BIOGRAPHICAL SKETCH

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NAME: Leanne Williams, Ph.D.

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

POSITION TITLE: Professor of Psychiatry and Behavioral Sciences, Stanford University

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
University of Queensland, Australia	BA	03/1987	Psychology
University of New England, Australia	BA, First Class Honors	02/1990	Psychology
University of New England, with scholarship to Oxford University, UK	PhD	03/1996	Cognitive Neuroscience

A. Personal Statement

I am a clinical translational neuroscientist dedicated to the vision of a transformative new paradigm for neuroscience-informed precision psychiatry. The goal of this paradigm is to diagnose, understand, and treat mental disorders based on the functioning of underlying brain circuits. The cumulative and integrative impact of my work reflects this vision and how I have made it a reality over the past 25 years. My research roadmap has prioritized **five inter-related goals** that I have achieved over this time. **First**, I have developed and tested 'biotypes' that account for the heterogeneity of mood and anxiety disorders. I developed a theoretical taxonomy for delineating biotypes of mood and anxiety disorders based on specific dysfunctions in underlying neural circuits and corresponding profiles of symptoms and behavior. In tandem, I have undertaken a series of empirical studies that test the clinical function of these biotypes in providing a mechanistic account of more homogenous subsets of mood and anxiety disorders. I have prioritized my focus on mood and anxiety disorders since 2006 in recognition of how rapidly they have become the leading cause of disability and the emergence of targets for investigation and treatment selection grounded in basic neuroscience. Prior to that time my focus was on specific subtypes of schizophrenia psychosis, given their disproportionate contribution to disability despite lower prevalence. I also continue secondary foci on trauma and attention disorders that co-occur with mood and anxiety disorders in adolescents and adults. Unifying this approach is the evidence for common or overlapping circuit dysfunctions across these disorders. To quantify such dysfunctions, I have used multiple approaches, spanning neuroimaging and electrophysiology, that allow for both high spatial and high temporal resolution measurement, integrated with behavioral and symptom measures that reflect clinical phenotypic expressions. Methodologically, I have developed pipelines for Common Data Elements that span these measurement domains and have enabled me to pool and share data across a large body of cumulative studies. These integrative approaches positioned me to lead one of the first Research Domain Criteria (RDoC) studies of depression and anxiety (2012-2016) and, currently, a Connectomes Related to Human Disease U01 project focused on advanced imaging of mood disorder biotypes. A **second goal** has been the implementation of biotype trials that test neural markers as predictors of treatment selection. From 2008-2012, I led the foundational trial known as the international Study for Predicting Optimized Treatment for Depression ("iSPOT-D") in which I discovered circuit predictors of antidepressant outcomes. I recently co-led the "ENGAGE" trial to identify circuit predictors of novel behavioral interventions for depression, under NIH's priority Science of Behavior Change initiative, which has discovered predictors for depression biotypes not served by pharmacotherapy. Throughout 2008-2012, I led as co-PI a Translational Center of Research Excellence that has identified novel circuit predictors and response biomarkers for exposure therapy relevant to fear-related anxiety and trauma disorders. My **third goal** is to use mechanistic trial designs to identify who benefits from novel interventions and why, focusing on biotypes that contribute most to poor outcomes with standard treatments. I currently lead as PI a project investigating mechanisms of ketamine and MDMA focusing on circuit targets that have functional equivalence with those used in animal models, within a NIDA P50 Center of Excellence. In parallel, I lead a multi-site mechanistic trial characterizing cognitive circuit dysfunction modified by Transcranial Magnetic Stimulation (TMS) in depressed individuals who are resistant to

standard antidepressants. A **fourth goal**, addressed in more recently developed research programs, has been to deploy leading-edge computational approaches to new discovery within the large datasets I have accumulated. Recent examples include the use of machine learning models to predict antidepressant outcomes for individual symptoms and a new regularized group canonical correlation analysis method for integrating circuit and phenotype dimensions within and RDoC framework. Under this goal, I have forged collaborations with leaders in machine learning and regularization, including Andrew Ng and Trevor Hastie at Stanford. **Fifth**, my recent innovations have focused on clinical translational goals to test the utility of circuit-informed biotypes for informing decisions in clinical practice. To accelerate translation I have developed and implemented a novel and reproducible method for quantifying circuit dysfunction at the individual subject level. This approach is the basis of active US and global patents, and, clinically, I have established a circuit assessment and report system that is approved for clinical use within Stanford Health Care hospitals and clinics. In fulfilling my roadmap for neuroscience-informed precision psychiatry I have founded and successfully led two major research centers. I founded the Brain Dynamics Center at Sydney Medical School (2002-2012). During my tenure in Sydney, I was first recruited on faculty in Psychology and subsequently recruited into the Sydney Medical School in a position created for me as the foundational Professor of Cognitive Neuropsychiatry. In my leadership of iSPOT, I established sites across 5 countries and Stanford University was set up as a leading academic site in conjunction with Sydney University. Following the success of iSPOT-D, I was recruited on to Stanford faculty under a waiver of search and, since 2013, I have been on the Stanford faculty as Professor of Psychiatry and Behavioral Sciences and Director of the Precision psychiatry And translational Neuroscience lab, PanLab. I hold a joint position as Director of Education and Precision Medicine at the Palo Alto VA Mental Illness Research, Education and Clinical Center (MIRECC). This year, I celebrate the 3-year anniversary of the new Center I founded at Stanford – the Center for Precision Mental Health and Wellness (PMHW) at Stanford Medical School (2018-present). The PMHW brings together expertise across psychiatry, psychology, neuroradiology, engineering and data science disciplines at Stanford to rapidly accelerate the validation and scaling of biotypes and novel treatments for mental disorders, focusing as a priority on depression. Through my research programs and Centers, I have had the distinctly rewarding opportunity to mentor many early stage investigators and to facilitate their independent careers. I have mentored 16 postdoctoral research fellows at Stanford and through the MIRECC advanced training fellowship programs, four of whom are MD or MD/PhD and four of whom have already obtained junior faculty level positions. During my previous position at Sydney Medical School, I mentored 11 postdoctoral fellows, 9 of whom are on faculty including two as full Professor, four as tenured Associated Professor and three as Assistant Professor/Senior Lecturer. Across my career, I have been the primary mentor for 38 graduate students. My women investigator mentees are equally represented among mentees who have successful independent faculty careers, including at full Professor and Chair.

I highlight the following publication outlining my theoretical framework for delineating circuit based biotypes:

1. **Williams LM** (2016). Precision Psychiatry: A neural circuit taxonomy for depression and anxiety**.** The Lancet Psychiatry, 3(5):472-480. PMID: 27150382 PMCID: PMC4922884

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

5U01MH109985-02
Williams (PI)
04/01/2017 – 4/30/2022 (NCE)
Mapping connectomes for disordered emotional states

1P50DA042012 - 01A1
Williams (Project 4 PI); Deisseroth (Overall Center PI)
08/15/2017 – 04/30/2022
Center of Excellence for Neural Circuit Dynamics of Drug Action (Project 4)

5UH2HL132368-03
Williams (co-PI with Ma)
09/01/2018 – 08/31/2021
Engaging self-regulation targets to understand the mechanisms of behavior change and improve mood and weight outcomes

R01 MH120126
Williams (PI)
09/10/2019 – 05/31/2024
Mechanistic circuit markers of transcranial magnetic stimulation outcomes in pharmacoresistant depression

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019 – present	Member, World Economic Forum Global Future Council on Technology for Mental Health
2018 – present	Founding Director of the Stanford Center for Precision Mental Health and Wellness
2015 – present	Member, Advisory Board, ONE MIND PsyberGuide, One Mind Institute
2014 – 2016	Member, Academic Promotions Committee for Psychiatry and Behavioral Sciences, Stanford
2013 – present	Director, Precision Psychiatry and Translational Neuroscience Lab, Stanford University
2013 – present	Professor, Psychiatry and Behavioral Sciences, Stanford University School of Medicine
2013 – 2016	Executive member (by peer nomination), ACNP membership committee
2013 – present	Fellow (by peer review), American College of Neuropsychopharmacology (ACNP)
2012 – present	Director of Education and Precision Medicine, MIRECC VISN21, VA Palo Alto
2012 – present	Faculty mentor, Career Development Institute for Psychiatry
2009	Advisory Board member, Pfizer Advisory board for Ziprasidone
2007 – 2013	Foundation Professor in Cognitive Neuropsychiatry, University of Sydney Medical School
2005 – 2016	Founding CEO/ President, BRAINnet Foundation, 501c(3) for data sharing across 37 countries
2004 – 2006	Associate Professor, Psychiatry, University of Sydney Medical School
2002 – 2004	Associate Professor, Psychology, University of Sydney
2002 – 2012	Founding Director, Brain Dynamics Center, Sydney Medical School
1999 – 2001	Senior Lecturer (tenured position), Psychology, University of Sydney

Honors

2016	Chairman's Award for Advanced Contributions to Science; Stanford School of Medicine.
2012	Ernst Strüngmann Award; "Schizophrenia evolution and synthesis".
2008	Presidential Award, US Society for Psychosomatic Medicine.
2005	Pfizer Foundation Senior Research Fellowship ($1M, internationally competitive award for "high-risk/high-reward" biomedical research; 1 or 2 awarded nationally per year).
2003	Australian Museum Eureka Prize for Science.
2001	Young Investigator Award, International Schizophrenia Congress.
2000	Senior Scientist Award, 10th Biennial Winter Workshop on Schizophrenia.
1998	Wellcome-Ramaciotti Research Award for advanced study, London Institute of Psychiatry.
1997	Outstanding Postgraduate Advisor of the Year award, University of New England.
1991	British Council Postgraduate Scholarship Award for PhD study at Oxford University, UK.
1990	Australian Postgraduate Research Award, a federal scholarship awarded to Honors program graduates who are ranked nationally in the top 1% of applicants for graduate study.
1989	Australian Psychological Society (APS) Prize for the most outstanding Honors year research dissertation. "Honors" is a 1-year post-bachelor's degree program comprising 60% independent research. The prize is awarded as equivalent to summa cum laude.

C. Contributions to Science

1. Integrating measures of human neural function and developing tasks and norms for probing human circuits grounded in basic neuroscience mechanisms. In my fundamental research, I have developed a new emotion paradigm for probing emotion processing relevant to the RDoC negative valence domains, under conditions of both automatic processing and conscious evaluation, validated by signal detection metrics. In one series of studies I combined high-temporal resolution EEG and event-related potential (ERP) measures with high-spatial resolution functional magnetic resonance imaging (fMRI). I also made concurrent physiological recordings as objective indices of responses to fear stimuli that do not rely on self-report. Through this integrative approach I have contributed new insights into how the brain responds to fear stimuli before we are consciously aware of these stimuli. I have demonstrated that the same stimuli are processed via a direct brain system that is engaged early (within a fifth of a second) and does not require conscious awareness. A parallel circuit is engaged later and supports more detailed processing of threat-related emotion stimuli. I have also demonstrated the utility of responses to these stimuli as objective circuit targets for modification by pharmacological interventions. These fMRI and ERP paradigms inform my novel biomarker trials and are now used by many other labs.

a. Liddell BJ, Brown KJ, Kemp AH, Barton MJ, Das P, Peduto AS, Gordon E, **Williams LM** (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. NeuroImage, 24(1):235-243. PMID: 15588615
b. **Williams LM**, Das P, Liddell BJ et al (2006). Mode of functional connectivity in amygdala pathways dissociates level of awareness for signals of fear. Journal of Neuroscience, 26(36):9264-9271. PMID: 16957082 PMCID: PMC6674508
c. **Williams LM**, Brown KJ, Palmer D, Liddell BJ, Kemp AH, Olivieri G, Peduto A, Gordon E (2006). The 'mellow years'?: Neural basis of improving emotional stability over age. Journal of Neuroscience, 26(24):6422-6430. PMID: 16775129 PMCID: PMC6674038
d. **Williams LM**, Liddell BJ, Kemp AH, Bryant RA, Meares RA, Peduto AS, Gordon E (2006). Amygdala-prefrontal dissociation of subliminal and supraliminal fear. Human Brain Mapping, 27(8):652-661. PMID: 16281289 PMCID: PMC6871444

2. Discovering the mechanisms of pathological cognitive and emotional brain function. I have developed and applied a multi-modal approach to studying emotional and cognitive functions in multiple mental disorders, recognizing that disturbances in these functions are a hallmark of most mental disorders. This approach allowed for novel measures of neural synchrony and neural circuit connectivity by integrating data from electrophysiology recordings, for temporal resolution and functional neuroimaging, for spatial resolution. For example, using this approach I have contributed new knowledge on the mechanisms of altered neural synchrony and connectivity underlying cognitive and emotional dysfunction in psychosis.

a. **Williams LM**, Das P, Harris AW, Liddell BJ, Brammer MJ, Olivieri G, Skerrett D, Phillips ML, David AS, Peduto A, Gordon E (2004). Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. American Journal of Psychiatry, 161(3):480-489. PMID: 14992974
b. Slewa-Younan S, Gordon E, Harris AW, Haig AR, Brown KJ, Flor-Henry P, **Williams LM** (2004). Sex differences in functional connectivity in first episode and chronic schizophrenia patients. American Journal of Psychiatry, 161(9):1595-1602. PMID: 15337649
c. Symond M, Harris AWF, Gordon E, **Williams LM** (2005). "Gamma synchrony" in first episode schizophrenia: A disorder of temporal connectivity? American Journal of Psychiatry, 162(3):459-465. PMID: 15741462
d. Whitford TJ, Grieve SM, Farrow TFD, Gomes L, Brennan J, Harris AWF, Gordon E, **Williams LM** (2007). Volumetric white matter abnormalities in first-episode schizophrenia: A longitudinal, tensor-based morphometry study. American Journal of Psychiatry, 164(7):1082-1089. PMID: 17606660 (focus of editorial)

3. Gene-stress modulation of human neural circuits. I have demonstrated that genetic variants interact with exposure to early life traumatic stress to impact both the structure and function of human neural circuits. These gene-stress-brain relationships are involved in susceptibility for disorders involving altered mood and cognition. In a related series of studies, I demonstrated that variants environment susceptible genes that code for P-glycoprotein, relevant to treatment resistance, and for expression of the corticotropin-releasing hormone, relevant to the stress response, are predictors of antidepressant outcomes in major depressive disorder. These results lay the foundation for understanding gene-stress-brain mechanisms for mood disorders and therapies.

a. Cohen RA, Grieve SM, Hoth K, Paul RH, Sweet L, Tate D, Gunstad J, Stroud L, McCaffrey J, Hitsman B, Niaura R, Clark CR, MacFarlane A, Bryant RA, Gordon E, **Williams LM** (2006). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. Biological Psychiatry, 59(10):975-982. PMID: 16616722
b. Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, Gordon E, Kemp AH, **Williams LM** (2009). Interactions between BDNF Val66Met polymorphisms and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Molecular Psychiatry, 14(7):681-695. PMID: 19153574
c. Schatzberg AF, DeBattista C, Lazzeroni L, Etkin A, Murphy Jr G, **Williams LM** (2015). ABCB1 genetic effects on antidepressant outcomes: A report from the iSPOT-D trial. American Journal of Psychiatry, 172(8):751-759. PMID: 25815420
d. O'Connell CP*, Goldstein-Piekarski AN*, Nemeroff CB, Schatzberg AF, DeBattista C, Carrillo-Roa T, Binder EB, Dunlop BW, Craighead WE, Mayberg HS, **Williams LM** (2018). Antidepressant outcomes predicted by genetic variation in corticotropin-releasing hormone binding protein. American Journal of Psychiatry, 175(3):251-261. PMID: 29241359 PMCID: PMC5832545

4. Development and implementation of neural circuit-informed biomarker trials to test predictors of treatment outcomes in major depressive disorder. I was the academic principal investigator of the landmark international study to predict Optimized Treatment in Depression; "iSPOT-D". Through iSPOT-D I established functional neuroimaging response and prediction biomarkers for response to currently available antidepressants. The results have already advanced our knowledge about the biomarkers that predict which patients are most likely to benefit from specific types of antidepressants. The technological innovations from iSPOT-D include the establishment of common data element protocols for imaging within a biomarker trial design**.** Tasks used to probe neural circuit biomarkers were based on NIH common data elements for neuroscience in emotion-related and cognitive systems.

a. **Williams LM**, Korgaonkar MS, Song YC, Paton R, Eagles S, Etkin A, Gordon E (2015). Amygdala reactivity to emotional faces in the prediction of general and medication-specific responses to antidepressant treatment in the randomized iSPOT-D trial. Neuropsychopharmacology, 40(10):2398-2408. PMID: 25824424 PMCID: PMC4538354
b. Goldstein-Piekarski AN, Korgaonkar MS, Green E, Suppes T, Schatzberg AF, Hastie T, Nemeroff CB, **Williams LM** (2016). Human amygdala engagement moderated by early life stress exposure is a biobehavioral target for predicting recovery on antidepressants. Proceedings of the National Academy of Sciences, 113(42):11955-11960. PMID: 27791054 PMCID: PMC5081583
c. Korgaonkar MS, Goldstein-Piekarski AN, Fornito A, **Williams LM** (2019). Intrinsic connectomes are a predictive biomarker of remission in major depressive disorder. Molecular Psychiatry, 25(7):1537-1549. PMID: 31695168 PMCID: PMC7303006
d. Tozzi L, Goldstein-Piekarski AN, Korgaonkar MS, **Williams LM** (2019). Connectivity of the cognitive control network during response inhibition as a predictive and response biomarker in major depression: Evidence from a randomized clinical trial. Biological Psychiatry, 87(5):462-472. PMID: 31601424

5. Advancing novel designs that integrate randomized controlled trials, multi-modal measurement and computational approaches to probe circuit biomarker target. I have developed and implemented novel designs that focus on circuit biomarker targets in psychiatry and that have facilitated the acquisition of large standardized data sets across disorders, new computational approaches for analyzing these data, new protocols for assessing the impact of intervention compounds on circuit target outcomes. These advances were possible because of new methodologies I developed for fusing repeated testing and longitudinal designs with the evaluation of common data elements, spanning imaging through self-report and grounded in neurobiological constructs aligned with RDoC. Computational approaches made possible because of these novel designs include connectomic analyses of neuroimaging data and machine learning prediction models applied in treatment prediction outcomes in depression. Development and implementation of these novel approaches relied on setting up standardized protocols for acquiring the data and delivering clinically applicable reports on the outcomes. I developed an integrated software system and database with common formats to fuse the quantified data, which could then be shared via the BRAINnet dissemination site I founded. These advances are helping to forge a new roadmap for understanding mental disorder based on the functioning of human neural circuit function, one that informs more precise classifications based on fusing brain and clinical information and for treatment tailoring.

a. **Williams LM**, Hermens DF, Palmer D, Kohn M, Clarke S, Keage H, Clark CR, Gordon E (2008). Misinterpreting emotional expressions in ADHD: Evidence for a neural marker and stimulant effects. Biological Psychiatry, 63(10):917-926 (included on cover). PMID: 18272140
b. Korgaonkar MS, Fornito A, **Williams LM** (2014). Abnormal structural networks characterize Major Depressive Disorder: A connectome analysis. Biological Psychiatry, 2014; 76(7):567-574. PMID: 24690111
c. Grisanzio KA, Goldstein-Piekarski AN, Wang MY, Ahmed APR, Samara Z, **Williams LM** (2018). Transdiagnostic symptom clusters and associations with brain, behavior, and daily function across mood, anxiety, and trauma disorders. JAMA Psychiatry, 75(2):201-209. PMID: 29197929 PMCID: PMC5838569
d. Rajpurkar P, Yan J, Dass N, Vale V, Keller A, Irvin J, Taylor Z, Basu S, Ng A, **Williams LM** (2020). Evaluation of a machine learning model based on pretreatment symptoms and electroencephalographic features to predict outcomes of antidepressant treatment in adults with depression. JAMA Network Open, 3(6):e206653. PMID: 32568399 PMCID: PMC7309440

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