BIOGRAPHICAL SKETCH

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NAME: Bret R Rutherford, MD

eRA COMMONS USER NAME (credential, e.g., agency login): BRETR8

POSITION TITLE: Associate Professor of Clinical Psychiatry

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
Harvard College, Cambridge, MA	B.A.	06/1998	Philosophy
Columbia University College of Physicians and Surgeons, New York, NY	M.D.	05/2002	Medicine
New York Presbyterian Hospital—Columbia University Medical Center, New York, NY		06/2006	Psychiatry residency
NIMH T32 Research Fellowship in Affective and Anxiety Disorders, New York State Psychiatric Institute and Columbia University, New York, NY		06/2009	Geriatric psychiatry

A. Personal Statement

My education, training, and current position provide me with the expertise and resources necessary to carry out the proposed work. After graduating from Harvard College and the Columbia University College of Physicians and Surgeons, I was trained in psychiatry at Columbia and completed an NIMH T32 Research Fellowship in Affective and Anxiety Disorders. Spending several years in the Division of Geriatric Psychiatry at Columbia and working in the Late Life Depression Research Clinic under Drs. D.P. Devanand and Steven Roose, I became interested in extending my work into geriatric patients, particularly those with Late Life Depression. To better understand factors associated with antidepressant non-response in this population, I began an R01 titled “Mechanisms of Antidepressant Non-Response in Late-Life Depression.” This project allowed me to collect data on the effects of cerebrovascular factors and the development of executive dysfunction on antidepressant response. I delved further into the inter-relationships between depression and cognition in a Collaborative R01 project aiming to elucidate the mechanisms by which treatment resistant depression poses an increased risk for dementia (“Neurocognitive and Neuroimaging Biomarkers: Predicting Progression Towards Dementia in Patients with Treatment Resistant Depression”). Broadening my research program on the pathways by which psychiatric disorders increase risk for AD/ADRD, I also began an R01 to investigate the mechanisms by which PTSD accelerates brain aging and hastens cognitive decline in older adults (“Cognitive and Neural Mechanisms of the Accelerated Aging Phenotype in PTSD”). As these studies involve similar methodology (e.g., multimodal neuroimaging, gait analysis, neurocognitive assessment and dementia adjudication), they constitute excellent preparation for the studies described in the present submission. My career goal is to conduct translational research at the intersection of aging and later life neuropsychiatric disorders in order to identify improved methods of supporting healthy brain aging and develop personalized, scaleable, and aging-informed treatments for prevalent and disabling conditions such as Late Life Depression.

1. Rutherford BR, Slifstein M, Chen C, et al. Effects of L-DOPA Monotherapy on Psychomotor Speed and [^{11}C]Raclopride Binding in High Risk Depressed Older Adults. Biol Psychiatry 2019; 86:221-229. PMCID 6641997.

2. Rutherford BR, Brewster K, Golub JS, Kim AH, Roose SP. Sensation and Psychiatry: Linking Age-Related Hearing Loss to Late-Life Depression and Cognitive Decline. Am J Psychiatry 2018; 175:215-224. PMCID 5849471.

3. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. J Gerontol A Biol Med Sci 2017; 72:343-352. PMCID 6433424.

4. Rutherford BR, Roose SP. A Model of Placebo Effects in Antidepressant Clinical Trials. Am J Psychiatry 2013; 170:723-733. PMCID 3628961.

B. Positions and Honors

Positions and employment

2002-2003 Internship in Internal Medicine, Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital-Columbia Campus, New York, NY.
2003-2006 Residency in Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York Presbyterian Hospital-Columbia Campus, New York, NY.
2006-2009 NIMH Research Fellow in Affective, Anxiety, and Eating Disorders, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY.
2009-2014 Assistant Professor of Clinical Psychiatry, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY.
2009-2016 Co-Director of Combined Treatment with Psychotherapy and Medication course provided to PGY III and IV psychiatry residents.
2014-2016 Herbert Irving Assistant Professor of Psychiatry, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY.
2009-pres. Director of Geriatric Psychiatry course provided to PGY III and IV psychiatry residents.
2009-pres. Research Psychiatrist, Research Foundation for Mental Hygiene, New York State Psychiatric Institute, New York, NY.
2012-pres. Assistant Director, House Staff Mental Health Service, Columbia University Medical Center, New York, NY.
2016-pres. Associate Professor of Clinical Psychiatry, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY.
2016-pres. Director, Neurobiology and Therapeutics of Aging Division, Columbia University Department of Psychiatry
2018-pres. Co-Director, Area: Brain Aging and Mental Health, Columbia University Department of Psychiatry

Honors

1998 Cum Laude General Studies, Harvard College, Cambridge, MA
2002 Alpha Omega Alpha, Columbia University College of Physicians and Surgeons, New York, NY
2005 Chief Resident, New York State Psychiatric Institute, New York, NY
2006 Samuel Perry Research Award, Columbia University, New York, NY
2007 American Psychiatric Association Research Colloquium for Junior Investigators
2007 American Society of Clinical Psychopharm. Workshop on Clinical Trials in Psychopharmacology
2014 Herbert Irving Scholarship for 2014-17, Irving CTSA, New York, NY

C. Contributions to Science

1. Elucidating the mechanisms linking age-related hearing impairment (ARHL), Late Life Depression (LLD), and cognitive decline. A major focus of my work for the past three years was inspired through the work of Frank Lin (Consultant on this proposal), among others, who rigorously documented the risk age-related hearing loss poses for cognitive decline and dementia. Along with a multidisciplinary team of colleagues at Columbia, I began by publishing on the hearing-cognition relationship myself, but I soon moved to ask the relatively unstudied question of whether LLD may also be among the adverse neuropsychiatric implications of ARHL. Similar to the case with dementia, we found in multiple data sets that ARHL dramatically increases risk for incident LLD, even when the magnitude of hearing loss is very modest. Moving beyond epidemiologic data, I became interested in investigating the pathophysiologic mechanisms linking ARHL, LLD, and dementia, particularly given that these three prevalent conditions in older adults are so inter-related. In an ongoing NIA-funded R21 project, I have investigated executive dysfunction at both behavioral and neural levels of analysis as a potential link between ARHL, LLD, and dementia that may also be a critical therapeutic target. In other work, I have extended my laboratory's work on mobility impairments associated with LLD and other psychiatric conditions of later life to ask whether alterations in gait kinematics may also mediate some of the risk posed by ARHL, especially when it is comorbid with LLD. Few if any other research groups are currently employing this type of mechanistic approach to study ARHL, LLD, and dementia.

1. Rutherford BR, Brewster K, Golub JS, Kim AH, Roose SP. Sensation and Psychiatry: Linking Age-Related Hearing Loss to Late-Life Depression and Cognitive Decline. Am J Psychiatry 2018; 175:215-224. PMCID 5849471.

2. Brewster KK, Ciarleglio A, Brown PJ, Chen C, Kim HO, Golub JS, Rutherford BR. Age-Related Hearing Loss and its Association with Depression in Later Life. Am J Geriatr Psychiatry 2018; 26:788-796. PMCID 6008216.

3. Golub JS, Brewster KK, Brickman AM, Ciarleglio AJ, Kim AH, Luchsinger JA, Rutherford BR. Audiometric Age-Related Hearing Loss is Associated with Depressive Symptoms in Hispanics. JAMA Otolaryngol 2019; 145:132-139. PMCID 6396846.

4. Golub JS, Brewster KK, Brickman AM, Ciarleglio AJ, Kim AH, Luchsinger JA, Rutherford BR. Subclinical Hearing Loss is Associated with Depressive Symptoms. In Press, Am J Geriatr Psychiatry.

2. Developing Precision Interventions for Late Life Depression. More broadly, much of my work focuses on Late Life Depression (LLD), which affects 8-25% of older adults, is a leading cause of morbidity and mortality in this population, and is difficult to treat effectively. Historically, treatments for LLD have been based on pathophysiologic models of depression in younger adults and have been efficacy-tested in clinical trials mostly enrolling younger patients. As development and validation of the Vascular Depression Hypothesis in the 1990s made clear, distinct processes (e.g., cerebrovascular aging and development of deep white matter hyperintensities [WMH]) may cause and perpetuate depressive disorders in later life as compared to earlier in the life course. More recently, I have identified other processes, such as dopaminergic decline and development of the syndrome of frailty, that may be pathophysiologic routes to developing or perpetuating LLD. By developing precision interventions for these age-related disease mechanisms and testing them in etiologically homogenous patient samples, I hope to achieve better outcomes for older adults.

1. Rutherford BR, Slifstein M, Chen C, et al. Effects of L-DOPA Monotherapy on Psychomotor Speed and [^{11}C]Raclopride Binding in High Risk Depressed Older Adults. Biol Psychiatry 2019; 86:221-229. PMCID 6641997.

2. Wang Y, Bernanke J, Peterson BS, McGrath P, Stewart J, Chen Y, Lee S, Wall M, Bastidas V, Hong S, Rutherford BR, Hellerstein DJ, Posner J. The Association between Antidepressant Treatment and Brain Connectivity across Two Double-Blind, Placebo-Controlled Clinical Trials: a treatment mechanism study. Lancet Psychiatry 2019; 6:667-674. PMCID 6937159.

3. Rutherford BR, Choi J, Slifstein M, O'Boyle K, Abi-Dargham A, Brown PJ, Wall MW, Vanegas-Arroyave N, Sakhardande J, Stern Y, Roose SP. Neuroanatomical Predictors of L-DOPA Response in Older Adults with Psychomotor Slowing and Depression: A Pilot Study. In Press, J Affect Disord. PMC Journal—In Process.

4. Brown PJ, Brennan N, Ciarleglio A, Chen C, Garcia CM, Gomez S, Roose SP, Rutherford BR, et al. Declining Skeletal Muscle Mitochondrial Function Associated with Increased Risk of Depression in Later Life. In Press, Am J Geriatr Psychiatry. PMC Journal—In Process.

3. Understanding the Influence of Psychiatric Illness on Trajectories of Aging. Advances in methods of measuring biological aging have made it possible to identify and intervene when individuals depart from normative aging trajectories to restore healthy aging and maximize the independent functioning of older adults. The occurrence of psychiatric disorders such as depression, schizophrenia, and PTSD across the lifespan have been associated with premature medical morbidity and indices of accelerated aging such as decreased leukocyte telomere length, increased levels of inflammation, and increased oxidative stress. My recent collaborations and NIH-funded grants focus on characterizing how psychiatric disorders influence aging-related processes such as vasculopathy, inflammation, and cellular senescence to confer increased vulnerability for developing the biological syndrome of frailty and adverse health outcomes.

1. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. J Gerontol A Biol Med Sci 2017; 72:343-352. PMCID 6433424.

2. Brown PJ, Rutherford B, Yaffe K, Tandler J, Ray JL, Pott E, Chung S, Roose SP. The Depressed Frail Phenotype: The Clinical Manifestation of Increased Biological Aging. Am J Geriatr Psychiatry 2016; 24:1084-1094. PMCID 5069140.

3. Brown PJ, Roose SP, Zhang J, Wall M, Rutherford BR, Ayonayon HN, Butters MA, Harris T, Newman AB, Satterfield S, Simonsick EM, Yaffe K. Inflammation, Depression, and Slow Gait: A High Mortality Phenotype in Later Life. J Gerontol Med Sci 2016; 71:221-227. PMCID 4723663.

4. Brown PJ, Fieo R, Roose SP, Liu X, Sneed JR, Rutherford BR, Devanand DP, Avlund K. Frailty and depression in older adults: A high-risk clinical population. Am J Geriatr Psychiatry 2014; 22:1083-1095. PMCID 3930630.

4. Placebo Effects in Depression. My early work focused on identifying the mechanisms of placebo effects in treatments for Major Depressive Disorder. High placebo response rates hamper efforts to detect signals of efficacy for new antidepressant medications in the drug development setting, but in clinical practice, enhancing the factors responsible for placebo response may represent a strategy for improving antidepressant treatments. I have conducted a series of meta-analyses, novel clinical trials, and neuroimaging studies to begin disentangling and identifying the disparate sources of placebo response in antidepressant treatments. This work has

specifically examined on the contributions of patient expectancy (patients' beliefs about whether and to what degree a treatment will help them) and therapeutic contact with health care staff as major drivers of placebo effects. Results from these studies have significant implications for the design of Phase III antidepressant trials as well as optimal clinical management strategies for patients with depression. My work on placebo effects led to the publication of a conceptual model for placebo response in antidepressant trials that has become influential in the field.

1. Zilcha-Mano S, Wang Z, Peterson B, Wall MM, Chen Y, Wager TD, Brown PJ, Roose SP, Rutherford BR. Neural Mechanisms of Expectancy-Based Placebo Effects in Antidepressant Clinical Trials. J Psychiatr Res 2019; 116:19-25. PMCID 6790474.

2. Rutherford BR, Wall MM, Brown PJ, Choo TH, Wager TD, Peterson BS, Chung S, Kirsch I, Roose SP. Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. Am J Psychiatry 2017; 174:135-142. PMCID 5288269.

3. Rutherford BR, Pott E, Tandler JM, Wall MM, Roose SP, Lieberman JA. Placebo Response in Antipsychotic Clinical Trials: A Meta-Analysis. JAMA Psychiatry 2014; 71:1409-1421. PMCID 4256120.

4. Rutherford BR, Sneed JR, Tandler J, Peterson BS, Roose SP. Deconstructing Pediatric Depression Trials: An Analysis of the Effects of Expectancy and Therapeutic Contact. J Am Acad Child Adolesc Psychiatry 2011; 50:782-795. PMCID 3143372.

5. Randomized controlled trial methodology and study design factors influencing treatment response. My colleagues and I been leaders in characterizing how study design features influence treatment response across diagnostic categories. We have utilized hierarchical linear modeling techniques to parcel out the variance in treatment response attributable to study design features, allowing for the development of improved methodology capable of enhancing signal detection. For example, we have shown in antidepressant clinical trials that higher probabilities of receiving active medication as opposed to placebo greatly increases medication response rates. More contact with health care personnel greatly increases placebo response in antidepressant trials while leaving medication response relatively unaffected, a pattern which greatly diminishes drug-placebo effect sizes. Our work has also been important in assisting practicing clinicians to understand the literature and select appropriate studies on which to base treatment decisions.

1. Roose SP, Rutherford BR, Wall MW, Thase ME. Practicing Evidence Based Medicine in an Era of High Placebo Response: The Number-Needed-to-Treat Reconsidered. Br J Psychiatry 2016; 208:416-420. PMCID 4853640.

2. Rutherford BR, Bailey VS, Schneier FR, Pott E, Brown PJ, Roose SP. Influence of Study Design on Treatment Response in Anxiety Disorder Clinical Trials. Depress Anxiety 2015; 32:944-957. PMCID 4922308.

3. Rutherford BR, Sneed JR, Roose SP. Does Differential Drop-Out Explain the Influence of Study Design on Antidepressant Response? A Meta-Analysis. J Aff Disord 2012; 140:57-65. PMCID 3586309.

4. Rutherford BR, Cooper TM, Persaud A, Brown PJ, Sneed JR, Roose SP. Less is More in Antidepressant Clinical Trials: A Meta-Analysis of the Effect of Visit Frequency on Treatment Response and Drop-out. J Clin Psychiatry 2013; 74:703-715. PMCID 3898620.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/bret.rutherford.1/bibliography/40493618/public/?sort=date&direction=ascending

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

Ongoing Research Support

R33 MH110029 Rutherford (PI) 12/15/18-11/30/21
NIMH
Targeting Dopaminergic Mechanisms of Slowing to Improve Late Life Depression
Goal: This project tests whether administering levodopa to older depressed patients increases striatal dopamine release and increases processing speed and gait speed. Engaging these molecular and functional targets is hypothesized to result in depressive symptom improvement.
Role: Principal Investigator.

R01 MH111596 Rutherford (PI) 07/01/17-06/30/22
NIMH
Cognitive and Neural Mechanisms of the Accelerated Aging Phenotype in PTSD

Goal: This study will investigate the interplay between aging processes and PTSD, which may help identify novel therapeutic targets to promote healthier aging trajectories for PTSD patients.
Role: Principal Investigator.

R01 MH111596-03S1 Rutherford (PI) 07/01/17-06/30/22
NIMH
Administrative Supplement to Cognitive and Neural Mechanisms of the Accelerated Aging Phenotype in PTSD
Goal: This supplement augments the study assessment battery and allows for longitudinal follow-up of this later life neuropsychiatric population at ultra-high risk for cognitive decline and conversion to Alzheimer's disease and Alzheimer's disease Related Dementias (AD/ADRD).
Role: Principal Investigator.

R01 MH114980 Rutherford /Brown (PIs) 09/01/17-08/31/22
NIMH
2/5 Neurocognitive and neuroimaging biomarkers: predicting progression towards dementia in patients with treatment resistant late-life depression
Goal: The goal of the study is to clarify the risk mechanisms via which people with resistant depression in late-life may progress to dementia, and whether effective treatment of such depression mitigates that risk.
Role: Principal Investigator.

R21 AG059130 Rutherford (PI) 07/01/18-06/30/20
NIA
Sensation and Psychiatry: Linking Age-Related Hearing Loss to Late-Life Depression and Cognitive Decline
Goal: This project tests whether untreated age-related hearing loss (ARHL) represents a distinct pathophysiologic route to developing Late-life Depression (LLD) and whether individuals with comorbid ARHL/LLD are unlikely to respond to treatments (i.e., antidepressant medication) that do not treat the underlying hearing problem
Role: Principal Investigator.

TRD151133321 Lenze (PI) 10/1/2016-05/21/2022
PCORI
Optimizing Outcomes in Treatment-Resistant Depression in Older Adults
Goal: This study will address the huge evidence gap for depressed older adults. Quite simply, clinicians cannot weigh the comparative benefits and risks of management strategies for treatment-resistant depression in older adults.
Role: Co-Investigator.

T32 MH020004 Roose (PI) 07/01/1998-06/30/2024
NIMH
Goal: The goal of this program is to train young investigators committed to basic and clinical research in late life psychiatric disorders.
Role: Co-Investigator and Dean of Fellows.

Completed Research Support

R01 MH102293 Rutherford (PI) 01/01/14-12/31/18
NIMH
Mechanisms of Antidepressant Non-Response in Late-Life Depression
Goal: This project combined structural neuroimaging, neuropsychological assessment, and an antidepressant clinical trial to identify the mechanisms of antidepressant non-response in older depressed patients and facilitate the development of new treatment interventions capable of improving clinical outcomes in these individuals.
Role: Principal Investigator.

R21 AG053202 Brown (PI) 7/1/2016-06/30/2018
NIA
Physical and Mental Fatigability in Late Life Clinical Populations
Goal: The goal of this project was to establish concurrent and discriminant validity of mental and physical fatigability domains of the Pittsburgh Fatigability Scale across disorders common in late life in which fatigue is most prevalent.
Role: Co-Investigator.