

Division of Translational Imaging

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Overview

The area of research of the Division of Translational Imaging (DTI) at NYSPI has traditionally been the development of novel tools and techniques to study neurotransmission in the living human brain, and the application of these techniques to clinical studies to unravel chemical imbalances associated with severe mental illnesses, drug addiction and comorbidity, using molecular imaging techniques based on Positron Emission Tomography (PET). In this last year, the Division has taken a major step in enhancing its effort using additional imaging techniques, besides PET, including functional and structural MRI, Magnetic resonance spectroscopy (MRS) and Diffusion Tensor Imaging (DTI), by attracting new investigators with expertise and interest in these areas. The imaging approach has a translational emphasis, using imaging to identify phenotypes that can be tested in animal models or vice versa using models derived from preclinical knowledge to be tested in clinical populations.

Areas of PET research include the development and validation of new radiotracers (organic synthesis, chemical structure-activity relationship, in vitro evaluation, experiments in rodents and primates, dosimetry and toxicology evaluation, filing of IND, phase 1 and 2 studies in humans), as well as development of new imaging paradigms based on pharmacological challenges, cognitive tasks or other paradigms to measure responsivity of neurotransmitter systems.

Clinical investigations within the Division focus on schizophrenia, cannabis dependence and comorbidity with schizophrenia, MDMA dependence, design of paradigms to assess dopamine release in response to alcohol challenge and reward related tasks, identification of biomarkers for disease prevention or drug discovery and aid in drug development. Additionally, the Division performs imaging studies in collaboration with other investigators who specialize in the study of various disorders: anxiety disorders (Dr. Simpson), mood disorders (Dr. Schneier), personality disorders (Dr. Siever from Mt Sinai) and alcoholism (Dr. Krystal from Yale). The Division also collaborates with preclinical researchers within the institution, with Vincent Ferrera and Elisa Konofagu, we are using PET to examine the success of an ultrasound technique in opening the blood brain barrier in non human primates.

The Division also trains fellows in the acquisition of the expertise and skills required for clinical investigation using PET, with focus on pharmacology, neurochemistry, pharmacokinetics, in depth teaching of PET imaging, functional neuroanatomy, kinetic analysis on a region or voxel based approach, as well as general principles of clinical investigation (CGMP, statistics, drafting of IRB protocols).

Current Research

The Division of Translational Imaging (DTI) is the home of the Conte Center on **Dopamine Dysfunction in Schizophrenia** and Dr Anissa Abi-Dargham is the Center's PI and project 1's PI. Dopamine Dysfunction in Schizophrenia will test the central hypothesis that striatal dopaminergic hyperactivity during development leads to prefrontal cortical dopamine dysfunction in schizophrenia and the cognitive deficits that characterize the disorder. Project 1 of the Center (P1) uses a PET scanning paradigm to test whether the capacity for cortical dopamine (DA) release is altered in patients with schizophrenia. Studies with [¹¹C]FLB457 have continued this year at the Yale PET Center.

As the Columbia PET Center has reopened the Division has engaged and completed one PET receptor occupancy study for a new putative antipsychotic, funded by Pierre Fabre pharmaceutical company and is currently preparing for another three occupancy studies, highlighting its prominent role in the field of drug development and characterization of target engagement and dose definition.

Education and Training

New fellows:

Jared Van Snellenberg: Jared is using the self ordered working memory task in humans to test the working memory capacity of individuals undergoing functional magnetic resonance imaging. The goal is to investigate how the human brain shifts activation between networks to support task performance and compare patients with schizophrenia to healthy volunteers. His results in healthy volunteers have been submitted for publication (*paper under review*).
Elisabeth van de Giessen: Visiting from the Netherlands and funded by her own country to spend two years in the Division of Translational Imaging, she has an MD PhD degree, and is learning PET quantification methods.

Tiziano Colibazzi: Tiziana is acquiring a prospective longitudinal data set with multimodal imaging in the prodrome.

Guillermo Horga (to join formally in July 2013): Guillermo is working on model-based fMRI to study sensory prediction-errors within auditory cortex in persons with schizophrenia who report daily auditory visual hallucinations. He showed that predictive-coding deficits account for the resting hyperactivity of the auditory cortex associated with AVH (*paper under review*).

Clifford Cassidy (to join in August 2013), he has a PhD degree from McGill University and funding from Canada, he will study in our Division the use of imaging methodologies.

Honors and Awards

A Abi-Dargham was appointed as a member of the Board of Scientific Advisors to the NIMH Chief (BSC), this appointment is a five-year term.

A Abi-Dargham received funding for an R21 to study internalization of D2 receptors in schizophrenia using PET.

Mark Slifstein received funding from the Huntington Foundation to expand methods to measure glutamate in vivo in non human primates.

Guillermo Horga received a K12 award

Ragy Girgis received a Stanley Foundation Grant to test a treatment for inflammation in schizophrenia

Xu Xiaoyan received a NARSAD young investigator award to study effects of NET inhibition on cortical [¹¹C]FLB457 binding as a new imaging paradigm

Publications (Selected)

Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S: The Nature of Dopamine Dysfunction in Schizophrenia and What This Means for Treatment: Meta-analysis of Imaging Studies. *Arch Gen Psychiatry*. 2012, 69(8):776-86

Judy L. Thompson, Ph.D., Nina Urban, M.D., Mark Slifstein, Ph.D., Xiaoyan Xu, Ph.D., Lawrence S. Kegeles, M.D., Ph.D., Ragy R. Girgis, M.D., Yael Beckerman, M.A., Jill M. Harkavy-Friedman, Ph.D., Roberto Gil, M.D., Anissa Abi-Dargham, M.D.: Blunted Striatal Dopamine Release in Schizophrenia Comorbid with Substance Dependence, *Mol Psychiatry*, Epub 2012

L S. Kegeles, X Mao, A D. Stanford, R Girgis, N Ojeil, X Xu, R Gil, A Abi-Dargham, S H. Lisanby, D C. Shungu: Elevated Prefrontal Cortex γ -Aminobutyric Acid and Glutamate-Glutamine Levels in Schizophrenia Measured In Vivo with Proton Magnetic Resonance Spectroscopy, 2012, *Archives of Gen Psychiatry*. 69(5):449-59.

Girgis RR, Xu X, Miyake N, Easwaramoorthy B, Gunn RN, Rabiner EA, Abi-Dargham A, Slifstein. In Vivo Binding of Antipsychotics to D(3) and D(2) Receptors: A PET Study in Baboons with [(11)C]-(+)-PHNO. *Neuropsychopharmacology*. 36(4):887-95.

Poels EM, Girgis RR, Thompson JL, Slifstein M, Abi-Dargham A. - In vivo binding of the dopamine-1 receptor PET tracers [¹¹C]NNC112 and [¹¹C]SCH23390: a comparison study in individuals with schizophrenia. *Psychopharmacology (Berl)*. 2013

Divisional Highlights

The highlight has been the expansion of the Division in the MR field, with the influx of the following faculty and fellows:

New Faculty:

Alayar Kangarlu, PhD: MR Physics
Zhishun Wang, PhD: Functional MRI, Functional Connectivity
Zhengchao Dong, PhD: MR Spectroscopy
Yunsuo Duan, PhD: MR Coil Development
Liu, Feng, PhD: MR Pulse Sequence Development

New fellows:

Jared Von Snellenberg
Tiziano Colibazzi
Guillermo Horga
Clifford Cassidy

The second highlight is the continued exciting work within the Conte Center for the study of Dopamine Dysfunction in schizophrenia. Initial analyses provide novel data in patients and in mice models of the disease.