QATAR CLINICAL NEUROSCIENCE CONFERENCE

15th - 17th March 2014, The Four Seasons Hotel, Doha

www.nyas.org/qatarneuro2014
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On behalf of the Qatar Foundation for Education, Science, and Community Development; Weill Cornell Medical College in Qatar (WCMC-Q); and the New York Academy of Sciences, we are very pleased to welcome you to the Qatar Clinical Neuroscience Conference.

Injuries and disorders of the brain represent a significant global disease burden with high economic impact. This 2.5-day international, two-track conference will highlight new advances in clinical neuroscience for:

1) Depression, bipolar disorder, and other affective disorders; and
2) Cerebrovascular disease, stroke, and traumatic brain injury.

Each conference track will explore the latest in translational research, advanced brain imaging, novel diagnostics, investigative therapies, and cutting-edge findings from clinical trials.

Javaid I. Sheikh, MD
Dean and Professor of Psychiatry
Weill Cornell Medical College in Qatar

Matthew E. Fink, MD
Neurologist-in-Chief
New York Presbyterian Hospital/Weill Cornell

Ellis Rubinstein
President and Chief Executive Officer
The New York Academy of Sciences
This conference is designed to be a neutral forum for international, visionary neuroscientists, translational researchers, and practicing clinicians to stimulate discourse, collaboration, and research on the pathophysiology of stroke, traumatic brain injury, and mood disorders in order to improve the clinical care of patients suffering from these debilitating diseases.

Topics of discussion will cover: Translation of Animal Model Research, Advances in Neuropsychiatry, Clinical Approaches to Affective Disorders, and Pathophysiology and Therapeutic Insights regarding Stroke and Traumatic Brain Injuries. A keynote address by Huda Akil, PhD, University of Michigan, will provide an overview of affective disorders and highlight exciting new advances in neurobiology. Additionally, Karl Deisseroth, MD, PhD, of Stanford University, will present his latest research, which utilizes the most recent advances in high-resolution tools to elucidate the pathological dynamics underlying neuropsychiatric disease.

We anticipate that the open format of the meeting, including the poster session and networking reception will foster dialogue among all conference participants.

To disseminate the scientific information exchanged at this conference, a comprehensive, open-access multimedia report with a selection of presenter’s slides and audio — known as an Academy eBriefing — will be made available on the Academy’s website in the weeks following the event.

If you were not already a member of the New York Academy of Sciences at the time of registration for this conference, your registration includes a complimentary, 1-year membership to the Academy, enabling you to attend future Academy events for free or at reduced registration rates and providing you with free access to our every growing online library of unique scientific publications including Academy eBriefings and Annals of the New York Academy of Sciences.

We encourage you to become active members of our community and to build networks and exchange ideas with leaders like yourself. For more information about the Academy’s diverse live and online programming and your Academy membership, please visit www.nyas.org or email customerservice@nyas.org.

We ask you to take a moment to give us your feedback and help us further improve our scientific programming by completing the online survey for this event, which will be distributed via email following the conclusion of the conference.

We hope that this conference meets your expectations. Please do not hesitate to notify WCMC-Q or Academy staff with any questions or concerns.
Chair Persons

Matthew E. Fink, MD  
Weill Cornell Medical College

Javaid I. Sheikh, MD  
Weill Cornell Medical College in Qatar

Melanie Brickman Stynes, PhD, MSc  
The New York Academy of Sciences
Program Committee

Brooke Grindlinger, PhD
The New York Academy of Sciences

Jack D. Barchas, MD
Weill Cornell Medical College

Alan F. Schatzberg, MD
Stanford University
STAY CONNECTED

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FACULTY DISCLOSURES

All faculty participating in this activity are required to disclose to the audience any significant financial interest and/or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in his/her presentation and/or the commercial contributor(s) of this activity.

Huda Akil, PhD
None

Neeraj Badjatia, MD, MSc
Research Support
• Bard Medical
• Cumberland Pharmaceuticals
Consultant
• Bard Medical

Jack D. Barchas, MD
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• Elan
• Lilly
• Neurocrine

BJ Casey, PhD
None
Randall Chesnut, MD, FCCM, FACS
Not available at time of printing

David Chiu, MD
None

Nicholas Craddock, PhD, FRCPsych, FMedSci
None

Karl Deisseroth, MD, PhD
None

Matthew E. Fink, MD
None

Richard A. Friedman, MD
None

John F. Greden, MD*
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Ned H. Kalin, MD

Research Support
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Consultant
- Corcept Therapeutics

Share Holder
- Corcept Therapeutics

Barry E. Kosofsky, MD, PhD
None

Ziad Kronfol, MD
None

Francis Lee, MD, PhD
None

Andrew H. Miller, MD*
None

Ziad Nahas, MD, MSCR*

Research Support
- MECTA, Inc.
- Medtronic, Inc.
- Pfizer

Charles B. Nemeroff, MD, PhD

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Other Financial Support
- PharmaNeuroBoost
- CeNeRx BioPharma
- NovaDel Pharma
- Reevaq Pharma
- American Psychiatric Publishing
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<td>Kerry J. Ressler, MD, PhD</td>
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<td>Alan F. Schatzberg, MD*</td>
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<td>Lee Schwamm, MD</td>
<td>Research Support • Genentech</td>
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<td>Jon-Kar Zubieta, MD, PhD</td>
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<td>Ashfaq Shuaib, MD, FRPC</td>
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We request that you do not take photographs or make audio or video recordings of the conference presentations, or present unpublished data on any open-access websites, unless specific permission is obtained from the speaker.

TRACK 1  AFFECTIVE DISORDERS

DAY 1  SATURDAY, MARCH 15, 2014

2:00pm  Registration and Check-in Begins

5:00pm  Welcome and Introductory Remarks
         (Combined with Track 2)
         Javaid Sheikh, MD
         Weill Cornell Medical College in Qatar
         Alan F. Schatzberg, MD,
         Stanford University
         Jack D. Barchas, MD
         Weill Cornell Medical College
         Matthew E. Fink, MD
         Weill Cornell Medical College
         Ellis Rubinstein
         The New York Academy of Sciences
         Brooke Grindlinger, PhD
         The New York Academy of Sciences

5:45pm  Keynote Address
         Huda Akil, PhD
         University of Michigan

6:30pm  Reception
DAY 2  SUNDAY, MARCH 16, 2014

SESSION 1  FROM ANIMAL MODELS TO HUMANS
SESSION CHAIR  JACK D. BARCHAS, MD
WEILL CORNELL MEDICAL COLLEGE

8:30am  Genetic Mouse Models of Anxiety Disorders
Francis Lee, MD, PhD
Weill Cornell Medical College

9:05am  Risk for Anxiety and Implications for Treatment:
Developmental, Environmental, and Genetic Factors
BJ Casey, PhD
Weill Cornell Medical College

9:40am  Morning Break

10:00am  Altered Neural Circuitry Underlying the
Risk to Develop Anxiety and Depression:
Nonhuman Primate Translational Studies
Ned H. Kalin, MD
University of Wisconsin School of Medicine and Public Health

10:35am  Treatment Responses in Major Depression:
Biological Mechanisms of Placebo Effects
Jon-Kar Zubieta, MD
University of Michigan

11:10am  Moderated Discussion

11:30am  Networking Luncheon and Poster Session
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<tr>
<th>Time</th>
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<tr>
<td>1:00pm</td>
<td>Heartache and Heartbreak: Depression and Cardiovascular Disease</td>
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<td>Charles B. Nemeroff, MD, PhD</td>
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<td>University of Miami, Leonard M. Miller School of Medicine</td>
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<td>1:35pm</td>
<td>Epigenetics and Risk from Depression and PTSD</td>
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<td>Kerry J. Ressler, MD, PhD</td>
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<td>Emory University; Howard Hughes Medical Institute</td>
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<td>2:10pm</td>
<td>Afternoon Break</td>
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<td>2:30pm</td>
<td>Genetics of Bipolar Disorder</td>
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<td>Nicholas Craddock, PhD, FRCPsych, FMedSci</td>
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<td>Cardiff University</td>
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<td>3:05pm</td>
<td>Ketamine and Other Glutamatergic Treatments in Mood Disorders: Clinical</td>
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<td>and Neurobiological Correlations</td>
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<td>Dan V. Iosifescu, MD, MSc</td>
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<td>Icahn School of Medicine at Mount Sinai</td>
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<td>3:40pm</td>
<td>Moderated Discussion</td>
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<td>4:00pm</td>
<td>End of Day 2</td>
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## DAY 3  MONDAY, MARCH 17, 2014

### SESSION 3  ADVANCES IN NEUROPSYCHIATRY (COMBINED WITH TRACK 2)

**SESSION CHAIR**  JAVAID SHEIKH, MD, WEILL CORNELL MEDICAL COLLEGE IN QATAR

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<th>Affiliation(s)</th>
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<tr>
<td>8:30am</td>
<td>Keynote Address</td>
<td>Karl Deisseroth, MD, PhD&lt;br&gt;Karl Deisseroth, MD, PhD&lt;br&gt;Stanford University</td>
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<td>9:15am</td>
<td>Cytokines Sing the Blues: Mechanisms, Mediators, and Translational Implications</td>
<td>Andrew Miller, MD&lt;br&gt;Andrew Miller, MD&lt;br&gt;Emory University School of Medicine</td>
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<td>9:50am</td>
<td>Morning Break</td>
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<td>10:10am</td>
<td>Pathobiology of Vascular Dementia</td>
<td>Constantino Iadecola, MD&lt;br.Constantino Iadecola, MD&lt;br&gt;Weill Cornell Medical College</td>
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<td>10:45am</td>
<td>Improving Mitochondrial Bioenergetics to Treat Nervous System Dysfunction Early in the Course of Diabetes</td>
<td>Glen T. Prusky, PhD&lt;br&gt;Glen T. Prusky, PhD&lt;br&gt;Weill Cornell Medical College; Burke Medical Research Institute</td>
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<td>11:20am</td>
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<td>11:40am</td>
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SESSION 4  CLINICAL APPROACHES TO AFFECTIVE DISORDERS

SESSION CHAIR
RICHARD A. FRIEDMAN, MD,
WEILL CORNELL MEDICAL COLLEGE

1:00pm  Bipolar Disorders in the Arab World: Clinical and Genomic Data
Ziad Kronfol, MD
Weill Cornell Medical College in Qatar

1:35pm  Biomarker Development to Help, Prevent Treatment-Resistant Depression
John F. Greden, MD
University of Michigan

2:10pm  Afternoon Break

2:30pm  New Anti-Depressants
Alan F. Schatzberg, MD
Stanford University

3:05pm  Medial and Lateral Prefrontal Stimulation for Treatment-Resistant Depression
Ziad Nahas, MD, MSCR
American University of Beirut

3:40pm  Moderated Discussion

4:00pm  Closing Remarks
Conference Adjourns
TRACK 2  STROKE AND TRAUMATIC BRAIN INJURY

DAY 1  SATURDAY, MARCH 15, 2014

2:00pm  Registration and Check-in Begins

5:00pm  Welcome and Introductory Remarks
(Combined with Track 1)
Javaid Sheikh, MD
Weill Cornell Medical College in Qatar

Alan F. Schatzberg, MD
Stanford University

Jack D. Barchas, MD
Weill Cornell Medical College

Matthew E. Fink, MD
Weill Cornell Medical College

Ellis Rubinstein
The New York Academy of Sciences

Brooke Grindlinger, PhD
The New York Academy of Sciences

5:45pm  Keynote Address
Huda Akil, PhD
University of Michigan

6:30pm  Reception
DAY 2  SUNDAY, MARCH 16, 2014

SESSION 1  STROKE: PATHOPHYSIOLOGY AND THERAPEUTIC INSIGHTS
SESSION CHAIR  MATTHEW E. FINK, MD, WEILL CORNELL MEDICAL COLLEGE

8:30am  Recent Trials in Stroke
David Chiu, MD
Houston Methodist Hospital Neurological Institute; Weil Cornell Medical College

9:05am  Teleneurology for Acute Stroke (remote lecture)
Lee H. Schwamm, MD
Harvard Medical School; Massachusetts General Hospital

9:40am  Morning Break

10:00am  Transient Ischemic Attacks: What’s New in Pathophysiology and Treatment?
Ashfaq Shuaib, MD, FRPC, FAHA
University of Alberta, Edmonton

10:35am  Pregnancy-Associated Stroke
Matthew E. Fink, MD
Weill Cornell Medical College

11:10am  Moderated Discussion

11:30am  Networking Luncheon and Poster Session
SESSION 2  TRAUMATIC BRAIN INJURY: PATHOPHYSIOLOGY AND THERAPEUTIC INSIGHTS

SESSION CHAIR  RANDALL CHESNUT, MD, FCCM, FACS, UNIVERSITY OF WASHINGTON; HARBORVIEW MEDICAL CENTER

1:00pm  Pathophysiologic Insights Regarding Pediatric Traumatic Brain Injury
Barry E. Kosofsky, MD
Weill Cornell Medical College

1:35pm  Hypothermia as a Neuroprotectant in Traumatic Brain Injury
Neeraj Badjatia, MD, MSc
University of Maryland School of Medicine

2:10pm  Afternoon Break

2:30pm  What is Wrong with Current Therapy for Traumatic Brain Injury?
Randall Chesnut, MD, FCCM, FACS
University of Washington; Harborview Medical Center

3:05pm  Hyperosmolar Therapy for Brain Edema
Roger Härtl, MD
Weill Cornell Medical College

3:40pm  Moderated Discussion

4:00pm  End of Day 2
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<td>Improving Mitochondrial Bioenergetics to Treat Nervous System Dysfunction&lt;br&gt;Early in the Course of Diabetes&lt;br&gt;Glen T. Prusky, PhD&lt;br&gt;Weill Cornell Medical College; Burke Medical Research Institute</td>
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<td>11:20am</td>
<td>Moderated Discussion</td>
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<td>11:40pm</td>
<td>Networking Lunch Break and Poster Session</td>
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SESSION 4  DYSFUNCTION, DAMAGE, AND CLINICAL CARE

SESSION CHAIR  BASIM M. UTHMAN, MD, WEILL CORNELL MEDICAL COLLEGE IN QATAR

1:00pm  Epidemiology and Consequences of Pediatric Traumatic Brain Injury
Jose Pineda Soto, MD, MSc
Washington University School of Medicine; St. Louis Children’s Hospital

1:35pm  The Pathway Toward Optimal Traumatic Brain Injury Treatment
Randall Chesnut, MD, FCCM, FACS
University of Washington; Harborview Medical Center

2:10pm  Afternoon Break

2:30pm  Cerebral Collaterals and Acute Stroke
Ashfaq Shuaib, MD, FRPC
University of Alberta, Edmonton

3:05pm  The Immunology of Stroke
Constantino Iadecola, MD
Weill Cornell Medical College

3:40pm  Moderated Discussion

4:00pm  Closing Remarks
Conference Adjourns
SPEAKER ABSTRACTS

Speaker Abstracts are divided by Track 1 and Track 2 and are listed in order of presentation.

Keynote Address

*Huda Akil, PhD
University of Michigan, Ann Arbor, Michigan, United States

*Abstract not available at the time of printing.
The only evidence-based behavioral treatment for anxiety and stress-related disorders relies on desensitization techniques based on principles of extinction learning, yet as many as 40% of patients do not respond to this treatment. Converging evidence from human and rodent studies suggests that insufficient top-down regulation of subcortical structures, such as the amygdala, coincides with impairments in diminished prototypical fear extinction learning. Because this top-down prefrontal regulation mediates by prefrontal cortical regions is necessary for mediating successful extinction learning and may determine the efficacy of exposure therapy, during re-exposure therapy often used as part of cognitive behavioral therapy (CBT), it is important to discern how immaturity in this regulatory circuitry in developing populations influences fear extinction developing populations with immaturities in the circuitry required for top-down control will respond to classic fear extinction paradigms. Efforts have focused on individual differences in treatment response, but not on when during development treatments may be most effective. We have recently examined fear learning across development in mice and humans. Parallel behavioral studies revealed attenuated fear learning during adolescence, in both humans and mice, compared to younger and older age groups. Exploiting the mouse to investigate underlying neural circuitry and mechanism revealed altered synaptic plasticity of prefrontal cortical and amygdala regions implicated in suppression of fear responses across development. In addition, genetic mouse models containing a human SNP in the growth factor gene, brain-derived neurotrophic factor (BDNF) demonstrate that this form of plasticity is modulated by the level of BDNF signaling during this “sensitive period” in the transition into adolescence. These findings provide novel insights into optimizing treatment outcomes for when, during development, exposure therapies may be most effective.
Risk for Anxiety and Implications for Treatment: Developmental, Environmental, and Genetic Factors

BJ Casey, PhD
Catherine A. Hartley, Charles E. Glatt, and Francis S. Lee, MD, PhD
Weill Cornell Medical College, New York, New York, United States

Anxiety disorders are the most common of all psychiatric disorders, affecting as many as 10% of youth and peaking in prevalence during adolescence. A core component of these disorders is an unremitting fear in the absence of present threat. The only evidence-based behavioral therapies for anxiety disorders build on the basic principles of fear learning. Specifically, cognitive behavioral therapy identifies the source of anxiety and then desensitizes the individual to that fear. This desensitization process of repeated exposure to the anxiety-provoking event, in the absence of actual threat, is based on the principles of fear extinction learning. Unfortunately between 40–50% do not improve with this therapy. This presentation will provide an overview of recent empirical studies employing both human imaging and cross-species behavioral genetics to examine how fear regulation and extinction vary across individuals and across development, especially during adolescence. These studies have important implications for understanding whom may be at risk for anxiety disorders and for whom and when during development exposure-based therapies may be most effective. Based on these findings, we provide future directions for determining the efficacy of innovative therapies and preventive strategies for anxiety disorders as a function of age and potential genetic effects inferred from mice and humans.
Altered Neural Circuitry Underlying the Risk to Develop Anxiety and Depression: Nonhuman Primate Translational Studies

Ned H. Kalin, MD
University of Wisconsin, School of Medicine and Public Health, Madison, Wisconsin, United States

Anxiety and depressive disorders commonly present early in life. Therefore, an opportunity exists for early identification and intervention prior to the long-term sequelae of these disorders. Studies in children demonstrate that extreme anxious temperament (AT) is the phenotype most predictive of the later development of anxiety/affective disorders. We characterized the AT phenotype in developing rhesus monkeys and have discovered the altered neural circuitry that underlies AT (the central nucleus of the amygdala (Ce), anterior hippocampus, prefrontal cortex and periaqueductal gray). Heritability analyses demonstrate that AT is approximately 35% heritable and importantly we found differential heritability of the AT neural circuit. For example, AT associated anterior hippocampus metabolism is highly influenced by heritable factors, whereas metabolism in the Ce is more greatly influenced by environment. We have also found that alterations in PFC-amygdala regulation are associated with extreme AT likely contributing to the risk to develop anxiety and depression. To investigate molecular mechanisms, we performed genome wide transcriptome analyses that demonstrate a reduction in Ce neuroplasticity gene expression in individuals with extreme AT. These findings have led us to posit a maladaptive neurodevelopmental hypothesis such that decreased neuroplasticity in the amygdala may underlie the expression and maintenance of extreme early anxiety and the later risk to develop anxiety and depression. These data provide the foundation for the development of novel early treatment strategies aimed at the prevention of the later development of severe psychopathology.
Placebo-associated improvements are frequent in controlled trials across neuropsychiatric conditions. Work from our laboratory and others have suggested that specific neurotransmitter systems, involved in responses to reward expectation, mood, and stress regulation (e.g., endogenous opioid, dopaminergic, endocannabinoid) are implicated. Genetic influences on these mechanisms include functional polymorphisms regulating the function of these neurotransmitter systems, and include OPRM1 A118G and FAAH C385A functional genetic variants. In the case of Major Depression, we observe that endogenous opioid mechanisms are also involved in the formation of neurobiological placebo effects. The activation of the endogenous opioid system and µ-opioid receptors during placebo administration was associated with improvements in mood state. Placebo-induced endogenous opioid system activation in the subgenual anterior cingulate, medial thalamus, nucleus accumbens, hippocampus and amygdala was additionally associated with treatment response to open-label antidepressant administration. Individuals that demonstrated greater placebo responses at both subjective (patient report) and objective (activation of neurotransmission) levels showed greater response to antidepressant administration and rates of recovery from MDD. These data indicate that in addition of being a confound in clinical trials, placebo antidepressant responses demonstrate specific neurobiological effects that when activated, promote and are associated with recovery from illness. From that perspective, the study of placebo neurobiology allows for the examination of novel targets that could be utilized to maximize effects of current antidepressant treatments, but also the development of new therapeutic targets for chronic conditions such as Major Depression.
The close bidirectional relationship between depression and cardiovascular disease (CVD) is now well established. Major depression is an independent risk factor for development of coronary artery disease (CAD), and depressed patients exhibit a significantly worse outcome in both morbidity and mortality following acute cardiovascular events including myocardial infarction, congestive heart failure, cardiac valve surgery, and isolated systolic hypertension. In addition, patients with CVD are at increased risk for depression and suicide.

This presentation focuses on the putative pathophysiological mechanisms underlying the increased vulnerability for CVD in depressed patients. These include: (1) increased inflammation as assessed by measurement of cytokines and C-reactive protein (CRP) (2) increased clotting diathesis with alterations in multiple steps in the clotting cascade including platelet activation and aggregation (3) increased oxidative stress (4) a reduction in endothelial progenitor cells (EPCs) and associated reduction in arterial repair processes (5) decreased heart rate variability (6) increased rate of subclinical hypothyroidism (7) increased sympathoadrenal and hypothalamic-pituitary-adrenal (HPA) axis activity (8) single nucleotide polymorphisms (SNPs) that increase CVD risk (9) epigenetics, particularly in response to adverse early life events, which is associated with increased risk for both depression and CVD. Treatment of depression in patients with comorbid CVD and depression is summarized. Early identification of depressed patients; prevention of CVD; and when appropriate, aggressive treatment of depression is an important and attainable goal.
Dr. Ressler will examine recent work on epigenetic mechanisms underlying disorders of fear and stress regulation, such as Post-traumatic Stress Disorder (PTSD) and Depression. Specifically, he will examine work outlining roles of differential histone acetylation and DNA-methylation associated with consolidation, reconsolidation, and extinction in Pavlovian fear paradigms, and their relevance to human disorders. He will then focus on recently published data on FKBP5 regulation of glucocorticoid receptor function, particularly with regards to how childhood maltreatment, FKBP5 polymorphisms, and chromatin regulation interact to increase risk for PTSD. He will discuss how this process is modulated in animal models of PTSD and in human clinical populations via epigenetic mechanisms both in PTSD and Depression cohorts. As glucocorticoid regulation of memory consolidation is well established in fear and stress models, he will examine how these recent data contribute to our broader understanding of fear memory and stress regulation. The combined recent progress in epigenetic modulation of memory with the advances in fear and stress neurobiology suggest that this area may be critical to progress in our understanding of fear- and stress-related disorders, such as PTSD and Depression, with implications for new approaches to treatment and prevention.
Genetics of Bipolar Disorder

Nicholas Craddock, MB, PhD, FRCPsych, FMedSci

National Centre for Mental Health, Cardiff University, Cardiff, Wales, United Kingdom

Studies of families and twins show the importance of genetic factors affecting susceptibility to bipolar disorder and suggest substantial genetic and phenotypic complexity. Robust and replicable genome-wide significant associations have recently been reported in genome-wide association studies at several common polymorphisms, including variants within the genes CACNA1C, ODZ4, and NCAN. Strong evidence exists for a polygenic contribution to risk (i.e., many risk alleles of small effect). A notable finding is the overlap of susceptibility between bipolar disorder and schizophrenia for several individual risk alleles and for the polygenic risk. By contrast, genomic structural variation seems to play a smaller part in bipolar disorder than it does in schizophrenia. Together, these genetic findings suggest directions for future studies to delineate the aetiology and pathogenesis of bipolar disorder, indicate the need to re-evaluate our diagnostic classifications, and might eventually pave the way for major improvements in clinical management.
Several neuropharmacological agents with impact on glutamate metabolism have recently emerged as potential treatments in mood disorders. We will discuss data from studies involving three such agents: ketamine, memantine and minocycline. Firstly we will review the evidence base for ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist, as a novel treatment for treatment-resistant depression (TRD), including data from a recently completed multi-site randomized controlled trial. New data concerning neurocognitive and neuroplasticity parameters (such as BDNF) regulated by ketamine in TRD will also be presented. Secondly we will discuss data on memantine (a weaker glutamate NMDA receptor antagonist) for the treatment of cognitive deficits in bipolar disorder. In this population adjuvant memantine was associated with acute improvements on several cognitive domains (attention, short-term memory and delayed memory) and with increased hippocampus neuronal viability as measured with proton magnetic resonance spectroscopy (1H-MRS). Finally we will review positive preliminary data for the antidepressant effect of minocycline in bipolar disorder. The antibiotic minocycline has modulatory effects on glutamate neurotransmission, as well as anti-inflammatory, antioxidant, and neuroprotective effects. Minocycline treatment was also associated with increases in glutamate-glutamine (Glx) and glutathione (GSH) on 1H-MRS. Collectively, these studies highlight the promising clinical effects of several agents impacting glutamate metabolism and their possible links with neuroplasticity.
SESSION 3
Advances in Neuropsychiatry
(Combined with Track 2)

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*Abstract not available at time of printing.

Cytokines Sing the Blues: Mechanisms, Mediators, and Translational Implications

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Activation of the immune system and release of cytokines can lead to behavioral changes. Given the association of immune activation with medical illness as well as psychological stress, such cytokine-induced behavioral changes may contribute to the high rate of depression, anxiety and other behavioral alterations observed in medically ill and chronically stressed individuals. Using the inflammatory cytokine, interferon-alpha, our group and others have demonstrated that cytokines administered peripherally can access the brain and alter the function of the basal ganglia as measured by functional magnetic resonance imaging and positron emission tomography. Cytokine-induced alterations in basal ganglia function in turn have been associated with motor slowing, anhedonia, and fatigue and appear to be mediated by alterations in dopamine as well as glutamate metabolism. Cytokines also appear to activate brain areas including the dorsal anterior cingulate cortex that are associated with anxiety, arousal, and alarm. Interestingly, inhibition of cytokines using cytokine antagonists has been shown to reverse anhedonia and anxiety in patients with depression. Taken together, cytokine effects on behavior may subserve evolutionary survival priorities during infection and/ or wounding to conserve energy to fight pathogens and heal wounds while at the same time increasing vigilance against attack. Chronic activation of these brain circuits during illness or stress, however, may lead to behavioral pathologies in vulnerable individuals, which may be uniquely treated by therapies targeting the immune system and inflammation.
The brain is uniquely dependent on a well-regulated delivery of oxygen and glucose through the blood supply. The neurovascular unit, comprised of endothelial cells, smooth muscle cells/pericytes, astrocytes, perivascular cells, and neurons, is responsible for matching local cerebral perfusion to the metabolic needs of the brain (neurovascular coupling). Cognitive function is highly dependent on adequate cerebral perfusion, and alterations in regulation of the cerebral microcirculation have emerged as a key factor both in vascular causes of cognitive impairment, such as hypertension, and in dementia on neurodegenerative bases, such as Alzheimer’s disease. Clinical-pathological studies support the notion that vascular risk factors aggravate the deleterious effects of neurodegenerative pathology by reducing the threshold for cognitive impairment and accelerating the pace of the dementia. In the absence of mechanism-based approaches to counteract vascular or neurodegenerative dementia, targeting vascular risk factors, including hypertension, offers the opportunity to mitigate the impact of one of the most disabling human afflictions.
Improving Mitochondrial Bioenergetics to Treat Nervous System Dysfunction Early in the Course of Diabetes

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Diabetes has emerged as a profound health and economic challenge, with impaired function of the nervous system among the most common and debilitating consequences. Treating the neural complications of diabetes is typically directed at managing symptoms of metabolic dysfunction, which can slow but not reverse disease progression. Our approach to improve treatment is 1), to identify early biomarkers of progression to diabetes, using sensitive, non-invasive measures of behavioral function, and 2), to improve mitochondrial bioenergetics early in the course of metabolic decline to reverse the course of disease progression. We thus quantified thresholds for visuo-motor behavior in groups of mice fed a diabetic diet from 4 weeks of age (to induce obesity), administered streptozotocin at 8 weeks (to reduce insulin production), or both. Impaired function, graded by the nature of the metabolic challenge, was evident by 12 weeks; well before the emergence of typical diagnostic symptoms of diabetes. We then investigated whether MTP-131, a peptide that promotes efficient electron transport and AP synthesis, could treat the functional deficits. We found that systemic injections of MTP-131 from 12 weeks fully restored function in all groups by 30 weeks, without ameliorating concomitant obesity and elevated blood glucose. Eye drop delivery of MTP-131 from 12 weeks more rapidly restored function, and reversed more severe dysfunction with treatment from 34 weeks.

The results indicate that impairment of visuo-motor function is an early behavioral complication of chronic metabolic dysfunction, which can be selectively treated by improving mitochondrial bioenergetics.
SESSION 4
Clinical Approaches to Affective Disorders

Bipolar Disorders in the Arab World: Clinical and Genomic Data

Ziad Kronfol, MD1,3
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Bipolar disorder (BPD) is a major psychiatric disorder in the Arab World and as with other psychiatric disorders it is not well investigated. We have initiated a clinical study of BPD in Qatar and Lebanon with the aim to identify genetic variations that contribute to BPD in the Qatari and Arab population. For this purpose, we translated the Diagnostic Interview for Generic Studies DIGS and adapted it to the Arab culture (aDIGS). We hereby report on 84 BPD Arab patients who were evaluated and characterized clinically using the aDIGS. Clinical features include (1) high medical comorbidity, particularly for diabetes and asthma; (2) low psychiatric comorbidity, specifically alcohol and substance use; (3) high prevalence of psychosis during episodes, and (4) high prevalence of psychiatric illness in first degree family relatives. Whole Genome sequencing data on 62 Arab bipolar patients were compared to 108 Qatari population controls at a depth of 30x. Preliminary results will be presented. These data represent the first wave of whole genome sequencing of Arab BPD individuals. The data will be subsequently compared with BPD data from other global regions. Arab populations offer unique opportunities for genomic studies which include relatively genetically isolated populations, high frequency of consanguinity, and unusual clinical features.
Biomarker Development to Help Prevent Treatment-Resistant Depression

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Treatment Resistant Depression (TRD) is failure to achieve remission following at least two courses of evidence-based antidepressant treatments of adequate dose and duration. TRDs result in huge burdens, disabilities, and costs. Overlooked underpinnings include:

1) failure to differentiate among multiple pathophysiological causes of depressions and bipolar illnesses, e.g., genomic, inflammatory, trauma, toxins, stress-neuroendocrine, endothelial, and others; “one size treatment will never fit all”, yet that is prevailing practice; and

2. absence of effective strategies to evaluate biomarkers that have potential to differentiate among the array of “depressions” and prompt subsequent of development personalized, precision treatments.

This presentation will review underlying causes of TRD; challenges that impede biomarker development and steps to overcome them; and current perspectives about the most promising biomarker candidates:

Improvements will require: 1. Global collaborative networks (e.g., www.NNDC.org), registries and biorepositories to enable study of tens or hundreds of thousands, not tens or hundreds; 2. Sustainable networks analogous to cancer to enable long-term assessments; 3) Reverse testing paradigms, such as comparing biomarkers among those who respond to potential glutamatergic challenges (e.g., ketamine) vs. those who do not; 4) Re-establishment of new types of academic-industry partnerships to test “unconventional” treatments, e.g., anti-inflammatory agents among those with elevated interleukins; 5) Routine pharmacogenetic/pharmacokinetic profiles to identify poor, non, or rapid metabolizers that erroneously mimic non-response; and 6) Formation of a global task force to identify most promising biomarker candidates. Hypothetically, many TRD cases may be preventable through development and translation of biomarkers and personalized treatments.
New Anti-Depressants

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Although considerable progress has been made over the past 25 years in the development of antidepressants, there are many patients who fail to respond to initial trials of antidepressants or even to follow on treatments. Thus, there is a need for agents that work better and faster. Unfortunately, recent efforts in drug development have frequently failed to separate the new compound from placebo. In this presentation I will first review reasons for such failure, including high placebo response rates, problems with overestimating symptoms at baseline, inclusion of inappropriate subjects, poor target validation, brain penetrance, etc. I will then discuss a number of recent initiatives including ketamine and other glutamatergic agents, r-TMS, mifepristone, botulinum toxin, vilazodone, etioxetine, and vortioxetine. Lastly I will frame discussion of these various agents in the broader perspective of problems in antidepressant development with an eye toward building a framework for how best to utilize those agents that are likely to attain regulatory approval.
Medial and Lateral Prefrontal Stimulation in Treatment-Resistant Depression

Ziad Nahas, MD, MSCR

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This presentation reports on the current status of non-pharmacological brain stimulation therapies to treat mood disorders. It focuses on prefrontal cortical modulation. It includes discussion of transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT) and the related focally administered seizure therapy (ECT), and epidural prefrontal cortical stimulation (EpCS). It will also briefly review other functional neurosurgical procedures for psychiatric conditions. These somatic interventions are informed in part by the emerging functional neuroanatomy of different neuropsychiatric disorders. One of the recurring themes within each of the techniques is the currently inadequate understanding of the translational neurobiological effects of the ‘use parameters’. These are the pulse width, current direction, intensity, frequency, duty cycle, and the overall dose as well as dosing scheme. The future of the promising field of brain stimulation will undoubtedly involve better translating the knowledge gained about appropriate use parameters from preclinical cellular and non-human animal studies into clinical brain stimulation therapeutic uses.
Recent Trials in Stroke

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The recent stroke trials have explored key questions in stroke care, and their results have justifiably been highly anticipated and often illuminating, ground-breaking, and unexpected. Randomized clinical trials have reshaped the standard of stroke treatment, prevention, and management. They have introduced advances in therapies that have redefined the field, while also resulting in the modification or rejection of a number of previously widely held practices. Even “negative” trials have brought important new insights to our understanding of the pathophysiology and mechanism of cerebrovascular disease. In this talk, the focus will be on the stroke trials of the past two years, especially those in the areas of antithrombotic therapy, secondary stroke prevention, risk factor management, atrial fibrillation, endovascular intervention, and acute stroke treatment. SAMMPRIS, CHANCE, SPS3, IMS-3, POINT and others are among the recent major stroke trials which will serve as a launch point for a discussion of dual versus single antiplatelet therapy, the novel oral anticoagulants, intensive risk factor modification, the influence of stroke subtype, and the impact of timing and duration on outcomes of stroke therapy.
Teleneurology for Acute Stroke (remote lecture)

Lee H. Schwamm, MD
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Acute stroke is a high-impact, but low-frequency, event. It is the fourth leading cause of death and the leading cause of disability. There are 800,000 strokes each year across the United States, and about one practicing neurologist for every 20,000 Americans, or 50 to 60 strokes per neurologist per year. However, not all of these neurologists are experts in stroke care. Telestroke is a way to reallocate the expertise and make it available broadly. Intravenous tPA is known to be beneficial in stroke, but it requires immediate expertise to be available and there is disparity in its use. When it works, it dramatically increases the likelihood that patients will improve and return to a near-normal life. Treatment within the first 90 minutes of an acute stroke leads to a roughly 18-fold better chance of being helped than harmed, and benefit continues for 4.5 hours after stroke onset. Telestroke systems link under-resourced spoke hospitals to acute stroke center hubs to provide regionalized acute stroke care. Remote neurological consultation increases rates of IV tPA use and has gained acceptance through demonstrated reliability. The Partners National Telestroke Network is an academic medical center based program based at Massachusetts General Hospital that includes six regional US hubs serving 56 spokes. Other academic telestroke programs have emerged as well as independent, for-profit programs. Telestroke is an early and sustainable application of telehealth for stroke care, particularly acute stroke care. The evolution of telestroke required evidence, consensus of key stakeholders, ongoing education, and financial sustainability.
Transient Ischemic Attacks: What’s New in Pathophysiology and Treatment?

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Transient ischemic attacks (TIA) precede an ischemic stroke in more than 30% of patients. The risk of stroke is high in the 90 days following a TIA; the risk is especially high in the initial 24-48 hours. Stroke recurrence is particularly high in patients with risk factors, particularly hypertension and diabetes. Risk scores have been designed and validated to help clinicians evaluate TIA patients. Recent studies have shown that very early evaluation and aggressive management can significantly reduce the risk of subsequent vascular events. The EXPRESS study showed that this approach can reduce the risk of stroke by over 80%. Similar encouraging results were reported in the SOS study from Paris.

We have recently shown that the risk of stroke is particularly high in patients with abnormal brain imaging (arterial occlusions/stroke on MRI). Clinically, the approach to these patients is to: (a) confirm the diagnosis of TIA vs other neurological events; (b) stratify risk by clinical (motor, speech symptoms) and imaging (intracranial occlusion, carotid stenosis) features; (c) determine the potential etiology; (d) and implement immediate preventive treatment. Key etiologic diagnoses to make are: (1) carotid artery stenosis; (2) atrial fibrillation and other cardioembolic causes of stroke; (3) atypical non-atherosclerotic syndromes such as coagulopathies and vasculitis. Each of these ischemic stroke sub-types carries a specific approach to treatment. My presentation will focus on importance of early evaluation of suspected TIA patients. I will also review recent advances in diagnosis utilizing multi-model imaging and on the importance of dual antiplatelet therapy.
Pregnancy-Associated Stroke

Matthew E. Fink, MD

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Stroke during pregnancy and during the peripartum and postpartum periods are rare events, but the consequences may be catastrophic for these young women and their families. The highest risk, for both ischemic stroke and hemorrhagic stroke, is the peripartum period and the first two weeks of the postpartum period. The causes are usually not those that usually occur in the older age group, but are often more related to underlying cardiac anomalies, thrombophilias, and other hematologic and physiological disorders associated with pregnancy, such as pre-eclampsia and eclampsia. Cerebral venous thrombosis is also a common cause of pregnancy-associated stroke, and may occur without any underlying thrombophilic disorder.

In several prospective series from North America, the incidence of pregnancy-associated stroke appears to be 4-5 cases per 100,000 deliveries, which means that individual centers that have large obstetrical services, may only see one case per year. However, in a survey of US hospitalizations, using the National Inpatient Sample, which accounts for 20% of all hospital admissions in the US, there was a clear increase in the risk of all stroke types from the years 1994-95, compared to the years 2006-2007. This study revealed a 47% increase in the incidence of stroke during the antepartum period, and an 83% increase in the postpartum period. The reason for this increase in stroke appears to be the increasing age of pregnant women in the US in recent years, with an increase in risk factors, such as hypertension and cardiac disorders, including cardiac arrhythmias and valvular heart disease. Diabetes and obesity are also significant risk factors in the older pregnant population.
In this talk I will review our current understanding of the pathophysiology underlying traumatic brain injury (TBI) in the pediatric population. While the emphasis will be on concussion (mild TBI), which represents the largest component of pediatric TBI, moderate and significant TBI will also be discussed. It is said that TBI is the only injury from which children recover more slowly than adults. This may be a result of the fact that mechanisms underlying normal brain plasticity may prolong the duration of recovery, though may enable better long-term functional outcomes. The lack of reliable, valid, and objective measures of brain injury have limited our ability to diagnose, treat, and study affected individuals, and has prevented developing meaningful evidence-based guidelines.

Despite these challenges, recent research conducted in both animals and humans have identified the importance of distinguishing more focal injury induced by direct contact of the grey matter of the frontal and temporal poles with the bony skull, as compared with more diffuse injury induced by inertial forces resulting in diffuse axonal injury of the white matter. There appear to be separate mechanisms underlying primary vs. secondary brain injury: initially there is neuronal depolarization associated with increased release of potassium and glutamate, and increased calcium uptake, which combined with decreased cerebral blood flow results in initial cell death and secondary apoptosis. Examples of how recent application of non-invasive brain imaging methods including MRI, MRS, and PET can provide the opportunity to better understand such mechanisms and the underlying pathophysiology of TBI will be presented.
Hypothermia as a Neuroprotectant in Traumatic Brain Injury

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The application of hypothermia after traumatic brain injury (TBI) can have very different effects based upon patient selection as well as the timing, duration and depth of cooling. Cooling within minutes to hours after the injury is designed to act as a primary neuroprotectant, mitigating many of the cellular mechanisms that eventually result in further damage. Three multi-center randomized controlled trials that tested early short-term (max. 48 h) hypothermia, found no benefit with regards to survival and neurological outcome. As hours and days post injury continue, the cumulative effect of these mechanisms is observed clinically, where therapeutic hypothermia can also be applied as an effective therapy for processes leading to raised ICP. The magnitude of the effect of therapeutic hypothermia on ICP reduction is estimated to be approximately 10 mm Hg (range 5–23 mmHg). However, the optimal target temperature of hypothermia when used for ICP control is not well defined. There is experimental evidence that decreasing body temperature to 35–35.5 °C effectively treats intracranial hypertension, while maintaining sufficient cerebral perfusion pressure without cardiac dysfunction or oxygen debt. Similarly the optimal duration of hypothermia is not well understood. Instead of applying fixed targets, cooling may be better applied by titrating both depth and duration of hypothermia to maintain ICP below 20 mmHg weighed against the risk associated with deep sedation and impaired immune function that accompany prolonged cooling.
What Is Wrong With Current Therapy For Traumatic Brain Injury

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Recent research highlights incongruities between the pathophysiology of traumatic brain injury (TBI) and our treatment of it. Intracranial pressure (ICP), long recognized as an important indicator of injury severity, has been misconstrued as a stand-alone aspect of the injury itself. Treatment protocols commonly apply a single threshold to all TBI types, at all stages of injury. Uniform treatment protocols are applied to all patients and any ICP elevation above the uniform threshold (20-25 mmHg) prompts increasingly hazardous treatment.

Similar issues obtain for cerebral perfusion pressure (CPP), which has also become a stand-alone treatment entity possessed of a uniform treatment threshold. Studies documenting the hazards of overestimating this threshold have resulted in its moderation but use of hypervolemia and pressors to uniformly maintain a CPP of 60 mmHg is frequent. Indeed, the entire concept of a CPP threshold as more than a proxy for avoiding early cerebral hypotension remains unproven.

Related to the above, the clinical application of our understanding of post-traumatic cerebral autoregulation has also been confounded. Not recognizing the difference between static and dynamic autoregulation has prompted misinterpretation of published studies and the widespread impression that static pressure autoregulation is usually disrupted after TBI. This not only leads to overtreatment but may also result in a misguided treatment approach. Reappraisal of the available literature prompts reconsideration of our current treatment algorithms and a shift in focus towards targeted treatment based on multi-modality monitoring of underlying physiology rather than applying universal thresholds. The second lecture outlines such a physiology-based approach.
Hyperosmolar Therapy for Brain Edema

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Hyperosmolar agents currently in clinical use for traumatic brain injury (TBI) are mannitol and hypertonic saline (HS). Mannitol is widely used for the control of raised ICP following TBI. Its use is advocated in two circumstances. First, a single administration can have short-term beneficial effects. Second, mannitol has been used as a prolonged therapy for raised ICP. There is, however, a lack of evidence to recommend repeated, regular administration of mannitol over several days. Although there are data regarding its basic mechanism of action, there are few human studies that validate different regimens of mannitol administration. Current therapies used for ICP control (mannitol, barbiturates) bear the risk of further reducing perfusion to the brain either by lowering blood pressure and cerebral perfusion pressure (CPP) or by causing cerebral vasoconstriction (hyperventilation). Ideally, a therapeutic intervention should effectively reduce ICP while preserving or improving CPP. The use of HS for ICP control was discovered from studies on “small volume resuscitation” in poly traumatized patients. Hypertonic saline solutions were tested in poly-traumatized patients with hemorrhagic shock. The subgroup with accompanying TBI showed the greatest benefit in terms of survival, and hemodynamic parameters were restored effectively. The findings that HS may benefit patients with TBI while preserving or even improving hemodynamic parameters stimulated further research on the effects of HS solutions on increased intracranial pressure. The best current evidence suggests that mannitol is effective in reducing ICP in the management of traumatic intracranial hypertension. Current evidence is not strong enough to make recommendations on the use, concentration, and method of administration of hypertonic saline for the treatment of traumatic intracranial hypertension.
Traumatic brain injury (TBI), a leading cause of death and disability in children, is projected to become the third largest cause of global disease burden by the year 2020. Pediatric TBI is classified as mild, moderate and severe. Outcome is influenced by patient demographics, severity of injury and exposure to secondary insults that can aggravate the initial injury. Examples of secondary insults include hypotension, fever and hyperventilation. Challenges encountered by healthcare providers treating children with TBI include: a) partially understood, complex neuropathology; b) the unique epidemiology of pediatric trauma; c) outcome variability within centers and; d) the need for practical long term functional outcome measures. Ongoing efforts to overcome these challenges aim at reducing mortality and disability after pediatric TBI.
The Pathway toward Optimal Traumatic Brain Injury Treatment

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Since we currently have no proven therapies for reversing primary brain injury, the goal of management is optimizing the injured brain’s healing environment. This must be done in the setting of polytrauma, with the recognition of the risks of varying treatment approaches and modalities. The two major goals are meeting the metabolic demands of the brain and avoiding the consequences of increased tissue volume. Initially, treatment must be preemptive, using targets with built-in margins of error (e.g. ICP ≤ 20 mmHg and CPP ≥ 60 mmHg). Subsequently, based on frequent clinical examination, serial imaging, and multi-modality monitoring, the therapeutic approach should be individualized as the injury evolves and our understanding improves. Elevated ICP should prompt the search for and treatment of underlying causes. Assessing the patient’s ICP course in terms of trends and inciting events allows adjusting the ICP threshold based on cerebral compliance. Monitoring the balance of substrate delivery and metabolic demand (directly or indirectly) facilitates individualizing cerebral perfusion parameters. Additionally, comparing and contrasting different monitors with overlapping physiological targets minimizes the potential for error associated with their individual limitations.

The goal of targeted therapy based on multi-modality monitoring is to detect patients who do not need treatment, who respond appropriately to treatment, who require increases in treatment, and who require radical alterations in treatment, based on understanding the physiology of the injured brain. Multi-modality monitoring should not simply increase treatment; it should target it towards improving outcome. This mandates attentive bedside Neurologically-oriented Critical Care.
Cerebral Collaterals and Acute Stroke

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Acute stroke is an extreme medical emergency and is no different than an acute coronary syndrome or cardiac arrest and evolves quickly. Every minute that the middle cerebral artery remains occluded, 1.9 million neurons and 12 km of myelinated axons are destroyed. The goals of therapy are to reestablish blood flow to the ‘at-risk’ cerebral tissue. The two most important determinants of successful treatment are the time to reestablishment of flow and the competence of the pial collateral circulation. Collateral imaging can identify patients with excellent collaterals (> 30% of patients) quickly and allow for an extended time window for reperfusion therapies. Collaterals are also amenable to change and can be augmented with intervention immediately following an acute stroke.

This presentation will focus on experimental research on collateral enhancement in focal ischemia, how to identify pial collaterals with CT imaging, especially in patients with proximal vessel occlusion. The results of recently completed and on-going interventional trials will be reviewed in the context of the underlying collaterals. I will also review completed and on-going studies on augmentation of collaterals following an acute stroke.
Immunity and inflammation are key factors of the pathophysiology of stroke, a devastating illness second only to cardiac ischemia as a cause of death worldwide. The immune system contributes to the brain damage produced by cerebral ischemia. Thus, inflammatory signaling is activated at all stages of the ischemic cascade, starting from the early damaging events triggered by arterial occlusion, to the infiltration of inflammatory cells, and the late regenerative processes underlying post-ischemic tissue repair. Recent developments have revealed that stroke, like multiple sclerosis, engages cellular and molecular responses typical of both innate and adaptive immunity. But, unlike multiple sclerosis, adaptive immunity triggered by newly exposed antigens in the damaged brain does not contribute to the acute phase of the damage. Nevertheless, modulation of certain T cell-mediated responses can exert a remarkable protective effect on the ischemic brain and offers the prospect of new stroke treatments. However, immunomodulation is not free of deleterious side effects. Therefore, gaining a better understanding of the reciprocal interaction between systemic immunity and the ischemic brain is essential to harness the full therapeutic potential of the immunology of stroke.
Neurotechnology encompasses electrical, chemical, and medical devices and products that can interact with or intervene in the activity of the central nervous system. These technologies include neuroprosthetics, neuroengineering, neuroimaging, optogenetics, neuromodulation and neural stem cell therapies. Translating neurotechnologies from the laboratory into clinical and commercial products has been an arduous process. Yet many of these new tools show great potential to revolutionize the treatment of neurological diseases and disorders including depression, pain, headache, epilepsy, neuromuscular disease, Alzheimer’s disease, Parkinson’s disease, and traumatic brain injury.

Visit www.nyas.org/Neurotechnology-eB to access this eBriefing.
Treatment-Resistant Depression: Glutamate, Stress Hormones, and their Role in the Regeneration of Neurons

Clinical depression, (major depression) is a devastating illness, which occurs in about 15% of the population, and leads frequently to death by suicide or organic consequences, such as increased cardiovascular risk. Only around one in ten patients treated with the current standard of care antidepressant medication, like SSRIs or SNRI, demonstrate clinical response that extends beyond the effects of placebo. Therefore the current paradigm, which has been in use for the past 50 years and is based on specific effects on monoamines, shows drastic limitations. A paradigm shift is on the way focusing on a completely different neurotransmitter system, namely glutamate and its receptors. A model compound, ketamine, has demonstrated unusually fast improvements in patients, who did not respond to other treatments. The molecular basis for this phenomenon has been partially characterized. The glutamatergic system is integrated in the well-established stress machinery, and the involvement of stress hormones in the regulation of this system has become apparent. Importantly, the older paradigm of the role of serotonin can also be integrated into this new perspective, which seems to be valid in a subset of patients. Astonishingly one overlap between the stress system and the glutamatergic system is the regulation of electrolytes, and in particular magnesium. Both ketamine and magnesium can lead to a sprouting of neuronal synapses in the brain and by this reverse stress-induced changes. The importance of these changes in the structure of neurons and their functional consequences for the amelioration of defective brain function and the related depressive symptoms will be highlighted.

Visit www.nyas.org/treatmentresistantdepression-eB to access this eBriefing.
Thrombolysis and Acute Stroke Treatment: Preparing for the Next Decade

Edited by:
Gregory J. del Zoppo
University of Washington, Seattle, Washington
and Andrei V. Alexandrov
University of Alabama, Birmingham, Alabama

Volume 1268, September 2012, 157 Pages, 23 Papers

This Annals volume presents work from leading and emerging investigators from within and outside the immediate area of cerebrovascular disease. These short reviews explore the state-of-the-art and future directions of research and clinical practice leading to enhanced medical care in the acute treatment of ischemic stroke. Papers in this volume highlight various facets of acute intervention and issues related to the medical setting for stroke that affect clinical outcomes and provide opportunities for improving treatment. Collectively, this volume examines the generation of data-driven, multidisciplinary ideas to explore ischemic stroke as a systemic disease related to other disease entities (hypertension, diabetes, and disorders of aging), and to better address the evolution of ischemic brain injury.

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**CELL PHONES AND ELECTRONIC DEVICES**

In consideration of fellow participants, it is requested that all cell phones and other electronic devices be turned off or set to silent mode during all Scientific Sessions to avoid disruption.
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