

## Clinical Psychobiology

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### Overview

This department focuses on the use of imaging, combined with clinical, genetic and cognitive assessments to study the pathophysiology of schizophrenia, alcoholism and related mental illnesses in order to develop biomarkers for early diagnosis, subgroup characterization and to better guide treatment including new drug development. Dr Abi-Dargham became Chief of the Division of Functional Brain Mapping in January 2006 and assumed the responsibility of providing imaging services to other researchers within the Institute, for example for the study of anxiety disorders with Blair Simpson and Frank Schneier, and to collaborators in Mt Sinai who study autism and personality disorders (Hollander and Seiver).

### Current Research

#### *Pathophysiology Research*

**Cortical D1 Imaging:** We discovered that the available D1 tracers [11C]SCH23390 and [11C]NNC112 are not selective in the cortex for D1 versus 5HT2A receptors both in non human and human primates. We will need a more selective tracer to continue the investigation of D1 transmission as a marker of dopamine tone in the cortex.

**Striatal and extrastriatal D2 function:** studies with the high affinity [18F]fallypride tracer combined with the amphetamine challenge will begin in patients with schizophrenia to assess the status of dopamine release in extrastriatal regions in schizophrenia and replicate the findings within the substructures of the striatum. We are also assessing with microdialysis in monkeys the correspondence between the PET measured DA release and actual intrasynaptic increase.

[18F]Fdopa studies in prodromal patients in collaboration with Cheryl Corcoran and the COPE clinic have started. The study will involve longitudinal follow-up of prodromal patients to assess whether high [18F]fdopa uptake in the striatum is an indicator of who will convert to schizophrenia.

#### *Treatment Research*

Atomoxetine challenge in patients with schizophrenia and controls with COMT val/val alleles and cognitive testing is underway to test the effects of NET inhibition on improving cortical dopamine transmission and related cognitive functions.

Preparations for the D1 agonist clinical trial funded by NIMH (PI: J. Lieberman) is underway. IND application has been submitted and is currently under review. This will provide a proof of concept for cognitive enhancement in schizophrenia with subacute administration of a D1 agonist. PET occupancy will be measured. Initial experiments in monkeys showed an effect on D1 binding of different doses of the same drug.

#### *MRS Research*

Completed study: "Evaluation of anatomic variation in macromolecule contribution to the GABA signal using metabolite nulling and the J-editing technique at 3.0 T", submitted for presentation to ISMRM annual meeting. This MRS study examined the well-known phenomenon of contamination of GABA signal by macromolecules, and evaluated its magnitude and anatomic variability on the GE 3T system. The study showed that while both GABA and macromolecule signal have significant anatomic variability, the percent contribution is stable anatomically and was determined by this study. This will provide a correction factor

for ongoing and future clinical studies using these methods.

### *Alcoholism Research*

As PI on a project within the Center for Translational Neuroscience of Alcoholism (CTNA) we will study alcohol induced dopamine release in ventral striatum of at risk family positive young healthy controls matched with family history negative subjects matched for drinking. This is a first step in investigating whether low D2 stimulation is a vulnerability factor in alcoholism.

### **New Funding:**

Dana Foundation, Jan. 2006, PI L. Kegeles: Title: "Mapping abnormal excitatory and inhibitory neurochemical circuitry in schizophrenia with rTMS and MRS". This study aims to use high-field MR spectroscopy to measure GABA and glutamate in the prefrontal cortex and striatum with the goals of finding their correlations with rTMS interventions and finding abnormalities in these transmitter systems in schizophrenia.

GSK contract: PI: Mark Slifstein PHD, pharmacological evaluation of new compounds in non-human primates.

NIMH: R01 to Blair Simpson to study serotonin transmission in OCD.

### **Awards/Honors**

Please list awards, honors, and recognitions received by faculty and trainees in your department during the Fiscal Year 05/06.

Abi-Dargham became Vice President Elect of the Brain Imaging Council of the Society for Nuclear Medicine.

Abi-Dargham will be the new Field Editor for Brain Imaging for Neuropsychopharmacology, the official ACNP journal.

### **Publications**

Martinez D, Gil R, Slifstein M, Hwang DR, Huang Y, Perez A, Kegeles L, Talbot P, Evans S, Krystal J, Laruelle M, Abi-Dargham A. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry*. 2005 Nov 15;58(10):779-86. Epub 2005 Jul 14.

Frankle WG, Lombardo I, Kegeles LS, Slifstein M, Martin JH, Huang Y, Hwang DR, Reich E, Cangianno C, Gil R, Laruelle M, Abi-Dargham A. Serotonin 1A receptor availability in patients with schizophrenia and schizoaffective disorder: a positron emission tomography imaging study with [(11)C]WAY 100635. *Psychopharmacology (Berl)*. 2006 Dec;189(2):155-64. Epub 2006 Sep 5.

Frankle WG, Slifstein M, Gunn RN, Huang Y, Hwang DR, Darr EA, Narendran R, Abi-Dargham A, Laruelle M. Estimation of serotonin transporter parameters with 11C-DASB in healthy humans: reproducibility and comparison of methods. *J Nucl Med*. 2006 May;47(5):815-26.

Slifstein M, Hwang DR, Martinez D, Ekelund J, Huang Y, Hackett E, Abi-Dargham A, Laruelle M. Biodistribution and radiation dosimetry of the dopamine D2 ligand 11C-raclopride determined from human whole-body PET. *J Nucl Med*. 2006 Feb;47(2):313-9.