

**Neurobiology of HIV, Psychiatric and Substance Abuse Comorbidity
December 1-2, 2005, Bethesda, MD**

Overviews: Keynote addresses

Welcome by NIH (Kathy Kopnisky & Woody Lin)

NeuroAIDS and psychiatry - Igor Grant

Substance abuse and HIV interactions: Behavior to genetics - M.J. Kreek

Genetic Epidemiology: Chair - Ming Tsuang

Genotype effects on behavior through intermediate phenotype - David Goldman

Immunogenetics of viral infection - Pat Martin

The genetics of substance abuse disorders - Joel Gelertner

Neurobiological Factor: Chair - Steven Douglas

Dopamine and SIV replication, brain cytokine production and SIV encephalitis - Eleni Koutsilieri

Dopamine systems: toxic HIV proteins and cocaine - Rosemarie Booze

HIV, MDD and candidate neurobiological factors - Iain Everall

Substance P and HIV infection - Steven Douglas

Relationship between genotype, neurochemistry, behavior and disease progression - John Capitanio

Neural influence (ANS) on HIV - Steve W. Cole

Inflammation, the Brain and Psychiatric Disease: Chair - Keith Kelley

Overview: Cytokines as players in neuroimmune communication pathways - Keith W. Kelley

Cytokine-induced depression in humans: Clinical and pathophysiological correlates - Andrew Miller

The issue of comorbidity: Do depression and NeuroAIDS share similar pathogenic mechanisms? - Robert Dantzer

Brain pro-inflammatory cytokines and memory: Implications for HIV-associated cognitive impairment
Steve Maier

How do stress and inflammation interact to increase the risk for neuropsychiatric disorders? - Hymie Anisman

Impact of drugs of abuse on the microgliopathy of HIV - Phil Peterson

Molecular mechanisms of depression and addiction: Are there implications for HIV comorbidity research? Bill Carlezon

Day 2

Inflammation and pathogenesis in the Brain: Chair - Avindra Nath

SIV neuropathogenesis and inflammatory markers - Janice Clements

Stages of neuroAIDS: The consequences of chronic infection - Howard Fox

Role of chemokine CCL-2 in neuropathogenesis of HIV infection - Joan Berman

BDV mice, serotonergic neurotransmission and behavior - Mikhail Pletnikov

Social & restraint stress and animal models of viral infection - John Sheridan

Microglial activation and drug induced neurotoxicity: Nexus between HIV and methamphetamine-induced neuronal damage - Donald Kuhn

Methamphetamine- and HIV-1 tat-induced mitochondrial dysfunction - William Maragos

Opiate drugs and HIV neuropathogenesis: A central role of astroglia - Kurt Hauser

Effect of drugs of abuse on HIV replication and dissemination - Avindra Nath

Neuro-Assessment & Treatment: Chair – Jack Gorman

Neuroassessment-HIV and psychiatric/substance disorders - Jack Gorman

HAART, opiate abuse, and HIV-associated brain damage - Jeanne Bell

Detecting brain inflammation and damage with neuroimaging - Terry Jernigan

Limits of genetics association analysis – George W. Nelson

Dr. Yu “Woody” Lin at NIDA and Dr. Kathy Kopnisky at NIMH co-organized a 1.5 days workshop entitled “The Neurobiology of HIV, Psychiatric and Substance Abuse Comorbidity” on December 1 and 2, 2005. This workshop featured presentation by scientists from multiple disciplines on potential mechanisms underlying neural dysfunction associated with HIV/psychiatric/substance abuse comorbidity. The workshop revealed that:

- Neuroinflammation, characterized by microglia activation and the consequent unregulated release of pro-inflammatory molecules, was commonly triggered by multiple insults, including HIV and stressors (addictive drugs and social stress) that were accompanied by psychiatric disorders.
- The combination of methamphetamine use and HIV infection had a synergistic deleterious effect on the brain.
- In HIV-infected persons and in SIV-infected animals, morphological and functional changes were evident in the mesolimbic dopaminergic system as well as in the amygdala. These results linked both pathological causes and psychological factors to the depressive disorders in individuals with HIV/AIDS. Presented data suggested that treatments that increased dopamine release enhanced the signs of neurotoxicity.
- The concept of sickness behavior was introduced. This refers to the constellation of clinical symptoms that were commonly seen in patients who suffered from chronic stress, which included inflammatory reactions, psychiatric illness and/or a drug withdrawal syndrome. It is closely associated with unregulated production of the pro-inflammatory cytokines in the brain and may precipitate depression in vulnerable individuals.
- Neuroinflammation during the transition phase from sickness behavior to depressive behavior might compromise endogenous neuroprotection, sensitize the brain to further stress, including exposure to abused drugs, and functionally and structurally alter neuronal circuits associated with psychiatric disorders. Therefore, neuroinflammation might serve as a marker for early detection (and subsequent control) of HIV-associated neural dysfunction.
- The identification of regional pathology within the brain and its temporal course emerged as an important area needing more research.
- Participants agreed that the development and utilization of appropriate models were critical. Both *in vitro* and *in vivo* studies are important, as are studies using banked human tissues.
- There is also a need to develop better therapeutic approaches for the comorbid psychiatric disease in HIV-positive persons.

Meeting participants recommended that, in order to move the field forward, next steps in research should be targeted toward addressing the following issues or answering the following questions:

1. HIV-related cognitive impairment can be fluctuating. How can this be explained?
2. Who is vulnerable to cognitive impairment in the context of HIV infection? What is the influence of host genetics? Are there genetic markers that reflect this vulnerability? How do other host factors such as sex, race/ethnicity, age, geography, stress, past psychiatric history, and medications influence the development and evolution of HIV-related cognitive impairment?
3. Who is vulnerable to mood disorders in the context of HIV infection? What is the influence of host genetics? Are there genetic markers that reflect this vulnerability? How do other host factors such as sex, race/ethnicity, age, geography, stress, past psychiatric history, and medications influence the development and evolution of mood disorders?

4. Can we identify behavioral “endophenotypes” for studies of genetic vulnerability? Is it possible to model components of depression in animals?
5. How do we get from clinical phenotypes to genes and mechanisms?
6. How do we uncover the molecular mechanisms responsible for various behaviors?
7. How do the various above-mentioned factors effect the expression of psychiatric symptoms in HIV?
8. How do specific drugs of abuse modulate neuroinflammation?
9. How do different types of stress modulate neuroinflammation?
10. Neurofibrillary tangles are found in the brains of drug abusers, primarily opiate abusers, even those dying at a young age. How many and what kind of tangles are these and how do they compare to the neurofibrillary tangles found in dementia and other forms of neuropathology?
11. Hepatitis C and other infections seem to be factors in explaining which HIV-infected patients get neurocognitive impairment and depression. What mechanisms are involved?
12. HIV-related neurocognitive impairment has rekindled interest in studying the relationship between infection and genetics. More work should be done in this area. First we should ascertain whether there are any new population samples or other databases that would be useful in examining the relationship between infection and genetics.
13. Pharmacodynamics, pharmacogenetics, and pharmacogenomics are important areas for further study because they will provide guidance for the development of appropriate pharmacotherapy.
14. Metabolomics, proteomics and other research into small molecules must be encouraged as well.
15. Glial activation imaging is very exciting and looks very promising. How can this technology be applied to answering our research questions?
16. More research is needed on the HIV virus in terms of virus-cell interactions.
17. More research is needed on specific cytokines and chemokines and their relevant receptors in the various regions of the brain.
18. More research is needed on adhesion molecules in the CNS, and effects on the blood-brain barrier.
19. Parallel studies need to be conducted in the systemic immune system and the brain immune system with neuropathology factored in as well.

20. The introduction of Highly Active Anti-Retroviral Therapy (HAART) has introduced changes in the manifestations and evolution of HIV-related cognitive impairment. Studies comparing tissues and/or patients from the pre-HAART era with patients and/or tissues of patients who have received HAART would be very informative.
21. Further research looking at early, mid, and late phases of CNS HIV infection in animal models is needed.