BIOGRAPHICAL SKETCH

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NAME: Amira Latif-Hernandez

eRA COMMONS USER NAME (credential, e.g., agency login): LATIF-HERNANDEZ

POSITION TITLE: Instructor

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 Sevilla, Spain	B.Sc	09/2010	Neuropsychology
University of Sevilla, Spain	M.Res.	06/2012	Neurophysiology
University of KU Leuven, Belgium	Ph.D.	06/2017	Neuroscience
Stanford University, Palo Alto, CA	Postdoc	09/2020	Neuroscience
Stanford University, Palo Alto, CA	Instructor	Present	Memory Disorders

A. Personal Statement

My research interest focuses on understanding the specific molecular and cellular events that govern synaptic failure during Alzheimer's disease and related dementias (ADRD) with the ultimate goal of developing mechanism-based therapeutics. During my predoctoral studies in Dr. Balschun's lab I develop a synaptic depotentiation electrophysiology protocol using 'plasticity-neutral' theta frequency of 5 Hz to detect synaptopathies in AD. This experience galvanized my interest in electrophysiology. During my PhD in Dr. Balschun's and D'Hooge's lab, in collaboration with the group of Dr. Bart de Strooper, (KU Leuven) and Takashi Saito (Riken Institute), I characterized electrophysiology and brain synchronicity in the prefrontal cortex and hippocampus of the new APP knock-in (KI) mouse lines to demonstrate their validity as clinically valid models of AD model. I sought postdoctoral training in molecular biology, drug target validation/manipulation and genetics to understand transcriptome-based signaling pathways during neurodegeneration. The Longo lab is an ideal fit for my translational research training, where I coordinated collaborations with Wyss-Coray lab at Stanford to identify activity-dependent gene expression and translate preclinical findings into insights derived from clinical human data (*Alzheimer's & Dementia, 2024*); and with Andreasson lab at Stanford to demonstrate that lipid messenger prostaglandin E_2 contributes to age-associated inflammation and synapse dysfunction (Nature, 2021), and that the transcription of glycolytic genes and astrocytic lactate transfer in mouse brain and human induced pluripotent stem cells (*Science, 2024*). My research has led to 11 publications and 12 invited oral presentations at international conferences, and several academic awards, demonstrating my contributions to the field of ADRD. After 3 years of productive research, training achievements, and collaborative work as a postdoctoral researcher, I was nominated for Instructor, which constituted a reliable criterion our senior faculty envision me as a successful candidate for independent faculty position. My proposal for the recently awarded BrightFocus Standard Award in ADRD research aims to understand the mechanisms of neuroplasticity and genetics associated to the pathophysiology of neurodegenerative diseases in the context of synaptic stimulation. My research plan is designed to identify novel activity-dependent mechanisms of Interneuron/Astrocyte communication that fail in ADRD. By elucidating these mechanisms, I aim to identify potential therapeutic targets that can be modulated to restore synaptic dysfunction and ameliorate ADRD progression. As a result, I began an exciting and highly productive collaboration with Dr. Birgitt Schuele to provide primary cell culture expertise, as we unravel key activity-dependent transcriptomic signatures that may contribute to synaptic dysfunction in ADRD.

a) **Latif-Hernandez A.***, Shah D., Craessaerts K., Saido T., Saito T., De Strooper B., Van der Linden A., D'Hooge R. (2017). Subtle behavioral changes and increased prefrontal-hippocampal network synchronicity in APP NL-G-F mice before prominent plaque deposition***. Behavioral Brain Research***.

b) **Latif-Hernandez, A.**, Sabanov, V., Ahmed, T., Craessaerts, K., Saito T., Saido T and Balschun, D. (2020). The two faces of synaptic failure in *App*$^{NL-G-F}$ knock-in mice. ***Alzheimer Research & Therapy***.

c) Minhas S, P.**, Latif-Hernandez, A.***, McReynolds, M.***, Wang, Q., Joshi U, A., Gauba, E., He, J., Liu, L., Durairaj, A., Rubin, A., Linde, M., Moon K, P., Majeti, R., Weissman, I., Mochly-Rosen, D., Longo, F., Rabinowitz D, J., Andreasson I, K. (2021; ***** first-author). Metabolic rejuvenation of myeloid cells reverses age-associated cognitive decline. ***Nature***.

d) Minhas S, P.***,** Jones R, J.***, Latif-Hernandez, A.*, …** Andreasson I, K. (2024; *****first-author). Restoring hippocampal glucose metabolism rescues cognition across Alzheimer's disease pathologies. ***Science***.

B. Positions, Scientific Appointments and Honors

Positions and Employment

2020- Present	Instructor in Memory Disorders, Neurology department, Stanford Medicine, CA
2017-2020	Postdoctoral researcher, Neurology department, Stanford Medicine, CA
2013-2017	Graduate student, Biological psychology department, KU Leuven, Belgium
2012-2013	Junior researcher, Biological psychology department, KU Leuven, Belgium

Honors

2024-2027	BrightFocus Standard Award ($300,000) winner
2024-Present	Member of the NIH Early Career Reviewer Program - CMND study section
2022	Fellowship Award - Tau2022 Global Conference
2020	Fellowship Award - Tau2020 Global Conference
2019	Trainee Professional Development Award - Society for Neuroscience

C. Contribution to Science

1) **Pre-doctoral career:** The role of ionotropic and metabotropic neuronal receptors for metaplasticity:

One of the most gratifying contributions during my early career was the development of a synaptic depotentiation electrophysiology protocol using 'plasticity-neutral' theta frequency of 5 Hz that allowed us to detect synaptopathies by examining the reversal of long-term potentiation (LTP), a biological correlate of learning and memory that deteriorates with aging and in AD. Before my graduate work, I elucidated a functional dissociation between metabotropic glutamate receptor type 1 (mGluR1) and type 5 (mGluR5) in two related and consecutively induced types of NMDA-dependent synaptic plasticity, with far reaching consequences for their role in plasticity and learning under normal and pathological conditions. Throughout that time, I trained acute hippocampal slices preparation from rodents and recorded synaptic plasticity for ≥4h. I was very passionate already at the time to understand how an electrophysiology setup functions, and the application of pharmacological agents to determine the role of specific neuronal receptors in synaptic plasticity in several transgenic mouse models.

a) **Latif-Hernandez A.**, Faldini E., Ahmed T. and Balschun D., (2014). NMDA and mGluR1 receptor subtypes as major players affecting depotentiation in the hippocampal CA1-region. ***Frontiers in System Neuroscience***.

b) **Latif-Hernandez A.**, Faldini E., Ahmed T. and Balschun D., (2016). Separate ionotropic and metabotropic glutamate receptors functions in synaptic depotentiation versus LTP: A distinct role for group I mGluR subtypes and NMDARs. ***Frontiers in Cellular Neuroscience***.

2) **Early Graduate career**: Hippocampal-prefrontal cortex network activity, neuroplasticity and cognitive flexibility in a chemical model of neurodegeneration and in ADRD models.

Hippocampus (HC) and medial prefrontal cortex (mPFC) are two main vulnerable regions to pathology in Alzheimer's disease, and many studies have shown that they both have an important role for a variety of memory processes. However, there were not that many reports on how these two crucial brain areas connect to each other to support more complex mechanisms of learning and memory, the so-called cognitive flexibility, the ability to adjust behavior flexibly in response to changing environmental demands. To answer this question, I first used a chemical model of neurodegeneration giving an intracerebral injection of the excitotoxic, endogenous tryptophan metabolite, quinolinic acid (QA) locally into the prefrontal cortex. This was the most challenging experimental schedule I had during my graduate training. I hypothesized that the behavioral and cognitive effects of mPFC lesions could be attributed to changes in functional connectivity (FC) between these brain regions. My findings demonstrated the central functional importance of rodent mPFC as well as the validity of QA-induced mPFC damage as a preclinical rodent model of the early stages of neurodegeneration. In addition**,** early in my graduate training I was involved in a cutting-edge study that received a distinguished prize at the Molecular Imaging conference in Germany (2016). In this study, I demonstrated that reducing Amyloid β early in the disease progression completely restored LTP in AD mice in collaboration with Van der Linden lab, at Antwerp University in Belgium, which identified earliest changes in synaptic function and brain connectivity that are of interest for development of early biomarkers. Using a similar approach, I demonstrated early markers of prefrontal and hippocampal tau pathology in a mouse model of tauopathy by identifying abnormalities in LTP, behavior and brain synchrony.

a) **Latif-Hernandez A**., Shah D., Lo A., Ahmed T., Callaert-Vegh Z., De Wit J., Van der Linden A., Balschun D. and D'Hooge R., (2015). Medial prefrontal cortex ablation results in impaired spatial memory and hippocampal long-term potentiation with increased functional connectivity in vivo. ***Frontiers in Neuroscience***.

b) **Latif-Hernandez A**., Shah D., Ahmed T., Lo A., Callaert-Vegh Z., Van der Linden A., Balschun D. and D'Hooge R., (2016). Quinolinic acid injection in mouse medial prefrontal cortex affects reversal learning abilities, cortical connectivity and hippocampal synaptic plasticity. ***Scientific reports***.

c) Shah D., Praet J.*, **Latif-Hernandez A.***, Höfling C., Anckaerts C., Bard F., Morawski M., Detrez JR., Prinsen E., Villa A., De Vos WH., Maggi A., D'Hooge R., Balschun D., Rossner S., Verhoye M. and Van der Linden A., (*second author) (2016). Early pathological amyloid causes hypersynchrony of BOLD resting-state networks in transgenic mice and provides an early therapeutic window before amyloid plaque deposition. ***Alzheimer's and Dementia***.

d) **Latif-Hernandez A**., Schreurs A., Ahmed, T., Shah D., Van Leuven F., Van der Linden A., D'Hooge R., Balschun D., (2016). Early markers of tau pathology in young Tau. P301L mice: synaptic plasticity, cognition and neuronal synchrony. ***Journal of Neurochemistry.***

3) **Late Graduate Career**: Synaptic plasticity, *in vivo* brain synchrony and behavioral deficits that depend on mPFC and HC in next generation APP Knock-in mouse models for Alzheimer's disease.

In the middle of my PhD phase, I realized that 60% of the phenotypes observed in traditional AD mouse models could have been mere "artifacts" leading to misconceptions about AD pathology. This is because the overexpression mouse models can cause multiple artificial problems, including axonal transport disruption. Then I learned that these problems can be overcome by creating models that overproduce Aβ42 without overexpressing APP, the knock-in (KI) models of humanized Aβ. This led me to get in close collaboration with the group of Bart de Strooper, in KU Leuven (a world leader in Alzheimer's research), who provided with all necessary mice required for me to characterize more controlled functional consequences of the KI strategy on complex behavioral and cognitive abilities, neural plasticity and brain circuitry. Therefore, I evaluated the validity of the APP KI mouse lines as mouse models of clinical AD. I investigated various cognitive domains in these mice using behavioral tasks that have been established to assess not only learning abilities but also higher-order functions. In addition, activity-dependent synaptic changes in prefrontal and hippocampal slices were evaluated in an attempt to understand how Aß-specific pathology affects the synaptic functions that underlie behavioral and cognitive performance. Synaptic dysfunction, elicited by soluble Aβ, have been shown to impair communication between brain regions, neuronal networks, and eventually also the behavioral and cognitive abilities that depend on their integrity. Therefore, we used functional magnetic resonance imaging (rsfMRI) to assess connectivity between brain regions and brain network integrity, which could be affected by synaptic dysfunction as well as form the basis of the behavioral changes observed in these mice. These are the first demonstrations of brain network alterations, synapse dysfunction and high

order cognitive deficits in these novel mouse models of AD. During this time, I also I contributed to a paper as first author where we commented on a paper about APP as a mediator of synapse dysfunction.

a) **Latif-Hernandez A.***, Shah D.*, Craessaerts K., Saido T., Saito T., De Strooper B., Van der Linden A., D'Hooge R., (*first author) (2017). Subtle behavioral changes and increased prefrontal-hippocampal network synchronicity in APP NL-G-F mice before prominent plaque deposition***.** ***Behavioral Brain Research***.

b) Shah D.*, **Latif-Hernandez A.***, De Strooper B., Saito T., Saido T., Verhoye M., D'Hooge R. and Van der Linden A., (*first author) (2018). Spatial reversal learning defect coincides with hypersynchronous telencephalic BOLD functional connectivity in APPNL-F/NL-F knock-in mice. NPJ ***Scientific Reports*****.**

c) Schreurs A.*, **Latif-Hernandez A.***, and Uwineza A.*, (*first author) (2018). Commentary: APP as a Mediator of the Synapse Pathology in Alzheimer's disease. ***Frontiers in Cellular Neuroscience****.*

d) **Latif-Hernandez, A**., Sabanov, V., Ahmed, T., Craessaerts, K., Saito T., Saido T and Balschun, D., (2020). The two faces of synaptic failure in *App*$^{NL-G-F}$ knock-in mice. ***Alzheimer Research & Therapy***.

4) **Postdoctoral career**: Therapeutic candidates to restore synaptic dysfunction and transcriptomic alterations in ADRD models.

Along my scientific career, I have always been interested in developing and understanding the effect of therapeutics to restore synapse dysfunction in AD. Long-term potentiation (LTP) has been associated with the formation of new dendritic spines, increases in perforated postsynaptic densities and with the enlargement of spine heads. In my studies, I have employed electrophysiology protocols that artificially reproduce the conditions in the living brain. I assumed that there is an interesting causal relationship between memory and LTP, since it has been revealed that LTP consists of distinct phases involving different molecular mechanisms. I have always found very inspiring the fact that treating ADRD mice with certain drugs could restore the ability of synapses to be stronger again and produce LTP, which can translate to memory improvements in AD patients. For that reason, during my postdoc at Stanford, I was fortunate to train in a lab where the most promising small molecules to treat AD were developed. So, I initiated projects on the effect of small molecule treatment in vivo in several neurodegeneration mouse models, all of which will lead to publications in top-tier journals.

a) **Latif-Hernandez A.,** Moran-Losada P., Yang T., C. Tran K., Liu H., Lehallier B., M. Massa S. and M. Longo F., (2020). Elucidating emerging therapeutics: P75 receptor modulation reverts tauopathy-associated alterations in synapse-relevant gene expression signatures*.* ***Alzheimer's & Dementia***.

b) **Latif-Hernandez A.,** Moran-Losada P., Yang T., C. Tran K., Liu H., R. Butler R., M. Massa S. and M. Longo F., (2021). Activity-dependent dysfunctional gene expression patterns are normalized by *in vivo* treatment of late-stage Aβ pathology mice with a TrkB/C small molecule ligand. ***Alzheimer's & Dementia****.*

c) **Latif-Hernandez A.,** Moran-Losada P., Yang T., R. Butler R., C. Tran K., Liu H., M. Massa S., Wyss-Coray T. and M. Longo F., (2022). p75NTR modulation counteracts alterations in neuronal and glial activity-dependent profiles of gene co-expression networks in tauopathy mice. ***Alzheimer's & Dementia****.*

d) **Latif-Hernandez, A**., Yang T., R. Butler R., Moran-Losada P., Minhas P., White H., C. Tran K., Liu H., Simmons D., Langness V., Andreasson K., Wyss-Coray T., and M. Longo F., (2023). A TrkB and TrkC partial agonist restores deficits in synaptic function and promotes activity-dependent synaptic and microglial transcriptomic changes in a late-stage Alzheimer's mouse model*.* ***BioRvix.***

5) **Instructor career**: Maladaptive myeloid phenotypes in aging and disease.

As part of my transition from postdoctoral scientist to Instructor, I established solid collaborations with the Andreasson lab to understand how restoring healthy myeloid metabolic and immune responses can positively affect hippocampal plasticity and function. To answer this question, I used innovative electrophysiogical approaches that helped me to demonstrate that inhibition of a critical proinflammatory pathway, the PGE2 EP2 myeloid pathway, can restore synaptic plasticity in aging rodents to youthful levels. In addition, I contributed to elucidate that microglial BMAL1 function is critical to maintaining hippocampal plasticity and memory in aging**.** Finally, I found a remarkable restoration of hippocampal synaptic plasticity by inhibition the kynurenine pathway in Familial Alzheimer's disease mice (Minhas*, Jones* & Latif-Hernandez*, *Science*). In parallel, my research continued to be focused on unraveling the specific synaptic molecules and protein

modifications underlying Aβ and tau-induced memory and synapse dysfunction in Alzheimer's disease (ADRD). Therefore, during this time, I also built on my established collaboration with the Wyss-Coray lab at Stanford to explore activity-dependent alternative splicing (AS), a phenomenon linked to ADRD pathophysiology. While existing studies mainly investigated cultured neurons, I am pioneering AS analysis in stimulated brain tissue undergoing LTP, hypothesizing that disease-specific disruptions in AS patterns may only be revealed during this process that could be disrupted in AD mice, many of which might be relevant to human AD transcriptional changes. Excitingly, my preliminary RNA-seq data from LTP-induced AD brain slices reveals novel disease-related changes in synaptic plasticity-associated AS isoforms, including those in genes like *Gria1, Cacna1h, Lrp6, and Prickle*, which are relevant to neuronal and glial function in ADRD. This opens avenues for targeted therapeutic interventions by understanding how AS contributes to synaptic dysfunction in AD.

a) Minhas S, P.***,** Jones R, J.***, Latif-Hernandez, A.*, …** Andreasson I, K. (2024; *****first-author). Restoring hippocampal glucose metabolism rescues cognition across Alzheimer's disease pathologies. ***Science***.

b) Minhas S, P., **Latif-Hernandez, A.***, McReynolds, M.*, Wang, Q., Joshi U, A., Gauba, E., He, J., Liu, L., Durairaj, A., Rubin, A., Linde, M., Moon K, P., Majeti, R., Weissman, I., Mochly-Rosen, D., Longo, F., Rabinowitz D, J., Andreasson I, K. (2021; *second author). Metabolic rejuvenation of myeloid cells reverses age-associated cognitive decline. ***Nature***.

c) Agbaegbu Iweka, C., Seigneur, E., **Latif-Hernandez, A.**, Herrera Paredes, S., Cabrera, M., Blacher, E., Tsai Pasternak, C., Wang, Q., Longo, F., de Lecea, L., and Andreasson, K. (2022). Myeloid deficiency of the intrinsic clock protein Bmal1 disrupts microglial synaptic pruning and accelerates cognitive decline. ***Journal of Neuroinflammation***.

e) **Latif-Hernandez A.,** Moran-Losada P., Yang T., White H., C. Tran K., Liu H., M. Massa S., Wyss-Coray T. and M. Longo F. (2023). Neuronal stimulation-regulated RNA splicing defects in tauopathies are corrected by treatment with a p75 NTR modulator. ***Alzheimer's & Dementia***.

For a complete list of my publications please follow this link:
https://www.ncbi.nlm.nih.gov/myncbi/amira.latif%20hernandez.1/bibliography/public/