The Clinical Neurosciences Training program
Anesthesiology, Neurology, Neuropathology, Neuroradiology, Neurosurgery, Ophthalmology, Otolaryngology & Psychiatry

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• The Clinical Neuroscience Training program (CNST) was established to nurture medical students' interest & involvement in the clinical neurosciences including Anesthesiology, Neurology, Neurosurgery, Neuropathology, Neuroradiology, Psychiatry, Ophthalmology and Otorhinolaryngology.

• The goal of the CNST is to train clinical neuroscience specialists who will participate at the forefront of academic clinical practice & related research.

• Eligibility for CNST: The CNST is open to all Penn School of Medicine students with an interest in clinical neuroscience. Although designed for four-year medical students, combined degree and graduate students are welcome.

• Structure of the CNST: The CNST consists of an expanded clinical neuroscience curriculum within a four-year medical school structure:
  • Clinical Research and Careers in Neuroscience Seminars
  • Interdisciplinary Case Conferences
  • Mentoring & Shadowing
  • Special Academic and Social Events
  • Clinical Neuroscience Research Opportunities
Advisory Board

Dr. Roderic Eckinhoff - Anesthesiology
Dr. Richard Doty - Otorhinolaryngology
Dr. Neal Malhotra - Neurosurgery
Dr. Paolo Nucifora - Neuroradiology
Dr. Ken Shindler - Ophthalmology
CNST Certificate Program

• Seminar participation during MS1 and MS2
• Research Clinical between MS1 & MS2
• 2 Neuroscience electives
• Scholarly pursuit in a clinical neuroscience during MS3 & MS4.

• Individual meetings with program directors each year to review plans and progress
• Formal recognition of complete participation
# CNST Seminar Series Fall 2011

All seminars are held in Barchi Library – Room 140 John Morgan Building unless otherwise notified.

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<td>Orientation &amp; Introduction</td>
<td>Psychiatry &amp; Neurology</td>
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<td>September 30, 2011</td>
<td>David M. Raizen, M.D., Ph.D.</td>
<td>“What Purpose Does Sleep Serve”</td>
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<td>Noam A. Cohen, M.D., Ph.D.</td>
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<td>John Q. Trojanowski, M.D., Ph.D.</td>
<td>“Biomarkers of Neurodegenerative Diseases”</td>
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<td>Ronald L. Wolf, M.D., Ph.D.</td>
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<td>Dec – 2011</td>
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<td>Arjun G. Yodh, Ph.D.</td>
<td>“Optical Monitoring of Brain, Brain Injury, &amp; Brain Injury Treatment”</td>
<td>Physics &amp; Astronomy</td>
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John H. Morrison, Ph.D.
Dean of Basic Sciences and the Graduate School of Biological Sciences
Professor, Department of Neuroscience
Mount Sinai School of Medicine

“Age – Related Alterations in Cortical Neurons, Synapses, and Neuronal Plasticity: Implications for Cognitive Decline”

Friday, September 23, 2011
The Barchi Library – 140 John Morgan Building
1:00pm – 2:00pm
Summer Research

2008:
- 5 students funded for CNST summer research
- CNST arranged for 1 student to receive funding from the German government for a CNST summer internship abroad

2009:
- 8 students funded for summer internships through CNST.
- 1 summer internship abroad arranged by CNST with external funding from German government,
- 1 student received an AOA stipend for his CNST project

2010:
- 8 applicants for 4 potential funded spots
- 4 were selected for CNST funding.
- 1 student received external funding from ANA
- 1 student funded through a grant from ACNP
Summer Research

2011:

• 12 applicants for 4 potential funded spots
• 4 were selected for CNST funding.
• 4 received extramural funding with support from CNST process
Social Events

Resuming this year under the auspices of Dr. Richard Doty

First Session is 9/16
Adler lecture 9/23
Translational Biomarkers of Schizophrenia & Autism
Collaborative Studies in Humans & Mice

Steve Siegel, MD, PhD

CNST 9/15/11
Schizophrenia: Mouse Models

**Goals:** Predictive, functional biomarkers of neural deficits in schizophrenia (and autism) that:

- Reflect genetic or environmental etiology
- Inform underlying neural mechanisms of
- Impaired capabilities and/or symptoms and
- Can be *directly* modeled in animals

Steven J. Siegel, M.D., Ph.D.
Mouse latency is 40% of that in humans

Steven J. Siegel, M.D., Ph.D.
Objectives

1. Gamma Oscillation Overview
2. Gamma Synchrony in Schizophrenia
3. Gamma Synchrony in Mouse Models of Schizophrenia
4. Pharmacologic Rescue of Gamma Deficits
5. Overlap between Autism & Schizophrenia
Gamma Oscillations

- 30-80 Hz rhythmic neural activity
- **Correlates** - Working memory, selective attention, perceptual ‘feature binding’
- **Neural Mechanisms** - fast-spiking inhibition from PV+ interneurons - pyramidal cells
- **Impaired gamma synchrony in SZ**
  - Working memory tasks (Lewis DA, 2008)
  - Auditory evoked, steady state deficits (Light GC, 2006; Leicht G, 2010)
- **Symptom correlations**
  - Cognitive performance (Lewis DA, 2008; Light G, 2006)
  - Negative symptoms (Lee KH, 2004)
- **Heritable** (Lee KH, 2004)

Uhlhaas P, 2010  Steven J. Siegel, M.D., Ph.D.
Gamma Measures: Power

- **Baseline**
  - Background Noise
- **Stimulus Evoked**
  - Sensory processing

Baseline Power Spectrum

Evoked Time-Frequency Plot

Steven J. Siegel, M.D., Ph.D.
Gamma Measures: Phase Locking

EEG
Gamma
Filtered

- Phase Locking = 1 – circular variance of phase across trials (e.g. inter-trial coherence)
Cortical Dysfunction in Schizophrenia

Pathogenesis

↓ NMDA-R Signaling

↓ PV+ Interneurons

Disruption in Gamma Synchrony

Deficits in cognitive, sensory functioning

Neurophysiology

Clinical Syndrome

Steven J. Siegel, M.D., Ph.D.
1. Gamma Oscillations: Overview
2. Gamma Synchrony in Schizophrenia
3. Gamma Synchrony in Mouse Models of Schizophrenia
4. Pharmacologic Rescue of Gamma Deficits
5. Autism and Schizophrenia

Steven J. Siegel, M.D., Ph.D.
Schizophrenia EEG Study
in collaboration with Bruce Turetsky

Auditory oddball stimuli (n=20/group); standard tones

Schizophrenia → Reduced N1 amplitude, theta to gamma shift in EEG power

Steven J. Siegel, M.D., Ph.D.
Auditory oddball paradigm (n=20/group) standard tones

Schizophrenia → gamma PLF deficits, elevated at baseline

Elevated baseline and reduced evoked = Reduced SNR

Gamma Phase Locking

Wavelet Transform

Steven J. Siegel, M.D., Ph.D.
1. Gamma Oscillations: Overview
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3. Gamma Synchrony in Mouse Models of Schizophrenia
4. Pharmacologic Rescue of Gamma Deficits
NR1 Hypomorph Schizophrenia Model

- **Glutamate hypothesis of Schizophrenia pathophysiology**
  - ↓ NMDAR signaling

- **NMDA NR1\(^{neo-/-}\) Mice**
  - 12% expression of NMDA NR1 subunit
  - Model negative, cognitive sx: social withdrawal, PPI deficits, learning and memory impairments (Mohn A, 1999; Dzirasa K, 2009; Halene T, 2009)

- **Acute MK-801 administration**
  - Selective NMDAR antagonist
  - Clinical syndrome indistinguishable from schizophrenia
  - Mice: PPI deficits, hyperlocomotion, cognitive dysfunction

Steven J. Siegel, M.D., Ph.D.
NR1 -/- Mice

Electrophysiology

Baseline

Stimulus-Evoked

Steven J. Siegel, M.D., Ph.D.
Acute MK-801

Baseline

Stimulus-Evoked

Power (dB)

Frequency (Hz)

SAL

MK801

**

Steven J. Siegel, M.D., Ph.D.
SCZ  NR1-/-  MK801

Reduced SNR with Impaired sensory processing

Gamma Power (dB)

Time (s)

Baseline  Sensory Evoked

Steven J. Siegel, M.D., Ph.D.
Cortical Dysfunction in Schizophrenia

Pathogenesis

↓ NMDA-R Signaling

↓ PV+ Interneurons

Disruption in Gamma Synchrony

Deficits in cognitive, sensory functioning

Neurophysiology

Clinical Syndrome

Steven J. Siegel, M.D., Ph.D.
NR1-/- Mice: Immunohistochemistry

Parvalbumin

- Calcium binding protein
- Selective for fast-spiking interneurons (basket, chandelier cells)
- PV+ Interneurons: necessary & sufficient for gamma synchrony (Sohal V, Nature 2009)
NR1-/- Mice: Protein Expression

Specificity of Deficits for Fast-Spiking Interneurons

- Calbindin, Calretinin: CBP markers for non-fast spiking interneurons
- GAD65/7: rate limiting enzyme for GABA synthesis

Steven J. Siegel, M.D., Ph.D.
Cortical Dysfunction in Schizophrenia

Pathogenesis

↓ NMDA-R Signaling

↓ PV+ Interneurons

Neurophysiology

Reduced Gamma Power, PLF

Clinical Syndrome

Deficits in cognitive, sensory functioning

Steven J. Siegel, M.D., Ph.D.
1. Gamma Oscillations: Overview
2. Gamma Synchrony in Schizophrenia
3. Gamma Synchrony in Mouse Models of Schizophrenia
4. Pharmacologic Rescue of Gamma Deficits
5. Autism and Schizophrenia
mGluR₅ agonist will potentiate NMDA receptor currents on GABAergic interneurons and enhance inhibition of pyramidal cells.

mGluR₅ antagonist will reduce NMDA receptor currents on GABAergic interneurons and reduce inhibition of pyramidal cells.

mGluR₂/₃ agonist will reduce presynaptic glutamate release.

mGluR₅ agonist potentiate currents at NMDA receptors and attenuate hypexcitability from reduction of NR1 on pyramidal cells.

mGluR₅ antagonist will reduce NMDA receptor currents on pyramidal cells.
Schizophrenia Models: Pharmacologic Rescue

NR1-/- Mice

Baseline

Acute MK-801

Stimulus-Evoked

Normalized γ Power

Δγ Power (dB)

γ Phase Locking

Δγ Phase Locking

Baclofen (mg/kg)

Baclofen (mg/kg) + MK801 (0.7 mg/kg)

0 5

0 0.5 2.5

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Steven J. Siegel, M.D., Ph.D.
Schizophrenia Models: Pharmacologic Rescue

**L-838,417**: selective GABA\(_A\) \(\alpha\)-2,3,5 receptor agonist

- Antagonist at \(\alpha\)-1 subunit which mediates sedative, tolerance building, adverse cognitive effects of benzodiazepines
- Assessed effects on gamma power and working memory in recent clinical trial of schizophrenia (Lewis DA, *Am J Psych* 2008)
NR1-/-

MK801

Translational Neuroscience Program

Gamma Power (dB)

Time (s)

Baseline Sensory Evoked

Steven J. Siegel, M.D., Ph.D.
NR1-/-
  + Baclofen
MK801
  + Baclofen

Gamma Power (dB)

Time (s)

Baseline Sensory Evoked

Steven J. Siegel, M.D., Ph.D.
GABA\(_B\) and Schizophrenia

- GABA\(_B\)-receptors down regulated in HC, temporal cortex, PFC in schizophrenia (Ishikawa M, 2005)
- GABA\(_B\) signaling reduced in schizophrenia (Daskalakis, Z. J., 2008)
- Baclofen reverses PPI deficits caused by acute MK-801, PCP, & amphetamine (Fejkin K, 2009; Arai S, 2008), &NMDAR1 hypomorphism
- Baclofen reverses object recognition deficits induced by chronic amphetamine (Arai S, 2009)
- Baclofen evaluated for positive symptoms in 1970s - negative clinical trail (Bigelow, L. B., 1977)
- AR-Baclofen (Seaside therapeutics) currently in clinical trails for autism.

↓ PFC GABA\(_B\) expression in Schizophrenia (Ishikawa M, 2005)

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Cortical Dysfunction in Schizophrenia

Pathogenesis
↓ NMDA-R Signaling
↓ PV+ Interneurons

Neurophysiology
Reduced Gamma Power, PLF

Clinical Syndrome
Deficits in cognitive, sensory functioning

GABA_B Agonist

Treatment

??

Steven J. Siegel, M.D., Ph.D.
Gamma Deficits: Functional Implications

Treatment Biomarkers
- Prepulse inhibition of startle
- Locomotor activity

Negative Symptoms
- Social Interaction
- Working memory – T-maze

Steven J. Siegel, M.D., Ph.D.
**Translational Neuroscience Program**

**Previous Post Docs:**
Jenny Phillips, Ph.D.
Tobias Halene, M.D., Ph.D.

**Previous Students:**
Jonathan Kahn
Danielle Trief
Sonalee Majumdar
Michelle Mergenthal
Jennifer Fleisher
Jonathan Abelson
Jack Kent
Danit Mayor
Karen Rudo
Josh Stillman
Julia Glasser
William Beckerman
Neal Ghandi
Rachel Klein
Suzanne Wilson
Omid Motobar
Cara Rabin
Jon Talmud
Steve Luminaise
Julie Sisti
Christina Bodarky
Kerstin Klook
Catherine Jutzeler
Sarah Doherty
Eric Chu
Randal Toy
Viral Gandhi
Karen Ryall
Jing-Yuan Ma
Joe Crisanti
Stephen McKenna
Amar Bains
Xavier Readus
Lillia Rodriguez
Jennifer Croner
Rachel Rosenberg
James Wang
Mia Wang
Marcella Chung
Kimia Pourrezaei
Victoria Behrend
Philip Santoiemma
Stefanie Fazio
Dheepa Sekar
Yufei Cao
Tony Thieu

**Previous Staff:**
Mary Dankert
Farzin Irani
Christina Maxwell
Kayla Metzger
Patrick Connolly
Breanne Weightman
Wendy Zhang
Debbie Ikeda
Jake Burnbaum.
Chalon Majewski-Tiedeken.
Noam Rudnick
Richard Ehrlichman
Laura Amann
Brianna Weightman

**Collaborators**

**Basic:**
Steve Arnold, Konrad Talbot
Chang-Gyu Hahn, Greg Carlson
Ted Abel, Diego Contreras
Julie Blendy, Ted Brodkin
Lief Finkel, M. Lazarewicz

**Clinical:**
Neuropsychiatry: Raquel Gur,
Ruben Gur, Bruce Turetsky

TTURC: Caryn Lerman, Andrew Strasser

CAR/CHOP : Tim Roberts & Chris Edger

**Steven J. Siegel, M.D., Ph.D.**