



# Psychiatry

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## POSTGRADUATE EDUCATION NEWSLETTER

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### UPCOMING 2002 COURSES

Upcoming continuing education courses in the year 2002, offered by the Department of psychiatry at the Massachusetts General Hospital, are as follows:

#### **Psychiatry: A Comprehensive Update and Board Preparation**

Monday-Saturday, September 9-14, 2002  
The Westin Hotel, Copley Place, Boston

#### **Psychopharmacology**

Friday-Sunday, October 11-13, 2002  
The Westin Hotel, Copley Place, Boston

#### **Understanding and Treating Aggressive, Noncompliant and Delinquent Youths**

Thursday-Saturday, November 14-16, 2002  
The Fairmont Copley Plaza Hotel, Boston

#### **Home Study on Audio Cassettes: Child and Adolescent Psychopharmacology**

### FOR MORE INFORMATION:

For information about this and other courses presented by the Department of Psychiatry at MGH, please visit our web site, call, write, or email our administrative staff, at:

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Postgraduate education newsletter

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## Psychiatric Neuroscience: A Primer for Clinicians

June 20-22, 2002

### COURSE DIRECTORS:

Jerrold F. Rosenbaum, M.D., Scott L. Rauch, M.D., Stephen Heckers, M.D., John B. Herman, M.D.

### COURSE ADMINISTRATIVE STAFF:

Gail E. Dickson, M.P.A., Stephanie Lipka Hackett., Arlene Lietz, Katherine Pike, M.S.W and Susan Kepnes Rosenwasser, M.Ed

The Massachusetts General Hospital's Department of Psychiatry, headed by Dr. Jerrold F. Rosenbaum, presented this state-of-the-art course on Psychiatric Neuroscience. This course was carefully designed for clinicians in practice that were eager to remain abreast of the cutting edge of our field. More than ever, we chose faculty whose attention to crystal clear teaching conveyed the excitement sweeping across the frontiers of psychiatry.

Keeping apace of this progress requires that clinicians equip themselves with a new vocabulary, knowledge of new research tools, and the most up-to-date concepts regarding the elegant workings of the human nervous system. Plain-talking lecturers guided course participants to an understanding of neurotransmitter systems, neuroreceptor mechanisms, genetics, functional neuroanatomy, neuroimaging technology, and integrated models of specific psychiatric diseases (e.g., schizophrenia, major depression, substance use disorders, and Alzheimer's disease).

Each of the approximately 400 attendees of this three-day continuing education course (held at the Westin Hotel, Copley Place, Boston, MA, 02116) received a comprehensive course syllabus. Continuing Education certificates were provided for physicians, psychologists, social workers, and nurses who attended this course.



Here are some facts from the Massachusetts General Hospital's "Psychiatric Neuroscience: A Primer for Clinicians" Course:

### NEUROANATOMY: CELLS AND CIRCUITS

Stephan Heckers, M.D.

Dr. Stephan Heckers presented a remarkable review of the functional neuroanatomy of the brain and provided a framework of how to understand the neural basis of abnormal behavior. The presentation enabled an informed discussion of functional localization. The architecture of the cortex, as well as the structure and function of several neuroreceptor systems (dopaminergic, noradrenergic, glutamatergic, GABAergic) were reviewed. Several important points included:

- Information processing in the brain includes the reception of sensory information, the creation of an internal representation, and a response based on the evaluation of the mental representation.
- The anatomical structures involved in these three steps are the thalamus, the cortex, the medial temporal lobe, and the basal ganglia.
- Neurochemical systems that allow fast information processing include the glutamatergic and GABAergic systems.
- Several neurochemical systems (dopaminergic, serotonergic, cholinergic) can modulate the efficiency of information processing in the thalamus, cortex, medial temporal lobe, and basal ganglia.
- Technologies that allow us to study the neural correlates of abnormal mental states include neuroimaging, post-mortem studies, and molecular studies.

### BEHAVIORAL PARADIGMS: FROM RODENTS TO MAN

Neal R. Swerdlow, M.D., Ph.D.

Dr. Swerdlow delivered an elegant discussion of behavioral paradigms and animal models. He reviewed the concepts of face validity, predictive validity, and construct validity and described how investigators can use drugs to understand behavior and the brain. Examples of behavioral paradigms were used to highlight the principles of behavioral genetics. Specific points from his presentation included:

- Face validity, the "lowest" level of validity, is achieved when there is phenomenological similarity between the model and the clinical condition.
- Predictive validity is achieved if predictions made by the model can be validated in the human condition being modeled.
- To demonstrate construct validity, the theoretical rationale behind the model must be consistent with what is known about the "psychopathological construct" of the disorder in humans.
- By selecting appropriate drugs and behavioral assays, it is often possible to draw conclusions about more complex aspects of CNS organization.
- Most complex behavioral paradigms do not measure the identical phenomenon across species.
- A variety of behavioral paradigms are used in behavioral pharmacology. These include unconditioned (e.g., catalepsy, emesis, immobility), conditioned (e.g., extinction, lever release tasks), and classical conditioning (e.g., taste aversion, conditioned fear, maze learning tasks) responses.

### ALZHEIMER'S DISEASE

Marilyn Albert, Ph.D.

Dr. Albert presented an elegant and comprehensive review of the major research findings in Alzheimer's Disease. She reported on the neuropathology of neurofibrillary tangles, neuritic plaques, and decreases in acetylcholine. She also described the currently accepted procedures for diagnosis and treatment (including cholinesterase inhibition). She outlined the neurobiological changes found in Alzheimer's Disease (including genetic factors) and introduced current hypotheses regarding the cause of the disease, the potential relationship to treatment, and the relationship to cognitive changes in afflicted individuals. Several important facts were highlighted:

- The prevalence of Alzheimer's Disease in people over the age of 85 is estimated between 25% and 50%.
- The estimated cost of AD in the US is \$80-\$90 billion/year.
- Several forms of early onset AD (< 60 years of age) have been linked to mutations (on chromosomes 1, 14, and 22).



- Most AD patients suffer from a sporadic form with late onset. One risk factor for this form of AD is the APOE4 allele (increases risk at least 4 fold).
- The processing of the amyloid precursor protein by enzymes called secretases is a target for drug development.
- Neuroimaging may be used in the future for the early detection of AD.

### NEUROPHARMACOLOGY OF THE SEROTONERGIC SYSTEM: DISEASES AND TREATMENTS

Pierre Blier, M.D., Ph.D.

Dr. Blier provided a series of graphs and schematics to illustrate and highlight the neuroanatomic and neurochemical basis for the therapeutic effects of antidepressant medications. He reviewed the efficacy of antidepressants in patients with major depression, panic disorder, and OCD and correlated these results with our knowledge of neurotransmitters and their receptors. Several important facts were reviewed:

- Antidepressants act primarily on the serotonergic and the noradrenergic systems.
- Antidepressants act on postsynaptic receptors, presynaptic receptors, and reuptake transporter proteins.
- The differential response of several receptors (e.g., 5HT1a and 5HT1b) may explain the onset and duration of antidepressant drug effects.
- Long-term administration of selective serotonin reuptake inhibitors leads to structural and functional changes of the serotonergic neuron.

### NEUROIMAGING

Scott L. Rauch, M.D.

Dr. Rauch presented data from a variety of neuroimaging techniques performed on patients with Obsessive-Compulsive Disorder [OCD] to highlight our knowledge of the cortico-striato-thalamo-cortical circuitry in this illness. His review of psychiatric neuroimaging included:

- Neuroimaging techniques to assess structure (e.g., regional volumes with morphometric magnetic resonance imaging [mMRI]) have provided several interest-

ing findings about structural abnormalities in psychiatric disorders.

- Studies of brain function (e.g., metabolism with fluorodeoxyglucose positron emission tomography [FDG-PET]; blood flow with single photon emission computed tomography [SPECT], PET-O15, and functional MRI [fMRI]) have pinpointed specific circuits involved in the pathogenesis of disorders such as schizophrenia, depression, and OCD.
- Studies of brain chemistry and pharmacology (e.g., via receptor studies [using PET and SPECT] and via the study of chemical compounds using magnetic resonance spectroscopy [MRS]) have provided insight into the cellular basis of psychiatric disorders in the living human brain.

### THE COGNITIVE NEUROSCIENCE OF HUMAN MEMORY

Daniel Schacter, Ph.D.

Dr. Schacter provided a review of several research methods used by cognitive neuroscientists to study the neural correlates of mental states and cognitive processes. Using the study of processing systems (such as language) as an example, he reviewed how PET, fMRI, and optical imaging can deepen our understanding of the brain. Possible applications to psychiatry were also presented.

Dr. Schacter's review included:

- The contributions of cognitive psychology (with cognitive and behavioral theories) to the understanding of human cognition and behavior.
- The role of neuroscience (e.g., neuroanatomy and neurophysiology) in the study of cognitive processes.
- The power of computer science (e.g., computational analyses and computer models) for the understanding of cognition.



### **GENETIC MODELS FOR MAJOR PSYCHIATRIC DISORDERS: INSIGHTS FROM GENETICALLY ENGINEERED MICE**

Schahram Akbarian, M.D., Ph.D.

Dr. Akbarian eloquently discussed several candidate genes for major psychiatric diseases and described how one identifies and tests for candidate molecules for novel psychopharmacological approaches. Moreover, the principles of using genetically engineered mice, so-called "knock-out" mice were also reviewed. Case examples, such as the creation of nerve growth factor molecules, were used to highlight the principles discussed. Interesting experiments with application to psychiatry included:

- A gene deletion of MAO-A will result in aggression
- A gene deletion of the 5-HT1A receptor will lead to fear
- A gene deletion for dopamine reuptake will lead to hyperactivity.

### **NEUROIMAGING**

Randy L. Gollub, M.D., Ph.D. and Darin Dougherty, M.D.

Drs. Gollub and Dougherty teamed up to discuss the current and future uses of functional neuroimaging in psychiatry. They described how PET and fMRI measure brain activity indirectly, and can provide unprecedented spatial and temporal resolution. Highlighted facts from their presentation included:

- The physiological basis of the fMRI blood oxygen level-dependent signal depends on changes in neuronal activity, which are associated with local changes in energy metabolism (glucose and oxygen consumption).
- fMRI is being used for pre-surgical mapping, and for assessments of pain perception and cognitive deficits in schizophrenia.
- Positron emission tomography (PET) scanners have a ring of radiation detectors that detect simultaneously emitted photons; this information is registered by a computer to reconstruct images.
- PET scans offer sufficient spatial resolution (4-8 mm) to allow for measurement of metabolism, absolute quantification of blood flow, and receptor characterization.

- SPECT (single photon emission computed tomography) detects gamma rays, and allows blood flow studies and receptor characterization to be completed.
- SPECT is far more economical than PET, since it does not require use of a cyclotron.

### **GENOMICS AND PSYCHIATRY: INSIGHTS FROM EXPRESSION PROFILING AND HAPLOTYPE MAPPING**

Pamela Sklar, M.D., Ph.D.

Dr. Sklar treated attendees of her presentation to an outstanding overview of the state-of-the-art in new techniques (e.g., microarrays, expression profiling, and linkage disequilibrium mapping) in the neurosciences. She highlighted her presentation with examples of how these techniques are being applied to the identification of genetic abnormalities that predispose to clinical syndromes and suggested ways in which new treatments may be developed to minimize the disruption that these conditions cause. Facts offered by Dr. Sklar included:

- Microarrays can monitor the expression of thousands of genes, can be used to correlate gene expression with cellular physiology, and can classify tumor types and their progression..
- Expression profiling may demonstrate how myelin-related (and other genes) are down-regulated (or up-regulated).
- Linkage mapping in human families is difficult for complex diseases due to incomplete penetrance, multiple gene involvement, and a small number of informative family members.
- Large samples of patients with either bipolar disorder or schizophrenia have demonstrated evidence of genetic linkage.



## GENETIC EPIDEMIOLOGY

Jordan Smoller, M.D., M.S. and Deborah Blacker, M.D., Sc.D.

Drs. Smoller and Blacker joined forces to provide an overview of the genetics of mental disorders; they used the genetics of Alzheimer's disease as a model for how genetics of these disorders can be understood. They cogently described how studies rely on clinical epidemiology, genetic epidemiology, and linkage and association data, to educate us about clinical implications. Highlighted principles and facts from their presentation included:

- The prevalence of a disorder is the total proportion of cases in a population.
- The incidence is based on the number of new cases in a given time period.
- Family studies compare rates of a disorder in index cases (proband) with population rates, or rates in relatives of controls.
- Family studies are useful for establishing that a disorder is familial, but cannot establish that it is genetic.
- Diseases with Mendelian inheritance patterns are good candidates for linkage analyses.
- Trinucleotide repeats can predict the onset and severity of a neuropsychiatric illness.
- Complex disorders (such as the major psychiatric diseases) can be studied with affected sib pair studies and population association studies.
- Twin studies compare the concordance (i.e., both members of the twin pair having the disorder) rates of a given disorder in monozygotic and dizygotic twins.
- Adoption studies can disentangle genetic and environmental influences on why a disorder might run in families by comparing rates of a disorder in biological family members to those in adoptive family members.
- Genetic linkage studies are based on the association of particular alleles (variable forms of a gene) with a disease within families.
- Association studies are based on the association of particular genetic variants with a disease across families, or individuals. In general they are used to test for a role of candidate genes.

- For schizophrenia, there is a 10-fold increase in risk in first-degree relatives compared to the general population.
- ADHD runs in families; moreover, adoption studies have demonstrated that the risk of ADHD is higher among biological than among adoptive relatives of ADHD children.
- Concordance rates for monozygotic twins are markedly higher than those of dizygotic twins for autism.
- Family studies have consistently demonstrated familial transmission of bipolar disorder.

## FUNCTION OF THE FRONTAL LOBES

Cary R. Savage, Ph.D.

The frontal lobes are involved in many higher order cognitive functions. Dr. Savage presented a comprehensive review of the executive functions of this brain region. He described several psychological and neuroimaging experiments in normal subjects and patients with OCD to understand the role of the frontal lobes in memory. Dr. Savage provided several important facts about the frontal lobes:

- Executive functions are necessary to appreciate environmental context, make plans, implement strategic action, and monitor behavior.
- Typical tests of frontal lobe function that inform about executive function are the Wisconsin Card Sorting Test, tests of attention, and working memory tests.
- Frontal lobe deficits lead to memory problems that involve primarily strategic aspects.
- Patients with OCD show impaired organizational strategies when solving memory tasks.
- The orbitofrontal cortex is involved in making decisions in ambiguous learning situations.



### **ANTERIOR CINGULATE CORTEX: FROM ATTENTION TO EMOTION**

George Bush, M.D., M.M.Sc.

A brain region involved in both cognitive and affective/emotional processes is the anterior cingulate (AC) gyrus. Dr. Bush reviewed the literature and provided a succinct review of the field. He presented several of his own studies that have elucidated the role of the anterior cingulate gyrus in normal brain function and in psychiatric disorders. Several points of interest were:

- The anatomy of the anterior cingulate gyrus in the human brain is complex.
- The AC cortex can be subdivided into an anterior sector associated with limbic functions and a posterior sector associated with cognitive function.
- The anterior cingulate cortex is involved in the error detection.
- Depression has been associated with abnormalities in the anterior sector of the AC cortex.
- ADHD has been associated with abnormalities in the posterior sector of the AC cortex.

### **AMYGDALA, AMBIGUITY AND ANXIETY**

Paul J. Whalen, Ph.D.

The amygdala is a small brain structure in the medial temporal lobe. Despite its small size, it provides widespread modulation of several other brain regions, including the cortex. In a very lively demonstration of the importance of the amygdala for normal brain function, Dr. Whalen presented results of his research on the role of the amygdala in resolving ambiguous learning situations. Dr. Whalen noted that:

- The amygdala is recruited during several neuroimaging experiments that involve the recognition of faces.
- The amygdala is particularly sensitive towards the recognition of fearful stimuli.
- The function of the amygdala is to detect and learn about the predictive nature of biologically relevant stimuli. These stimuli often produce emotional responses, including fear.
- Several anxiety disorders are most likely associated with abnormal amygdala function.

### **UNDERSTANDING FRONTO-TEMPORAL INTERACTIONS: THE EXAMPLE OF PTSD**

Lisa Shin, Ph.D.

Dr. Shin's cogent explanation about how PTSD develops and can be assessed served to highlight the role of fronto-temporal interactions in the brain. Focusing on the amygdala, the anterior cingulate cortex, and the hippocampus, she described how the techniques of structural and functional neuroimaging (employing symptom provocation and cognitive activation) can be employed to further our understanding. Facts presented by Dr. Shin included:

- Hippocampal volumes (as measured by structural neuroimaging) are reduced in those with PTSD as compared with controls.
- Word-stem completion recall tasks (for cognitive activation) linked with functional neuroimaging help distinguish those with PTSD from controls.

### **TRANSCRANIAL MAGNETIC STIMULATION (TMS) AND DEEP BRAIN STIMULATION (DBS)**

Benjamin Greenberg, M.D., Ph.D.

Dr. Greenberg cogently reviewed the nature of the experimental techniques involved with transcranial magnetic stimulation (TMS), and discussed how it can be used as both a physiologic and anatomic probe for the study of mental disorders, such as obsessive-compulsive disorder and depression. Points of interest from his presentation included:

- TMS-induced current drops away rapidly with increasing distance from the coil on the scalp.
- Compulsive urges diminished for 8 hours after application of TMS to those with OCD.
- RTMS appears to have antidepressant effects, even in those with treatment-refractory depression.
- The site, frequency, intensity, and total dose (individualized for brain-scalp distance) still needs to be determined for TMS.



## SEX DIFFERENCES IN THE BRAIN

Jill Goldstein, Ph.D.

The brain develops differently in women and men. This is important for our understanding of psychiatric disorders. Dr. Goldstein reviewed the basic science and clinical implications of sex differences in the human brain. Dr. Goldstein reported that:

- Some psychiatric disorders are more prevalent in boys (e.g., conduct disorder, ADHD, Tourette's disorder, mental retardation, autism); others are more prevalent in girls (e.g., anorexia nervosa, bulimia nervosa, separation anxiety).
- The organizational and activational effects of sex steroid hormones during critical periods of development are likely mechanisms for this sex difference.
- The pace and timing of changes in postnatal brain development differ between the females and males.
- These sex differences have clinical implications, e.g., for the onset and expression of disorders, the role of cognitive rehabilitation, and psychopharmacological treatment.
- Pre-treatment with estradiol and progestin has been found to prevent excitotoxic and oxidative stress injury in hippocampus neurons in animals.
- Pre-menopausal women recover sooner and have less cognitive impairment from stroke than do men.

## SCHIZOPHRENIA

Stephan Heckers, M.D.

Dr. Stephan Heckers described the neural circuitry associated with schizophrenia and reviewed the results of anatomical and functional studies. Dr. Heckers' review of schizophrenia and the brain highlighted these findings:

- The structure of the dorsolateral prefrontal cortex is disturbed: neurons are displaced and the density of cells is abnormal. At the molecular level there are changes of the D1 receptors and the expression of GAD 67 mRNA.
- The function of the dorsolateral prefrontal cortex is abnormal, especially during the performance of working memory tasks.

- In the thalamus there is neuronal loss and a decrease in volume. Recent studies have linked thalamic pathology in schizophrenia to abnormal memory function.
- In the medial temporal lobe there is a loss of hippocampal volume but no marked loss of neurons. The GABAA and glutamate receptors are abnormal, and there is abnormal brain activity at rest and during the performance of memory tasks.
- Basal ganglia volume is increased, most likely as a result of treatment with neuroleptic drugs.
- Dopamine release is increased, primarily in patients with acute exacerbation of psychotic symptoms.

## SUBSTANCE USE DISORDERS

Scott E. Lukas, Ph.D.

Dr. Lukas reviewed the diagnostic criteria for a variety of substance use disorders and outlined current treatment strategies. Theories thought to explain the genesis and maintenance of these disorders were presented, and the neurobiology of reward was discussed. Dr. Lukas clarified the following issues:

- The terminology of substance abuse, addiction, habituation, and dependence.
- The cycle of substance abuse (antecedents, liability, dependence potential, and consequences).
- Current theories of substance abuse (classical conditioning, operant conditioning, social learning, biological theories).
- The neurobiology of reward (limbic system, nucleus accumbens, dopamine system).
- Recent fMRI studies have provided evidence for the activation of the reward circuitry in the human brain during the exposure to drug related cues.
- The notion that treatment does not work is a myth which has been proven wrong with elegant clinical studies.
- Nicotine is reinforcing and tobacco use can lead to dependence.



## MAJOR DEPRESSIVE DISORDERS

Helen S. Mayberg, M.D., FRCPC

Dr. Mayberg deftly handled a discussion of mood disturbances. She provided an historical perspective on the localization of mood, on lesion deficit studies, and on neurological disease models. She then described results of experimental strategies (involving neuroanatomy, neurochemistry, and neurophysiology) that encompassed fMRI, SPECT, PET, behavioral challenges, and treatment paradigms. Dr. Mayberg noted that:

- Lesions in several areas of the brain can lead to depression.
- Stroke is often associated with depression.
- Other neurological conditions that are often associated with depression include Parkinson's Disease and Huntington's Disease.
- Neuroimaging can be used to study the time course of brain changes associated with depression in neurological patients.
- The time course and treatment specific effects of antidepressants can be studied with neuroimaging studies.
- Depression is associated with limbic-cortical dysregulation, involving primarily the anterior (i.e., rostral) sector of the cingulate gyrus.

## CONTEMPORARY GENETIC METHODS FOR STUDYING DEVELOPMENTAL NEUROPSYCHIATRIC DISORDERS

David Pauls, Ph.D.

Dr. Pauls presented a dynamic presentation on contemporary genetic methods for studying developmental neuropsychiatric disorders. He identified terms used in the field, and reviewed strategies for how one studies a variety of conditions (such as dyslexia, OCD, and Tourette's syndrome). He also reviewed the principles of genetic linkage studies. Additional points raised by Dr. Pauls included:

- Neurodevelopmental studies depend in part on identification of the phenotype of a condition, on accurate diagnostic criteria, on the familial nature of a disorder (including the risk of the disorder in first-degree relatives and on the results of twin studies), and on association studies.
- Genes confer a risk for the expression of psychiatric diseases.
- The goals of gene discovery include understanding the pathogenesis of mental disorders, the establishment of epidemiological linkages, the promotion of novel targets for therapies, and provision of assistance in decision-making.



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