

BIOGRAPHICAL SKETCH

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NAME: Lawrence S. Kegeles

eRA COMMONS USER NAME (credential, e.g., agency login): LSK5XX

POSITION TITLE: Professor of Clinical Psychiatry (in Radiology)

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Princeton University, Princeton NJ	A.B.	06/1969	Physics
University of Pennsylvania, Philadelphia PA	Ph.D.	12/1974	Physics
Mount Sinai School of Medicine, New York, NY	M.D.	05/1991	Medicine
Columbia University and the New York State Psychiatric Institute, New York, NY	Residency Training	06/1995	Psychiatry
Columbia University and the New York State Psychiatric Institute, New York, NY	Postdoctoral Fellowship	06/1999	Psychiatry

A. Personal Statement

Dr. Kegeles' lab in the Psychotic Disorders research area at the New York State Psychiatric Institute focuses on neurochemical imaging in psychosis. Dr. Kegeles is Professor of Psychiatry and Radiology at the Columbia University College of Physicians and Surgeons, and Research Scientist and Associate Director for Operations, Area Psychotic Disorders (Dr. Lieberman, Research Director) at the New York State Psychiatric Institute. Dr. Kegeles' work has been funded through grants from NIMH, NARSAD, the Dana Foundation and industry contracts, and has focused on *in vivo* imaging studies of schizophrenia and other psychiatric disorders using MRI/MRS and neuroreceptor methods. He has worked extensively on the glutamate and GABA systems in schizophrenia, OCD, and depression and has used ketamine administration in the setting of both neuroreceptor and MRS imaging to assess acute effects on these neurochemicals and their relationship to dopamine. Current work is aimed at developing glutamate and GABA MRS-based measures integrated with multi-modal outcomes to generate biomarkers of treatment response and risk of conversion to psychosis. Dr. Kegeles has extensive experience working on multi-site studies funded by NIH, including as a multiple PI of a multi-site grant (1 R01 MH110270-01-A1) to Columbia/Cornell/Instituto Nacional de Neurología y Neurocirugía (Mexico City) and as a co-investigator of the recently completed FAST-PS contract (PI Lieberman). In summary, Dr. Kegeles has an established research record in neurochemical imaging-based biomarker development and validation studies, including multi-site studies, across a number of psychiatric diagnoses.

B. Positions and Honors**Positions and Employment**

1974-1976 Research Associate, University of Pennsylvania
 1976-1978 Research Associate, University of Alberta
 1978-1981 Research Associate, Stevens Institute of Technology
 1981-1987 Member of the Technical Staff, AT&T Bell Laboratories
 1991-1995 Resident in Psychiatry, Columbia Presbyterian Hospital and the NY State Psychiatric Institute
 1991- Adjunct Research Faculty, Department of Medicine, Mount Sinai School of Medicine
 1995-1998 Clinical Assistant Psychiatrist, Columbia Presbyterian Hospital

 1995-1999 Postdoctoral Clinical Fellow and Assistant in Clinical Psychiatry, Columbia University; and
 Research Fellow, the NY State Psychiatric Institute

1998-2006 Assistant Attending Psychiatrist, Columbia Presbyterian Hospital
1999-2006 Assistant Professor of Clinical Psychiatry, Columbia University
2000-2003 Herbert Irving Assistant Professor of Clinical Psychiatry (in Radiology), Columbia University
2006- Associate Attending Psychiatrist, New York Presbyterian Hospital
2006-2018 Associate Professor of Clinical Psychiatry (in Radiology), Columbia University
2015- Medical Director, MRI Unit, NY State Psychiatric Institute
2016-2018 Interim Director, Division of Translational Imaging, NY State Psychiatric Institute
2018- Associate Director for Operations, Area Psychotic Disorders, NY State Psychiatric Institute
2018- Professor of Clinical Psychiatry (in Radiology), Columbia University

Other Experience and Professional Memberships

1969- Member, Society of Sigma Xi
1997- Member, Society of Nuclear Medicine and Molecular Imaging
1998- Member, Society for Neuroscience
2004- Member, International Society for Magnetic Resonance in Medicine
2006-2013 Associate Member, American College of Neuropsychopharmacology
2007 Scientific session moderator, International Congress on Schizophrenia Research
2009-2014 Neuroscience/psychiatry subchair, scientific session moderator, Society of Nuclear Medicine and Molecular Imaging
2009- Annual meeting abstracts reviewer, Society of Nuclear Medicine and Molecular Imaging
2013- Member, American College of Neuropsychopharmacology
2014 NIH grant reviewer, special emphasis panel ZRG1 IFCN-Q (55)
2017 NIH grant reviewer, special emphasis panel ZRG1 BDCN J 02
2018- Fellow, American College of Neuropsychopharmacology
2019 NIH grant reviewer, special emphasis panel ZRG1 BDCN J 02
2020 NIH grant reviewer, NPAS study section

Journal reviewer, *American Journal of Psychiatry*, *Biological Psychiatry*, *Biological Psychiatry CNI*, *European Journal of Neuropsychopharmacology*, *Human Brain Mapping*, *International Journal of Molecular Sciences*, *JAMA Psychiatry*, *Journal of Clinical Psychopharmacology*, *Journal of Psychiatric Research*, *Journal of Psychopharmacology*, *Molecular Psychiatry*, *Neurobiology of Disease*, *NeuroImage*, *NeuroImage Clinical*, *Neuroscience*, *Neuropsychopharmacology*, *npj Schizophrenia*, *Psychiatry Research: Neuroimaging*, *Schizophrenia Bulletin*, *Schizophrenia Research*, *Synapse*, *Translational Psychiatry*

Honors

1989 Society of Nuclear Medicine Student Fellowship
1990 American Medical Association Rock Sleyster Memorial Scholarship
1990 Alpha Omega Alpha, Mount Sinai School of Medicine
1991 Nathan A. Selz Prize for Research in Renal and Cardiovascular Diseases, Mount Sinai School of Medicine
1991 M.D. With Distinction in Research, Mount Sinai School of Medicine
1995 Society of Biological Psychiatry/Eli Lilly Fellowship
1995 Alumni Association Award for Excellence in Research, Columbia Department of Psychiatry
1995-1997 NARSAD Young Investigator Award
1997-1999 NARSAD Young Investigator Award
1999 International Congress on Schizophrenia Research, Young Investigator Award
2000 ACNP/Bristol-Myers Squibb Travel Award
2000 Florence and Herbert Irving Clinical Research Career Award
2010-2012 NARSAD Independent Investigator Award
2017 Columbia Collaboratory Award for Biomedical Engineering course development in Magnetic Resonance Spectroscopy
2018 Pilot Award, EEG Core Research Program for Columbia Psychiatry

Invited Presentations

1996 "MRI/MRS Study of Glutamate in Schizophrenia", NARSAD Scientific Symposium, New York
2002 "Prefrontal D1 Receptors and Working Memory in Schizophrenia", Grand Rounds, St. Vincent's Hospital Dept. of Psychiatry, New York

- 2003 "Applications of MR Spectroscopy to Neuroscience", Innovation and Radiology Series, Columbia University Dept. of Radiology
- 2010 "Imaging Neurotransmitters in Schizophrenia", Grand Rounds, Elmhurst Hospital Dept. of Psychiatry, New York
- 2011 "PET Neuroreceptor Approaches to Biomarkers of Neurotransmitter Abnormalities", Keynote, International Society for Magnetic Resonance in Medicine, Workshop, "Neuroimaging Biomarkers of Psychiatric Disorders: What Are They?", Montabaur, Germany
- 2012 "Gamma-Aminobutyric Acid Alterations Across Psychiatric Disorders", New Clinical Drug Evaluation Unit, 52nd Annual Meeting, Phoenix, Arizona
- 2013 "Taking Stock of Glutamate in Schizophrenia", Discussant, Schizophrenia Research Forum Webcast
- 2013 "MR Spectroscopy and NMDA Receptor Hypofunction in Schizophrenia", Grand Rounds, University of New Mexico Dept. of Psychiatry, Albuquerque
- 2014 "NMDA Receptor Hypofunction in Schizophrenia: PET and MRS Studies", Grand Rounds, National Institute of Neurology and Neurosurgery, Mexico City
- 2015 "Neuroreceptor Imaging of Neurotransmitter Abnormalities", Advanced Imaging Seminar: Metabolic Neuroimaging Biomarkers of Psychiatric Disorders, American Society of Neuroradiology 53rd Annual Meeting, Chicago
- 2015 "Positron Emission Tomography Studies in Early Stages of Schizophrenia", Mexican Psychiatric Association 24th Annual Meeting, Cancun, Mexico
- 2017 "Excitation/Inhibition Imbalances in Schizophrenia", Grand Rounds, New York Medical College Dept. of Psychiatry, Valhalla, NY
- 2018 "Searching for Biomarkers of Psychosis", Grand Rounds, Stony Brook University Dept. of Psychiatry, Stony Brook, NY

C. Contributions to Science

1- Imaging biomarkers of ketamine-induced neurochemical alterations in humans

This work found neurochemical alterations induced by ketamine in healthy human subjects. Using SPECT, PET and MRS imaging Dr. Kegeles showed that ketamine induces changes in healthy humans in both dopamine and glutamate comparable to those seen in the brain in schizophrenia. These studies have added neurochemical and mechanistic validity to the symptom-based face validity of the NMDA receptor hypofunction model of schizophrenia.

Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL, Cooper T, Carlsson A, Laruelle M: Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry* 48:627-640, 2000. PMID: 11032974

Kegeles LS, Martinez D, Kochan LD, Hwang DR, Huang Y, Mawlawi O, Suckow RF, Van Heertum RL, Laruelle M: NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. *Synapse* 43:19-29, 2002. PMID: 11746730

Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, Shungu DC: Elevated prefrontal cortex γ -aminobutyric acid and glutamate-glutamine levels in schizophrenia measured *in vivo* with proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 69(5):449-459, 2012. PMID: 22213769

Kegeles LS, Stolz E, Mao X, Ojeil N, Massuda R, Pedrini M, Bayatmokhtari M, Slifstein M, Abi-Dargham A, Milak M, Rodriguez C, Chen C-M, Shungu DC: Disturbances in neural oscillations, glutamate, and GABA: effects of ketamine and comparison to schizophrenia. *Schizophrenia Bulletin* 44 Supplement 1;S2, 2018

2- Increased striatal intrasynaptic dopamine and receptor occupancy in schizophrenia: focus on the associative striatum and relationship to treatment response

These neuroreceptor imaging studies showed increased intrasynaptic receptor occupancy by endogenous dopamine measured with a depletion paradigm in patients with schizophrenia, present at onset. This increase is most prominent in the head of the caudate and predicts treatment response. These studies shift the focus from the mesolimbic hypothesis, guiding the search for cellular mechanisms for the dopamine dysfunction and the assessment of therapeutic effects.

Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, **Kegeles LS**, Weiss R, Cooper TB, Mann JJ, Van Heertum R, Gorman J, Laruelle M: Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *PNAS* 97:8104-8109, 2000. PMID: 10884434

Abi-Dargham A, Giessen EV, Slifstein M, **Kegeles LS**, Laruelle M.: Baseline and Amphetamine-Stimulated Dopamine Activity Are Related in Drug-Naïve Schizophrenic Subjects. *Biol Psychiatry* 65(12):1091-1093, 2009. PMID: 19167701

Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, Hwang D-R, Huang Y, Haber S, Laruelle M: Increased synaptic dopamine in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatry* 67(3):231-239, 2010. PMID: 20194823

3- Increased frontal cortex glutamate and GABA in unmedicated patients with schizophrenia

This work using MRS found increases in glutamate and GABA in the medial prefrontal cortex in schizophrenia in unmedicated patients, but normal levels in medicated patients. This finding was unexpected from the standpoint of postmortem studies but is consistent with ketamine effects on glutamate in preclinical studies and in humans measured with MRS. Together with the ketamine studies, it offers the potential of MRS-based assessment of therapeutic effects on the glutamate system.

Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, Shungu DC: Elevated prefrontal cortex γ -aminobutyric acid and glutamate-glutamine levels in schizophrenia measured *in vivo* with proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 69(5):449-459, 2012. PMID: 22213769

Chen CM, Stanford AD, Mao X, Abi-Dargham A, Shungu DC, Lisanby SH, Schroeder CE, **Kegeles LS**: GABA level, gamma oscillation, and working memory performance in schizophrenia. *Neuroimage Clin* 4:531-539, 2014. PMID: 24749063

Shungu DC, Mao X, Gonzales R, Soones TN, Dyke JP, van der Veen JW, **Kegeles LS**: Brain GABA Detection *in vivo* with the J-editing ^1H MRS Technique: A comprehensive methodological evaluation of sensitivity enhancement, macromolecule contamination and test-retest reliability. *NMR Biomed* 29(7):932-942, 2016. PMID: 27173449 PMCID: PMC4909570

Girgis RR, Baker S, Mao X, Gil R, Javitt DC, Kantrowitz JT, Gu M, Spielman DM, Ojeil N, Xu X, Abi-Dargham A, Shungu DC, **Kegeles LS**: Effects of acute N-acetylcysteine challenge on cortical glutathione and glutamate in schizophrenia: A pilot *in vivo* proton magnetic resonance spectroscopy study. *Psychiatry Res* 275:78-85, 2019. PMID: 30884334

4- Prefrontal GABA deficits and therapeutic use of ketamine in obsessive-compulsive disorder

In these MRS studies of GABA and glutamate in OCD, a baseline evaluation and a study of patients administered *i.v.* ketamine as a potential therapy, OCD patients were found to have prefrontal deficits of GABA but not glutamate. Correspondingly, ketamine had minimal effect on glutamate in a clinical trial, but increased GABA levels in these patients.

Simpson HB, Shungu DC, Bender J, Mao X, Xu X, Slifstein M, **Kegeles LS**: Investigation of cortical glutamate-glutamine and γ -aminobutyric acid in obsessive-compulsive disorder by proton magnetic resonance spectroscopy. *Neuropsychopharmacology* 37(12):2684-2692, 2012. PMID: 22850733

Rodriguez CI, **Kegeles LS**, Flood P, Simpson HB: Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry* 72(4):567-569, 2011. PMID: 21527129

Rodriguez CI, **Kegeles LS**, Levinson A, Feng T, Marcus SM, Vermes D, Flood P, Simpson HB: Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: Proof-of-concept. *Neuropsychopharmacology* 38(12):2475-2483, 2013. PMID: 23783065

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=kegeles+ls>

D. Additional Information: Research Support and/or Scholastic Performance **Ongoing Research Support**

R01MH110270
NIMH

Shungu / Kegeles / Girgis 07/01/2017 - 06/30/2022

Biomarkers of Conversion Risk and Treatment Response in Early Stage Schizophrenia

This project aims to develop a magnetic resonance spectroscopy (MRS)-based biomarker to assess target engagement, neurochemical effects, and risk of transition to psychosis in schizophrenia.

Role: PI (multiple PIs)

Completed Research Support

- 1 U01 MH094247-06 Lieberman 9/1/2017 – 08/31/2018
NIMH
Double Blind, two dose, cross-over clinical trial of the positive allosteric modulator at the alpha7 nicotinic cholinergic receptor AVL-3288 in schizophrenia patients
Perform an initial Phase 2 proof-of-principle clinical study of UCI-40083 in schizophrenia.
Role: Co-Investigator
- Dana Foundation Grant Girgis 01/16/14 – 12/31/18
Modulating the Glutamate/Glutathione System in Schizophrenia: an MRS-based Study
To use MRS to measure the effects of N-acetylcysteine on the glutathione system in schizophrenia
Role: Co-Investigator
- HHSN27100003 Lieberman 08/29/13 – 04/28/18
NIMH
mGluR2/3 Study/Trial HHSN271201200001 FAST-PS
Major Goals: Pilot/feasibility study to evaluate the ability of an mGluR2/3 agonist to reverse ketamine-induced GLX MRS, 13C MRS, Bold fMRI, and EEG alterations in healthy humans.
Role: Co-Investigator
- 1R21MH099508-01A1 Kegeles, Girgis 02/06/14 – 01/31/17
NIMH
Neurochemical and Clinical Effects of Glutamate Modulation in Schizophrenia
The project proposes to develop a Magnetic Resonance Spectroscopy (MRS) based biomarker to assess target engagement and neurochemical effects of glutamatergic agents in schizophrenia.
Role: PI / multi PI
- 1R34MH095377-01A1 Shungu 07/05/12 – 04/30/17
NIMH
Novel Medication Strategies Targeting Brain Mechanisms in Pediatric OCD
Subcontract with Weill Cornell Medical Center
To evaluate the efficacy and brain mechanisms of minocycline for treatment of pediatric OCD
Role: Subcontract PI