BIOGRAPHICAL SKETCH

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NAME: **Zanderigo Francesca, Ph.D.**

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

POSITION TITLE: Research Scientist IV, Research Foundation for Mental Hygiene;
Associate Professor, Columbia 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 Padova, Italy	M.S.	10/2003	Electronic Engineering
University of Padova, Italy	Ph.D.	04/2007	Bioengineering

A. Personal Statement

Dr. Zanderigo is a Bioengineer whose major focus is extraction of accurate quantitative information from medical images, for the purpose of improving disease diagnosis, prevention and treatment. One of the overarching goals of her work has been to simplify the acquisition of brain imaging data while maintaining the accuracy and precision of the information extracted from such medical images. She has performed extensive quantification, mathematical modeling and analysis of data from Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) for the investigation of cerebral hemodynamics and neuroreceptor systems, built a strong analytical expertise, and contributed to the literature in the field of *in vivo* imaging with several original works.

Dr. Zanderigo is an expert in the modeling of imaging data acquired with multiple PET tracers and in the development of new quantification approaches for PET, including model-free non-parametric approaches to quantification (1); blood-free non-invasive quantification methods that avoid invasive blood sampling from the subject during the PET scan (see for example 2 and 3); and methods to quantify radiotracer binding potentials that do not require the presence of a valid reference region (see for example 4). Dr. Zanderigo has also applied her expertise to quantification of data acquired in rodents and nonhuman primates.

Dr. Zanderigo is an expert quantitative translational scientist who focuses on the ideation of new models and quantification approaches that solve problems related to biological and clinical research, especially for *in vivo* imaging of the living brain, and in the conduction of comprehensive validation experiments of such models and approaches. The experience she has accumulated in collaborative research, and the understanding of the clinical challenges related to the investigation of brain diseases, that she has gained in many years spent within the Department of Psychiatry, make her the kind of quantitative researcher that is needed in translational science.

1. **Zanderigo F**, Parsey RV, Ogden RT. Model-free quantification of dynamic PET data using nonparametric deconvolution. J Cereb Blood Flow Metab, 2015; Vol. 35(8): 1368-79. doi: 10.1038/jcbfm.2015.65. PMID: 25873427.
2. **Zanderigo F**, Ogden RT, Parsey RV. Noninvasive blood-free full quantification of positron emission tomography radioligand binding. Journal of Cerebral Blood Flow and Metabolism, 2015; 35(1): 148-56.
3. Roccia E, Mikhno A, Ogden RT, Mann JJ, Laine AF, Angelini ED, **Zanderigo F**. Quantifying Brain [^{18}F]FDG Uptake Noninvasively by Combining Medical Health Records and Dynamic PET Imaging Data. IEEE J Biomed Health Inform 2019; 23(6): 2576-2582. doi: 10.1109/JBHI.2018.2890459. PMID: 30605111.
4. **Zanderigo F**, Mann J, Ogden T. A hybrid deconvolution approach for estimation of in vivo non-displaceable binding for brain PET targets without a reference region. PLoS One; 2017, 12(5): e0176636. doi: 10.1371/journal.pone.0176636.

B. Positions and Honors

Positions and Employment

8/07 -11/07 Post-doctoral fellowship as Research Scholar in the Department of Psychiatry, Columbia University, New York, NY, USA (PET analysis). Supervising Professor: Dr. Ramin V. Parsey.

1/08-3/11 Research Scientist in the Brain Imaging Laboratory, Molecular Imaging and Neuropathology Division, New York State Psychiatric Institute, New York, NY, USA.

4/11-6/12 Associate Research Scholar at the Italian Academy of Columbia University, New York, NY, USA (Bodini Fellowship in Developmental and Adolescent Psychiatry); Post-Doctoral Research Scientist, Molecular Imaging and Neuropathology Division, New York State Psychiatric Institute, New York, NY, USA.

7/12-6/14 Assistant Professor of Clinical Neurobiology (in Psychiatry), Department of Psychiatry, Stony Brook University, Stony Brook, NY, USA.

7/14-6/19 Assistant Professor of Clinical Neurobiology (in Psychiatry), Department of Psychiatry, Columbia University, New York, NY, USA.

6/14-present Research Scientist IV, Research Foundation for Mental Hygiene, Inc. at the New York State Psychiatric Institute, New York, NY, USA.

7/19-present Associate Professor of Clinical Neurobiology (in Psychiatry), Department of Psychiatry, Columbia University, New York, NY, USA.

10/14-present Director of the Laboratory of Brain Image Analysis within the Molecular Imaging and Neuropathology Area, New York State Psychiatric Institute, New York, NY, USA.

Grant Review Committees

2/2016 NIH, Center for Scientific Review, Early Career Reviewer; Biodata Management and Analysis Study Section (BDMA), Reviewer.

C. Contribution to Science

1) Dr. Zanderigo has been investigating alternative, less-invasive and non-invasive approaches for full quantification of *in vivo* PET data. Full quantification of PET data requires collection of blood samples during the scan via arterial line, and subsequent assay. Arterial cannulation is invasive, with risks of adverse events, and diminishes subject recruitment. Many minimally-invasive methods for PET quantification have been proposed, but to-date they have not eliminated the need for at least some blood sampling from the subject. Among these methods, Drs. Ogden and Zanderigo proposed the use of parametric simultaneous estimation of input function, which still requires one arterial blood sample for anchoring the input function. Dr. Zanderigo was able to further advance this method into a totally blood-free strategy for full quantification that uses training with biometrics collected from subjects[a,b,c]. Blood sampling can also be avoided if a region completely devoid of the target of interest can be found, by using reference region approaches. Dr. Zanderigo proposed her original Reference Region-based Likelihood Estimation in Graphical Analysis[d].

a. **Zanderigo F**, Ogden RT, Parsey RV. Noninvasive blood-free full quantification of positron emission tomography radioligand binding. Journal of Cerebral Blood Flow and Metabolism, 2014. doi: 10.1038/jcbfm.2014.191.
b. Mikhno A, **Zanderigo F**, Ogden R, Mann J, Angelini E, Laine A, Parsey R. Toward Non-invasive Quantification of Brain Radioligand Binding by Combining Electronic Health Records and Dynamic PET Imaging Data. IEEE J Biomed Health Inform. 2015; 19(4): 1271-82.
c. Roccia E, Mikhno A, Ogden RT, Mann JJ, Laine AF, Angelini ED, **Zanderigo F**. Quantifying Brain [^{18}F]FDG Uptake Noninvasively by Combining Medical Health Records and Dynamic PET Imaging Data. IEEE J Biomed Health Inform 2019; 23(6): 2576-2582. doi: 10.1109/JBHI.2018.2890459. PMID: 30605111.

d. **Zanderigo F**, Ogden RT, Parsey RV. Reference region approaches in PET: a comparative study on multiple radioligands. Journal of Cerebral Blood Flow and Metabolism, 2013, 33(6): 888-97. PMID: 23423188, PMC3677108.

2) Dr. Zanderigo has investigated the use of nonparametric deconvolution approaches for the characterization of signals from biological systems. In particular, she has focused on the quantification via contrasted MRI of human cerebral hemodynamics[a], and applied it to the case of elder patients affected by stenosis of the carotid arteries. An accurate characterization of the individual hemodynamics in this case is of crucial importance when making the decision on whether intervening surgically is proper or not. These characterization and quantification require solving a deconvolution problem. The most popularly used deconvolution methods in the field of contrasted MRI, however, carry limitations and bias in presence of delay and dispersion of the contrast agent bolus. Dr. Zanderigo proposed a new deconvolution method, based on nonlinear stochastic regularization, that was proven to be superior to other approaches, tested its performance on simulated data[b], and applied it to the analysis of clinical data[c]. The proposed nonlinear stochastic regularization was later extended, by independent investigators, and found application in the non-invasive quantification of cerebral blood flow with Arterial Spin Labeling[d].

a. Bertoldo A, **Zanderigo F**, Cobelli C. Assessment of cerebral blood flow, volume, and mean transit time from bolus-tracking MRI images: theory and practise in Advanced Image Processing in Magnetic Resonance Imaging, 2005, L. Landini Editor, Marcel Dekker Signal Processing and Communications Series, New York, NY.
b. **Zanderigo F**, Bertoldo A, Pillonetto G, Cobelli C. Nonlinear stochastic regularization to characterize tissue residue function in bolus-tracking MRI: assessment and comparison with SVD, block-Circulant SVD and Tikhonov. IEEE Transaction on Biomedical Engineering, 2009, Vol. 56(5): 1287-97. PMID: 19188118.
c. Peruzzo D, **Zanderigo F**, Bertoldo A, Pillonetto G, Cosottini M, Cobelli C. Assessment on clinical data of nonlinear stochastic deconvolution versus block-circulant singular value decomposition for quantitative dynamic susceptibility contrast magnetic resonance Imaging. Magn Reson Imaging. 2011; 29(7): 927-36. PMID: 21616625.
d. Ahlgren A, Wirestam R, Petersen ET, Ståhlberg F, Knutsson L. Perfusion quantification by model-free arterial spin labeling using nonlinear stochastic regularization deconvolution. Magn Reson Med, 2013; 70(5): 1470-80. PMID: 23281031.

3) Dr. Zanderigo has contributed to the literature of advanced quantification approaches in the field of *in vivo* imaging with original works that include development and application of methodologies for the generation of quantitative parametric images at the voxel level[a], alternative robust fitting approaches to improve statistical power and sensitivity[b], model-free quantification for PET reversible tracers[c], and likelihood-based estimation of a receptor's occupancy by a certain drug[d]. These approaches are in use for the quantification of PET tracers at the Molecular Imaging and Neuropathology Area of Columbia University, and in the Department of Psychiatry at Stony Brook University.

a. **Zanderigo F**, Ogden RT, Bertoldo A, Cobelli C, Mann JJ, Parsey RV. Empirical Bayesian estimation in graphical analysis: a voxel-based approach for the determination of the volume of distribution in PET studies. Nucl Med Biol. 2010;37(4):443-51. PMID: 20447556, PMC2896257.
b. **Zanderigo F**, Ogden RT, Chang C, Choy S, Wong A, Parsey RV. Robust fitting of [11C]-WAY-100635 PET data. J Cereb Blood Flow Metab, 2010; 30(7): 1366-72. PMID: 20179725, PMC2949218.
c. **Zanderigo F**, Parsey RV, Ogden RT. Model-free quantification of dynamic PET data using nonparametric deconvolution. J Cereb Blood Flow Metab, 2015; Vol. 35(8): 1368-79. doi: 10.1038/jcbfm.2015.65. PMID: 25873427.
d. Schain M, **Zanderigo** F, Ogden RT. Likelihood Estimation of Drug Occupancy for Brain PET Studies. Neuroimage, 2018; 178: 255-265.

4) Dr. Zanderigo has also conducted modeling and validation of novel PET tracers for *in vivo* imaging in humans (e.g. arachidonic acid[a] and harmine[b]), led the investigation on the normative and pathological brain *in vivo* using multimodal brain imaging[c], and contributed to the use of PET- and MRI-derived biomarkers for the treatment personalization and diagnosis (see for example d) of major depressive disorder and other disorders.

a. **Zanderigo F**, Kang Y, Kumar D, Nikolopoulou A, Mozley PD, Kothari PJ, He B, Schlyer D, Rapoport SI, Oquendo MA, Vallabhajosula S, Mann JJ, Sublette ME [^{11}C]arachidonic acid incorporation measurement in human brain: optimization for clinical use. Synapse 2018; 72(2).
b. **Zanderigo F**, D'Agostino AE, Joshi N, Schain M, Kumar D, Parsey RV, Delorenzo C, Mann JJ. [^{11}C]harmine binding to brain monoamine oxidase A: test-retest properties and noninvasive quantification. Molecular Imaging and Biology 2018 (in press).
c. **Zanderigo F**, Pantazatos S, Rubin-Falcone H, Ogden RT, Thapa-Chhetry B, Sullivan G, Oquendo MA, Miller JM, Mann JJ. In vivo relationship between serotonin 1A receptor binding and gray matter volume in the healthy brain and in major depressive disorder. Brain Structure and Function, 2018; 223(6): 2609-2625.
d. Rubin-Falcone H, **Zanderigo F**, Thapa-Chhetry B, Lan MJ, Miller JM, Sublette ME, Oquendo MA, Hellerstein D, McGrath P, Stewart J, Mann JJ. Pattern recognition of Magnetic Resonance Imaging-based grey matter volume measurements classifies bipolar and unipolar major depressive disorder. Journal of Affective Disorders, 2018; 227: 498-505.

5) Dr. Zanderigo has applied her analytical skills to the real-time prediction of blood glucose concentrations from data collected using glucose-level non-invasive continuous monitoring systems[a,b,c,d]. The possibility to predict ahead of time potential hypo- and hyper-glaecemic events, and to alert the diabetic patient of the risk, who can then take preventive actions to avoid the event (e.g., injection of insulin, sugar intake), can radically transform the daily routine of diabetic patients and significantly improve their quality of life. These predictive models were later translated into use with glucose meter systems by Menarini Group, Florence, Italy, and Abbott Diabetes Care, San Francisco, USA.

a. **Zanderigo F**. Sparacino G, Kovatchev B, Cobelli C. Glucose prediction algorithms from continuous monitoring data: assessment of accuracy via continuous glucose error-grid analysis. J Diabetes Sci Technol, 2007; 1(5): 645-51. PMID: 19718282, PMC2734107.
b. Sparacino G, **Zanderigo F**, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. IEEE Transactions on Biomedical Engineering, 2007; Vol. 54 (5): 931- 937.
c. Sparacino G, **Zanderigo F**, Maran A, Cobelli C. Continuous glucose monitoring and hypo/hyperglycaemia prediction. Diabetes Research and Clinical Practice, 2006; 74: S160-S163.
d. Facchinetti A, Sparacino G, **Zanderigo F**, Cobelli C. Reconstructing by deconvolution plasma glucose from continuous glucose monitoring sensor data. Conf Proc IEEE Eng Med Biol Soc. 2006; 1:55-8.

Dr. Zanderigo's full list of published work can be found at
http://www.ncbi.nlm.nih.gov/pubmed/?term=zanderigo+f+%5Bauthor%5D

D. Research Support

Ongoing Research Support

1R01EB026481-01 (PI: Zanderigo) 07/15/2018 - 06/30/2022
NIBIB
Noninvasive Quantification of Brain Glucose Metabolism Using a Portable Positron Emission Tomography Camera
New portable Positron Emission Tomography (PET) cameras with increased sensitivity over current PET scanners are paving the way for yet unexplored PET applications. However, a significant limitation in the use of portable PET devices, and PET imaging in general, is the need for continuous arterial blood sampling from the subject's arm during scan, for current gold-standard quantification of tracer uptake and binding to the target in relation to tracer blood levels. We will develop a new tissue- based, blood-free method to quantify the net influx rate of PET tracers with irreversible kinetics, validate the method using new collected [^{18}F]fluorodeoxyglucose data, and disseminate the software routines to allow use of this method for analysis of brain imaging data acquired with current and new generation PET scanners.

1R01EB024526 (PI: Ogden) 07/01/2017 - 06/30/2022
NIBIB
Advanced Modeling Techniques for Brain Imaging Data with PET

Positron emission tomography (PET) represents a powerful tool for investigating the biological base of depression, Alzheimer's disease, and other neuropsychiatric diseases. To analyze PET data and address the broader scientific questions we propose to develop powerful new analysis techniques that will model data across many subjects at once, allowing for greater flexibility and precision. These advances will also relax the requirements for PET imaging, allowing for much greater clinical applicability.
Role on Project: Subaward PI

5P50MH090964-06 (PI: Mann) 07/01/2018 - 06/30/2023
NIMH
Conte Center: Antecedents of Suicidal Behavior Related Neurobiology
The Conte Center will employ a multidisciplinary approach to study how reported childhood adversity can mold the diathesis for suicidal behavior. These projects will help elucidate how early adverse experiences affect gene expression and brain biology to increase risk of suicidal behavior later in life.
Role on Project: Co-Investigator, PET Project

5R01MH108032-03 (PI: Mann) 08/18/2015 - 4/30/2020
NIMH
Familial Early-Onset Suicide Attempt Biomarkers
We seek to determine both resilience and vulnerability phenotypes for suicide attempts in major depressive disorder (MDD). Both phenotypes may aid estimation of risk and provide new targets for prevention intervention.
Role on Project: Co-Investigator

Completed Research Support

5R01MH104512-03 (PI: DeLorenzo) 05/01/2015 - 01/31/2019
NIMH
Advancing Personalized Antidepressant Treatment Using PET/MRI
Currently, there are no objective methods for choosing an antidepressant treatment, leading to weeks of ineffective treatment trials, and increased burden on depressed patients, their families and the economy. In this proposal, an image-based method (that has already shown promising results) is developed that provides insight into the biology of major depression and can be used to predict an individual's likelihood of antidepressant response (prior to treatment). In addition, innovative techniques that would decrease the burden and cost of this imaging method are applied and validated.
Role on Project: Subaward PI

5P50MH090964-05 (PI: Mann) 07/19/2013 - 06/30/2018
NIMH
Conte Center: Antecedents of Suicidal Behavior Related Neurobiology
The Conte Center will employ a multidisciplinary approach to study how reported childhood adversity can mold the diathesis for suicidal behavior. These projects will help elucidate how early adverse experiences affect gene expression and brain biology to increase risk of suicidal behavior later in life.
Role on Project: Research Scientist, PET Project

1R21MH112037-02 (PI: Prabhakaran) 09/09/2016 - 8/31/2018
NIMH
Development of GSK-3beta PET Radioligands for in vivo Imaging in Brain
Glycogen kinase synthase-3 (GSK-3) has important role in psychiatric disorders and neurodegenerative diseases and are also targets for drug development. A specific GSK-3 positron emission tomography (PET) radiotracer can be a valuable tool for noninvasive imaging of the changes in GSK-3 in brain, thereby allowing accurate diagnosis, monitoring disease progression and accelerating the development of innovative medicines.
Role on Project: Co-Investigator