neurology and Neurosurgery
Director, UCLA Steve Tisch BrainSPORT Program

January 29th, 2015
Washington, DC
A head injury occurs every 15 seconds.

TBI is the #1 cause of death and disability <45 years of age. Over 40% were <15 years old.

It is estimated that the number of all military personnel who have suffered TBI is near 300-350,000.

Annual economic cost of TBI in the U.S. > $406 billion

Distinct injury types include child abuse, sports-related injuries and blast (combat) injury.
Brain metabolism is severely disrupted after TBI, even after mild TBI/concussion.

“Invisible” Early Post-Traumatic Seizures occur in 11% of adults and 17% of children

Vespa PM, et al., J. Neurosurg 1999
Arndt D, Lerner JT, et al., Epilepsia 2013

UCLA BIRC Research has fundamentally changed Neurocritical Care for both adults & kids

Early Post-Traumatic Seizures occur with increased brain swelling and metabolic crisis

Vespa PM, et al., Crit Care Med 2007
Vespa PM, et al., Neurology 2010
Stimulation of selected brain regions can improve memory function in humans

Suthana N, et al., NEJM 2013
Concussive Brain Injury Enhances Fear Learning and Excitatory Processes in the Amygdala

Maxine L. Reger, Andrew M. Poulos, Floyd Buen, Christopher C. Giza, David A. Hovda, and Michael S. Fanselow

TBI primes the brain for enhanced fear-based responses that are hard to get rid of. This provides an experimental model for testing TBI-PTSD.

Reger ML, et al., Biol Psych 2012
The FACTS - Sports

Numbers of Athletes

- NFL: ~1,800
- College Football: ~54,250
- High School Football: ~1,139,000
- Youth Football: >10,000,000
  - Soccer: >10,000,000
  - Ice Hockey: >500,000

1.6-3.8 million Sports-related TBIs occur annually in the U.S.
Concussion legislation

http://www.edweek.org/ew/section/infographics/37concussion_map.html
Public Concern:

Dementia Risk Seen in Players In NFL Study

LEAGUE OF DENIAL: THE NFL’S CONCUSSION CRISIS
October 8, 2013

FRENCHLINE reveals the hidden story of the NFL and brain injuries.
UCLA Steve Tisch BrainSPORT Program
Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability

Mayumi L. Prins, Daya Alexander, Christopher C. Giza, and David A. Hovda

2nd concussion before full recovery results in worse brain metabolism and worse memory.

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Glucose metabolism

Single TBI
2nd TBI BEFORE recovery from 1st TBI
2nd TBI AFTER recovery from 1st TBI

Metabolism Memory
Metabolism Memory
Metabolism Memory

Prins ML, et al., J Neurotrauma 2013
NR2A protein (IQ gene) is reduced after developmental TBI & so is brain activity.

Giza, Santa Maria & Hovda, J. Neurotrauma 2006

N-methyl-D-aspartate (NMDA) Receptor = IQ Gene

Human Control TBI

Rat Control TBI
From 2012-2014, we have:

- Evaluated over **528 athletes/patients** with over **949 clinic encounters**
- Established formal networks with 2 division I NCAA teams, 3 major high schools and 3 professional sports organizations (NFL, MLS, NHL)
- Developed ongoing collaboration with Operation MEND / military mild TBI

<table>
<thead>
<tr>
<th>Category</th>
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<td>Pre-high school</td>
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<tr>
<td>Military</td>
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<tr>
<td>Other</td>
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Return on Investment for UCLA Neurotrauma since 2010

- UCLA Brain Injury Research Center: $11,000,000
- UCLA Pediatric BIRC: $1,790,000
- UCLA Steve Tisch BrainSPORT: $10,180,000
- Operation MEND-WWP-UCLA BIRC: $15,300,000

- UCLA Restoring Active Memory: $14,600,000
- UCLA Spinal Neurotrauma: $5,900,000
What about the future?

- NCAA-DoD Grand Alliance
- Youth Sports Concussion Consortium
- PNCRG
- UCLA Steve Tisch BrainSPORT
- National Sport Concussion Outcomes Study (NSCOS)
- CDC
- UCLA Health System
- Operation MEND
- Wounded Warrior Project
- Child Neurology Foundation
- U.S. Soccer
- Los Angeles Unified School District
Credit where credit deserved!

**Funded by:** NS27544, HD061504, NCAA, Dept of Defense, Joseph Drown Foundation, UCLA BIRC, UCLA Steve Tisch BrainSPORT

**Consultant:** Alcobra, NHLPA, Pearson TLC

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- Grace Griesbach, Ph.D.
- Neil Harris, Ph.D.
- Mayumi Prins, Ph.D.
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- Rick Staba, Ph.D.

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- Lauren Fraund
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Dr. Bruce Miller
Director, Memory and Aging Center
UCSF
Memory and Aging Center

• Formed in 1998, housed in Department of Neurology
• 180 employees: 27 faculty (neurology, geriatrics, psychiatry, pathology, neuropsychology, nurses), social work, technology, research assistants
• Evaluate/treat 10,000 patients/year
• 70 research protocols
• 200 medical students, residents, fellows, nurses, pharmacists, students rotate through our clinics

Top Neurology Program in NIH Funding for Last 5 Years
(in $M)

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<th>Year</th>
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<th>2011</th>
<th>2012</th>
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Dementia Prevalence

- 5 million Americans live with Alzheimer’s disease (AD)
- 6th leading cause of death in US
- 1 in 3 seniors dies with AD or another dementia
- 2014 450,000 people in the US will die with AD
- Someone develops AD every 68 sec
- California has the most AD in US (500,000)
- In 20 years, the cost AD in California will double: $50 to $100 billion
- In California more than 1 million unpaid caregivers serve loved ones with dementia

Source: Alzheimer’s Association, 2009 Alzheimer’s Disease Facts and Figures (March 2009).
Dementia: $109 billion
Heart Disease: $102 billion
Cancer: $77 billion
direct health care expense
All degenerative dementias have:

- Genetic and sporadic form
- Cellular and animal model
- Preclinical, early symptomatic, and symptomatic phase
- Abnormal protein aggregation/circuit specific
- Proteins spread from cell to cell
Amyloid Imaging in Live Patients

- Alzheimer’s Disease
- Frontotemporal Dementia
- Control

DVR
0 2.5
68-year-old Retired NFL Player with Progressive Neurologic Decline
Adult Stem Cell Model of A152T Tau Mutation

A152A (mutation corrected)

A152T (average disease)

A152T/A152T (aggressive disease)
The UCSF and UNMC Dementia Care Ecosystem: Using Innovative Technologies to Personalize and Deliver Coordinated Dementia Care

- 3-year pragmatic clinical trial evaluating the benefits of a program that supports patients with dementia and their family caregivers
- Based on our experience caring for thousands of families
- Continuous contact with the entire family/care team surrounding each patient through Care Team Navigators
- Aims:
  1. improve costs of dementia care by delaying admission to long-term care, lower ER visits, preventing hospital costs, reducing ambulance costs, and cutting costs on prescriptions
  2. reduce family caregiver burden, improve satisfaction with care, increase proactive decision-making, protect patient and family finances and safety, improve medication management, and respond efficiently and effectively to issues facing patients and caregivers
- Supported by CMS-1C1-14-001 from the US Department of Health and Human Services, Centers for Medicare & Medicaid Services
Privately-Funded Consortia

**Tau Consortium**
- Commissions world-class research and drug discovery to treat and prevent progressive supranuclear palsy and other tauopathies
- Scientists work collaboratively to accelerate progress
- Goal: find 10 leading targets within 2 years and find 3 target compounds that will be ready for human trials within 4 years

**Consortium for Frontotemporal Dementia Research**
- UCSF-based consortium to accelerate research through collaborative science by the best minds in the field
- Goal: find a cure for FTD related to progranulin mutations within 10 years
University of California
Office of Federal Governmental Relations
www.ucop.edu/federal-governmental-relations

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