BIOGRAPHICAL SKETCH

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NAME: Abi-Dargham, Anissa, M.D.

eRA COMMONS USER NAME (credential, e.g., agency login): AA324X

POSITION TITLE: Professor of Psychiatry and Vice Chair for Research

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
St. Joseph University, Beirut, Lebanon	M.D.	05/1984	Medicine
University of Tennessee, Memphis, Tennessee	Residency	05/1989	Psychiatry
National Institute of Mental Health, Clinical Brain Disorders Branch, Washington, DC	Fellowship	05/1991	Neuropathology
Yale School of Medicine, New Haven, Connecticut	Fellowship	05/1992	Brain Imaging

A.   Personal Statement

I am a clinical and translational neuroscientist and a leader in the field of Positron Emission Tomography (PET) imaging. I have applied PET imaging in combination with multimodal MRI and clinical evaluations to study the neurobiology of severe mental illnesses, including schizophrenia, addiction and their comorbidities. My work revealed alterations in dopamine transmission in specific areas of the brain in patients with schizophrenia and addiction, and led to the generation of preclinical animal models aimed at understanding the mechanisms and consequences of these alterations, creating a truly translational program from men to mice and back. I have recently focused on understanding the disconnection between striatal and extrastriatal dopamine and how this contributes to altered perceptual inference, as a key model for hallucinations and psychosis. I have over 200 peer reviewed publications. I received continuous funding from NIMH over the last 20 years, including a P50 Silvio O Conte Center for the translational studies of dopamine in schizophrenia (Center director: 2009-2014), funding from NIDA, NIAAA, NARSAD, and funding from Industry including Lilly, BMS, GSK, Forest, and Pierre-Fabre. I am currently PI, multiple PI or co-I on 9 federally funded grants. In particular, I currently serve as the SBU site PI on a U01 in collaboration with Yale, Columbia and U Penn to test a D1 partial agonist in schizophrenia. I mentored more than 20 post-doctoral fellows in my career and co-directed the T32 for schizophrenia research for many years at Columbia University. I lead a CSHL short course on schizophrenia since 2014. I have founded the Long Island Network for Clinical And Translational Science (LINCATS) and led the effort over the last four years of implementing programs and services to facilitate clinical and translational science at SBU, assembling a dedicated team of scientists, administrators, community members and collaborators together to support the mission of LINCATS. I lead weekly meetings of the team, coordinate the budget and the administrative staff. I recruited a Chief Operating Officer who is assisting in the daily operations of the center. I oversee the organization, governance, collaborations, and communication through all the components of LINCATS, including our collaborating institutions, CSHL, BNL, and Northport VA. I also oversee the creation and implementation of an evaluation system to monitor quality and efficiency, in order to continue expansion and progress. Finally, I recently co-led an institutional Task Force and a Clinical Research Working Group, charged by President McInnis to review research and innovation at Stony Brook University. The Task Force met weekly for six months and made final recommendations that are currently in the implementation phase. This work has given me an in depth and broad overview of the opportunities and challenges for research within and across institutions.

Ongoing and recently completed research support that I would like to highlight include:

National Institute of Mental Health   1R01 MH109635-01 (PI)   09/16/2016 - 06/30/2022 (NCE)
Neurobiological correlates of auditory processing in health and disease: an RDoC study
The goal is to image dopamine receptor release and identify molecular and neural correlates of auditory perceptual disturbances in psychosis.

National Institute of Mental Health   R61 MH110029-01 (Sub PI)   08/01/2016 – 11/30/2021
Targeting dopaminergic mechanisms of slowing to improve late life depression
The goal is to test the administration of carbidopa/levodopa (L-DOPA) to enhance striatal dopamine neurotransmission and improve cognitive and motor slowing and improve depressive symptoms in older adults.

National Institute of Mental Health   1U01MH121766-01 (MPI: Krystal/Anticevic, SBU site PI)
09/01/19 – 08/31/22
A Translational and Neurocomputational Evaluation of a D1R Partial Agonist for Schizophrenia
D1 receptor (D1R) agonism is the highest priority experimental treatment mechanism identified by the NIMH MATRICS Initiative remaining to be rigorously tested. Here, we propose the first test in schizophrenia patients of the dose-related effects of a D1R/D5R partial agonist, PF-06412562, on neuroimaging biomarkers selected on the basis of a translational and computational neuroscience understanding of the role of D1R/D5Rs in cortical systems. Furthermore, we are testing this drug using a precision medicine strategy that targets a subpopulation of early course schizophrenia patients with spatial working memory deficits that might respond to D1R/D5R agonism.

NIDA   R21MH125454-01 (PI)   12/1/2020 – 11/30/2022
Preliminary imaging studies of the kappa opioid receptors in schizophrenia and their relationship to dopamine function
Goals: This pilot study will inform the design of a much larger study and provide POC for biomarker-driven investigations of KOR antagonists in schizophrenia by providing in vivo molecular measures and a link between KOR and dopamine dysfunction.

National Institute of Mental Health   1R01MH120293-01A1 (Co-I)   3/17/2020 – 1/31/2025
A data-driven reconceptualization of the RDoC construct of working memory: Neural correlates of underlying factors and implications for schizophrenia
The major goal of this project is to identify behavioral factors and neural circuits that underlie subconstructs of working memory, in both healthy individuals and patients with schizophrenia.

NIDA   R21DA051179 (Co-I)   5/1/2020-4/30/2022
Cholinergic transmission abnormalities associated with smoking behavior in humans
The goal of this study is to propose to use the novel radiotracer [18F]VAT, which targets the vesicular acetylcholine transporter (VAChT), to test the hypothesis that chronic smokers have deficits in striatal cholinergic tone that relate to clinical severity.

Citations:

a)   **Abi-Dargham A**. From "bedside" to "bench" and back: A translational approach to studying dopamine dysfunction in schizophrenia. Neurosci Biobehav Rev. 2018 pii: S0149-7634(18)30314-2. Review PMID: 3052837
b)   Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, **Abi-Dargham A**. Pathway-Specific Dopamine Abnormalities in Schizophrenia. Biol Psychiatry. 2017; 81(1):31-42. Review. PMID: 27206569
c)   **Abi-Dargham A**, Javitch JA, Slifstein M, Anticevic A, Calkins ME, Cho YT, Fonteneau C, Gil R, Girgis R, Gur RE, Gur RC, Grinband J, Kantrowitz J, Kohler C, Krystal J, Murray J, Ranganathan M, Santamauro N, Van Snellenberg J, Tamayo Z, Wolf D; TRANSCENDS Group, Gray D, Lieberman J.: Dopamine D1R Receptor Stimulation as a Mechanistic Pro-cognitive Target for Schizophrenia, Schizophr Bull. 2021, PMID: 34423843

B.   Positions, Scientific Appointments, and Honors
Positions
2020-	Associate Vice President for Clinical and Translational Science, Stony Brook University
2018-2020	Associate Dean for Clinical and Translational Science, Stony Brook University SOM
2018-	The Lourie Endowed Chair in Psychiatry, Stony Brook University SOM
2017-	Program Faculty, Dept. of Biomedical Engineering, Stony Brook University
2016-	Professor of Psychiatry and Radiology, Stony Brook University SOM, Stony Brook, NY
2016-	Vice Chair of Research, Dept of Psychiatry, Stony Brook University SOM
2007-2016	Chief, Division of Translational Imaging, Columbia Univ. and NY State Psychiatric Institute (NYSPI)
2007-2016	Director of Clinical and Imaging Research, Lieber Center for Schizophrenia Research, Columbia Univ. and NYSPI
2005-2007	Chief, Division of Functional Brain Mapping, Columbia Univ. and NYSPI
2003-2016	Professor of Clinical Psychiatry and Radiology, Columbia Univ. and NYSPI
1998-2003	Associate Professor, Clinical Psychiatry & Radiology, Columbia Univ. & NYSPI
1996-98	Assistant Professor, Dept. of Psychiatry, Columbia Univ. and NYSPI
1994-96	Unit Chief, Neuropsychiatric Studies Unit, West Haven VAMC
1992-96	Assistant Professor, Dept. of Psychiatry, Yale University
1991-92	Post-Doctoral Fellow in Brain Imaging, Yale University
1989-91	Visiting Associate, NIMH, Clinical Brain Disorders Branch, Washington, DC
1985-89	Categorical Internship, Psychiatric Residency & Chief Residency, University of Tennessee
1977-84	Medical School, St. Joseph University, Beirut, Lebanon

Honors
2020-2024	Membership committee, Vice Chair section 7A, National Academy of Medicine
2020	SUNY Distinguished Professor
2018-2022	Member, Program Committee, Society for Neuroscience
2018	Lieber Award for Outstanding Schizophrenia Research, Brain and Behavior Foundation
2017	APA Fellow
2016	Member, National Academy of Medicine
2016	ACNP President
2015	Dean Award, the American College of Psychiatrists
2014-2018	Member of the Board of Directors to the Schizophrenia International Research Society (SIRS)
2014-2014	Advisor to Schizophrenia Forum
2014- present	CSHL, Organizer of the course on Schizophrenia
2014	Program Committee Chair, SIRS
2013-2018	Member of the Board of Scientific counselors to the NIMH Director
2013-	Member of the Scientific Council for the Brain & Behavior Research Foundation
2012	Chair, Program Committee, ACNP
2011-	Deputy Editor, Biological Psychiatry
2010	Connie Lieber Research Award, NAMI
2009	President, Brain Imaging Council, Society of Nuclear Medicine
2008	NARSAD Distinguished Investigator Award
2007-	Associate Editor, Neuropsychopharmacology
2004-2006	Member, Brain Imaging Council, Society of Nuclear Medicine
2002	Gerald Klerman Honorable Mention Award by NARSAD for an outstanding Young Investigator
2000-	NARSAD Independent Investigator Award
2000	Member, American College of Neuropsychopharmacology
1997-	NARSAD Young Investigator Award (second)
1997-	Clinical Trials Award, Columbia University
1997	Associate member, American College of Neuropsychopharmacology
1997	Irving Scholarship Award, Columbia University
1995	Yale University Chairman's Award
1994	American College of Neuropsychopharmacology ACNP/Mead Johnson Award
1993-94	NARSAD Young Investigator Award (first)

C. Contributions to Science

1. <u>D1 receptors in prefrontal cortex in patients with schizophrenia</u>

This series of studies characterized the binding of a new radiotracer to the D1 receptor, its selectivity, reproducibility and vulnerability to endogenous competition. Studies in patients with schizophrenia showed alterations, especially in the drug naïve state. The impact is to provide rationale for developing D1 drugs for cognitive and negative symptoms in schizophrenia, and a well characterized radiotracer for target engagement studies. More specifically we showed that the in vivo binding of D1 tracers in the cortex is a mixed signal of D1 and 5HT2A, an important observation for the interpretation of the binding profile of new D1 drugs. This work led to the current U01 trial testing a partial D1 agonist in schizophrenia.

a) **Abi-Dargham A**, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci. 2002;22(9):3708-19. PubMed PMID: 11978847.

b) Slifstein M, Kegeles LS, Gonzales R, Frankle WG, Xu X, Laruelle M, **Abi-Dargham A**. [11C]NNC 112 selectivity for dopamine D1 and serotonin 5-HT(2A) receptors: a PET study in healthy human subjects. J Cereb Blood Flow Metab. 2007;27(10):1733-41. PubMed PMID: 17311076.

c) **Abi-Dargham A**, Xu X, Thompson JL, Gil R, Kegeles LS, Urban N, Narendran R, Hwang DR, Laruelle M, Slifstein M. Increased prefrontal cortical D(1) receptors in drug naive patients with schizophrenia: a PET study with [(1)(1)C]NNC112. J Psychopharmacol. 2012;26(6):794-805. Epub 2011/07/20. doi: 10.1177/0269881111409265. PubMed PMID: 21768159.

d) Slifstein M, Suckow RF, Javitch JA, Cooper T, Lieberman J, **Abi-Dargham A**. Characterization of in vivo pharmacokinetic properties of the dopamine D1 receptor agonist DAR-0100A in nonhuman primates using PET with [11C] NNC112 and [11C] raclopride. J Cereb Blood Flow Metab. 2011;31(1):293-304. PubMed PMID: 20571519; PMCID: PMC3049493.

2. <u>Increased striatal dopamine, amphetamine induced release and intrasynaptic occupancy: Focus on the associative striatum and relationship to psychosis</u>

These studies showed enhanced stimulant induced dopamine release in the striatum, as well as higher intrasynaptic occupancy 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 psychosis. These studies shift the focus from the mesolimbic hypothesis, aiding the search for cellular mechanisms for the dopamine dysfunction as well as the creation of mouse models and the assessment of therapeutic effects by providing accurate information from in vivo studies in patients with the disease.

a) **Abi-Dargham A**, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci U S A. 2000;97(14):8104-9. PubMed PMID: 10884434; PMCID: PMC16677.

b) Kegeles LS, **Abi-Dargham A**, Frankle WG, Gil R, Cooper TB, Slifstein M, Hwang DR, Huang Y, Haber SN, Laruelle M. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry. 2010;67(3):231-9. PubMed PMID: 20194823.

c) **Abi-Dargham A**, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M. Baseline and amphetamine- stimulated dopamine activity are related in drug-naive schizophrenic subjects. Biol Psychiatry. 2009;65(12):1091-3. PubMed PMID: 19167701.

3- <u>Deficits in extrastriatal dopamine release in schizophrenia: evidence and functional impact</u>

This work provides the first evidence for cortical hypodopaminergia and shows a more widespread deficit than prefrontal cortex. It also highlights the fact that dopamine excess in striatum is isolated, and specific to the striatum.

a) Slifstein M, van de Giessen E, Van Snellenberg J, Thompson JL, Narendran R, Gil R, Hackett E, Girgis R, Ojeil N, Moore H, D'Souza D, Malison RT, Huang Y, Lim K, Nabulsi N, Carson RE, Lieberman JA, **Abi-Dargham A**. Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: a positron emission tomographic functional magnetic resonance imaging study. JAMA Psychiatry. 2015;72(4):316-24. PubMed PMID: 25651194; PMCID: PMC4768742.

b) Van Snellenberg JX, Girgis RR, Horga G, van de Giessen E, Slifstein M, Ojeil N, Weinstein JJ, Moore H, Lieberman JA, Shohamy D, Smith EE, **Abi-Dargham** A. Mechanisms of Working Memory Impairment in Schizophrenia. Biol Psychiatry. 2016 Oct 15;80(8):617-26. PMID:

27056754

c) Van Snellenberg JX, Slifstein M, Read C, Weber J, Thompson JL, Wager TD, Shohamy D, **Abi- Dargham** A, Smith EE. Dynamic shifts in brain network activation during supracapacity working memory task performance. Hum Brain Mapp. 2015 Apr;36(4):1245-64. PMID: 25422039

d) Cassidy CM, Van Snellenberg JX, Benavides C, Slifstein M, Wang Z, Moore H, **Abi-Dargham** A, Horga G. Dynamic Connectivity between Brain Networks Supports Working Memory: Relationships to Dopamine Release and Schizophrenia. J Neurosci. 2016 Apr 13;36(15):4377-88. PMID: 27076432

4- Multimodal imaging: linking molecular and functional analyses
These are studies combining molecular and functional multimodal imaging to assess the impact of abnormal dopamine on basic cognitive processes and test computational models of biased perception that lead to hallucinations. They also serve to develop potential biomarkers such as neuromelanin sensitive MRI, validated against PET measures of dopamine release.

a) Horga G, Cassidy CM, Xu X, Moore H, Slifstein M, Van Snellenberg JX, **Abi-Dargham** A. Dopamine- Related Disruption of Functional Topography of Striatal Connections in Unmedicated Patients With Schizophrenia. JAMA Psychiatry. 2016 Aug 1;73(8):862-70. PMID: 27145361

b) Cassidy CM, Balsam PD, Weinstein JJ, Rosengard RJ, Slifstein M, Daw ND, **Abi-Dargham** A, Horga G. A Perceptual Inference Mechanism for Hallucinations Linked to Striatal Dopamine. Curr Biol. 2018 Feb 19;28(4):503-514.e4. PMID: 29398218

c) Cassidy CM, Zucca FA, Girgis RR, Baker SC, Weinstein JJ, Sharp ME, Bellei C, Valmadre A, Vanegas N, Kegeles LS, Brucato G, Jung Kang U, Sulzer D, Zecca L, **Abi-Dargham** A, Horga G. Neuromelanin- sensitive MRI as a noninvasive proxy measure of dopamine function in the human brain. Proc Natl Acad Sci U S A. 2019 Mar 12;116(11):5108-5117. PMID: 30796187

d) Wengler K, He X, **Abi-Dargham A**, Horga G, Reproducibility assessment of neuromelanin-sensitive magnetic resonance imaging protocols for region-of-interest and voxelwise analyses. Neuroimage. 2020, PMID: 31841683

5- Deficits in dopamine in addiction and schizophrenia comorbid with addiction
This work showed that alcoholism is associated with striatal dopamine deficits, which is also the case for alcoholism comorbid with schizophrenia. Low dopamine relates to severity of addiction and has been shown to relate to relapse. In schizophrenia, the study highlighted the fact that D2 stimulation, even within a low range of capacity for dopamine release, induces psychosis, suggesting that D2 may have abnormal sensitivity to agonist stimulation, due to unknown mechanisms.

a) Thompson JL, Urban N, Slifstein M, Xu X, Kegeles LS, Girgis RR, Beckerman Y, Harkavy-Friedman JM, Gil R, **Abi-Dargham A**. Striatal dopamine release in schizophrenia comorbid with substance dependence. Mol Psychiatry. 2013;18(8):909-15. PubMed PMID: 22869037; PMCID: PMC4128915.

b) 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;58(10):779-86. PubMed PMID: 16018986.

c) Van de Giessen E, Weinstein JJ, Cassidy CM, Haney M, Dong Z, Ghazzaoui R, Ojeil N, Kegeles LS, Xu X, Vadhan NP, Volkow ND, Slifstein M, **Abi-Dargham** A. Deficits in striatal dopamine release in cannabis dependence. Mol Psychiatry. 2017 Jan;22(1):68-75. PMID: 27001613

d) Kegeles LS, **Horga** G, Ghazzaoui R, Rosengard R, Ojeil N, Xu X, Slifstein M, Petrakis I, O'Malley SS, Krystal JH, **Abi-Dargham** A. Enhanced Striatal Dopamine Release to Expectation of Alcohol: A Potential Risk Factor for Alcohol Use Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 Jul;3(7):591-598. PMID: 29803635

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=abi-dargham