OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02-28-2023)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

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	Neuroscience

A. Personal Statement

The decision to commit to a postdoctoral project stemmed from my passion for translational research and the development of therapeutic strategies for neurodegeneration, which ultimately prompted me to find an enriching scientific environment where to achieve my research goals.
I am a Research Instructor in the Neurology department at Stanford University working under the mentorship of Frank Longo, where I am elucidating the signaling pathways that are involved in the pathophysiology of neurodegenerative disorders, with a focus on Alzheimer's disease and related dementias. Within the Alzheimer's field, my work has resulted in 8 international publications that have touched on diverse topics including neuronal plasticity from different brain regions, in vivo brain synchrony, neurocognitive deficits and pharmacological applications.

To complement my expertise in slice electrophysiology, animal behavior and in vivo surgical manipulations developed during my undergraduate and graduate research experiences, I specifically sought postdoctoral training in molecular biology, drug target validation and genetics to understand transcriptome-based signaling pathways during neurodegeneration. The Longo lab is an ideal fit for my translational research training, aspect that will complete my expertise in order to translate basic science to clinical applications. I have learned biochemical analyses such as western blots, immunostaining and confocal microscopy methodologies and completed experiments on the underlying mechanisms of synaptic plasticity. These studies provided novel insights into synapse dysfunction in several disease mouse models and identified candidate mechanisms by which several drug compounds rescue alterations in synapse function. This is key to understand the mechanisms by which candidate drugs work to rescue cells from dying and even better, restoring their ability to survive and be plastic again. To me, synaptic plasticity is the most exciting term in Neuroscience. It represents the ability of neurons to adapt to changes and insults in order to be efficient for learning and store memory, capacity that we all need to survive. I was so passionate about this that after my graduate training, I was able to establish on my own, for first time, an electrophysiology recording system in the Longo lab for the purpose of recording synapse physiology from several disease models treated with drugs to understand the signaling pathways of drug efficacy. For example, working together with the

Andressson lab at Stanford University, we demonstrated that lipid messenger prostaglandin E_2 contributes to the development of age-associated inflammation and synapse dysfunction, which gained me a second authorship in a neuroimmunology paper currently in the second round of revisions in *Nature Journal*. This study required me to perform long-term electrophysiology experiments to assess brain plasticity using very old mice (24-25 months), a capacity that only a few labs can do. In addition, together with the same lab, I also worked on assessing whether inhibition of Indolamine 2,3-dioxygenase 1 (IDO1) could rescue synaptic plasticity in two mouse models of amyloid pathology (gained a shared 1st authorship in a manuscript in preparation). In the Longo lab, I have made considerable progress in discovering new mechanisms through which novel small molecules can reverse synaptic impairment in ADRD models. For example, I have found that treatment of tauopathy mice with LM11A-31, a small molecule modulator of p75 neurotrophin receptor signaling, normalizes LTP. Similarly, modulation of TrkB/C signaling with PTXBD10-2 prevented Aβ-induced LTP deficits and reduced changes in structural and signaling components consistent with restoration of underlying machinery mediating synaptic function.

During the second year as a postdoc and after having collected all this data, I became interested in the emerging field of RNA sequencing approaches to elucidate the mechanistic patterns of gene expression underlying synaptic plasticity in ADRD mouse models. As a result, I began an exciting and highly productive collaboration with Tony Wyss-Coray's laboratory to provide data science and transcriptomic expertise, as we unraveled key candidate mechanisms that may contribute to synapse pathology and synaptic function restoration by small molecule treatments in disease models (Latif-Hernandez & Moran-Losada et al., *manuscript in preparation*). This proposal will support my training in the field of RNA transcripts produced by the genome under specific circumstances during plasticity in specific cell types. I will also learn how to analyze transcriptome data and experimentally validate transcripts that emerge from the resulting analyses so that I may use and build upon these approaches in the independent R00 phase.

Given my previous training in neurophysiology, the current environment with solid collaborations, and my expertise in electrophysiological recordings from disease mouse models and therapeutic approaches, I have the expertise, training, motivation and support from my community, all necessary to the successful execution of the Aims outlined in this proposal. In fact, I have been recently nominated for a formal appointment as an Instructor in the Neurology Department, at Stanford, as recognition for my productivity, research and training achievements, and engagement in multiple collaborations with research teams. This appointment was recently approved by the School of Medicine and it constitute a reliable criterion our senior faculty envision me as a successful candidate for independent faculty position.

B. Positions and Honors

Positions and Employment

2020- Current	Research Instructor, 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

Professional Memberships

2018-Present	ISTAART member, Alzheimer's association International conference
2014-Present	Member, Society for Neuroscience
2014-2018	Member, Federation of European Neuroscience societies
2015-2017	Member, Belgian Society for Neuroscience

Academic and professional honors

2020	Travel fellowship - Tau2020 Global Conference, Washington
2019	Trainee Professional Development Award **-** Society for Neuroscience, Washington.

2019	Selected oral nanosymposium at SfN, Chicago
2018	Invited lecturer in Master of Neurophysiology by University of Seville
2018	Travel grant application - University of Seville
2017	Invited speaker - Belgian Society for Neuroscience, Belgium
2017	Travel grant -International Conference Alzheimer and Parkinson's diseases, Austria
2016	Invited oral symposium at BAPS conference, Belgium
2016	Invited speaker at CEBE symposium, Belgium
2015	Invited oral presentation - Belgian Society for Neuroscience, Belgium
2015	Invited lecturer in Master of Neurobiology – University of Sevilla, Spain
2011	Erasmus grant to study 1 year abroad and get equivalent degree for Master's

C. Contribution to Science

1) Uncovering the role of ionotropic and metabotropic neuronal receptors for metaplasticity:

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 was able to train in how to prepare acute hippocampal slices from rodents and record synaptic plasticity for ≥4h, something extraordinary that only 3 labs in the world could do (the Kandel, Frey and Balschun's labs). 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)**.

a) **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***, 10, 252.

2) Deciphering the role of hippocampal-prefrontal cortex network activity for neuroplasticity and cognitive flexibility in a chemical neurodegeneration mouse model:

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. First, 60 mice were subjected to a behavioral paradigm, then brain surgeries were performed, and after they recovered they returned to behavioral procedures to assess cognitive flexibility. Immediately the next day, their brains were used for electrophysiological recordings in order to examine the acute and delayed effects of QA injections into mPFC on hippocampal synaptic plasticity. Furthermore, I further hypothesized that the behavioral and cognitive effects of mPFC lesions could be attributed to changes in functional connectivity (FC) between these brain regions. We therefore included resting-state functional MRI (rsfMRI) methodology **(a).**

a) **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***.

3) Understanding synaptic plasticity, *in vivo* brain synchrony and behavioral deficits that depend on mPFC and HC in next generation 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 (a, b, c). 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 (a). 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 (c). 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. Finally, we used functional magnetic resonance imaging (rsfMRI) to assess connectivity between cortical 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 (a, b). These are the first demonstrations of brain network alterations, synapse dysfunction and high order cognitive deficits in these novel mouse models of AD.

a) **Latif-Hernandez A.***, Shah D.*, Craessaerts K., Saido T., Saito T., De Strooper B., Van der Linden A., D'Hooge R., **(*shared 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., **(*shared 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) **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*** 12**,** 100.

4) Examining the effect of therapeutic candidates to restore synaptic plasticity deficits in Alzheimer's disease and other related dementias:

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 AD mice with certain drugs could restore the ability of synapses to be stronger again and produce LTP. For that reason, during 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 performed all the electrophysiology experiments from mice I treated previously in the Van der Linden lab, at Antwerp University in Belgium (a). Shortly after, I contributed to a paper as first author where we commented on a paper about APP as a mediator of synapse dysfunction (b) by the lab of Dr. Ottavio Arancio (collaborator in my K99 proposal). Later, 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 (c), all of which were presented both with oral and poster presentations at international conferences and will lead to publications in top-tier journals. Finally, 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 (d). To answer this question I used innovative electrophyiological 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. In addition, I also collaborated on a second project focusing on the kynurenine pathway in Familial Alzheimer's disease mice, where I am finding a remarkable restoration of hippocampal synaptic plasticity with inhibition of this pathway.

a) 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., **(*shared 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 disease and Dementia***.

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

c) Selected oral symposium: **Amira Latif-Hernandez**, Patricia Moran-Losada, Tao Yang, Kevin C. Tran, Harry Liu, Benoit Lehallier, Stephen M. Massa and Frank M. Longo (2020). Elucidating emerging therapeutics: P75 receptor modulation reverts tauopathy-associated alterations in synapse-relevant gene expression signatures. Alzheimer's Association International Conference, virtual meeting.

d) 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., **(*shared second author**). Metabolic rejuvenation of myeloid cells reverses age-associated cognitive decline. Under second round of review in ***Nature.***

5) Training, mentorship, and teaching in the neurosciences

Throughout my career as a scientist, I have been dedicated to teaching and mentoring at all levels. It is my view that mentorship and teaching are skills worth cultivating and are important parts of a career in academic research. I truly enjoy conveying knowledge to young students, and putting the seed of the science in their minds so that they start feeling as passionate as I am myself. During my graduate training, I supervised 3 master's degree students, I trained them in behavioral methods, data analysis and graph preparation and report writing. One of them has currently graduated and is PhD in Neuroscience from the KU Leuven, from the same lab where I graduated. Another one is currently a scientist at a company in Belgium, and the other one is an established PhD psychologist in Mons, Belgium.
In addition, I have been invited to give lectures for the Master of 'Neural basis of brain damage and applied psychopharmacology" from the University of Seville, Spain (two consecutive years 2018, 2019), for which I was awarded a competitive grant to cover flight from Stanford, accommodation and meals.
Lastly, during my postdoctoral work at Stanford, I trained a talented undergraduate student in the development, analysis and application of a novel immunostaining protocol to look at co-localization of proteins during forms of synaptic plasticity, something that the Longo lab had never done before. I trained her also in confocal microscope analysis. We are publishing her exciting results in a top-tier journal.

For a complete list of my publications please follow this link:
https://scholar.google.com/citations?user=mTnOk-4AAAAJ&hl=en

D. Additional Information: Research Support

Ongoing funding:

Scully Initiative	Longo (PI)	03/01/2017-03/01/2021
Taube Family Foundation	Longo (PI)	03/01/2017-03/01/2021
Jean Perkins Foundation	Longo (PI)	12/01/2015-12/01/2018

The goal of these projects are to examine the mechanisms by which neurotrophin receptor small molecule modulators restore cognitive dysfunction, neuropathology and synapse function in mouse models of neurodegeneration.
Role: Research Investigator.

Completed funding applied to:

G.0327.08 and G.0D76.14 D'Hooge and Balschun (PIs) 01/15/2013- 01/15/2017
Research Foundation-Flanders

Cognitive and synaptic dysfunction in mouse modes of Alzheimer's disease
The goal of this project was to examine reversal learning deficits and mechanisms of synaptic impairments that underlie neurodegeneration, as well as identify the role of prefrontal cortex and hippocampus in these.
Role: Main research Investigator.