

BIOGRAPHICAL SKETCH

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NAME: Díaz-Ríos, Manuel E.

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

POSITION TITLE: Professor

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 Puerto Rico, Río Piedras campus	BS	1996	Biology
University of Puerto Rico, Medical Sciences campus	PhD	2003	Anatomy/Neurobiology
Cornell University	Postdoc	2003-06	Neurophysiology

A. Personal Statement

Since my introduction to scientific research as an undergraduate student more than 24 years ago, my fascination on how our external and internal environment shapes and changes behavior has increased 100-fold. Specifically, the relationship between neural networks and the induction and control of a behavior has personally become a passion. I was very fortunate during my graduate (doctoral) training to work on and appreciate the vast contribution that large identifiable neurons and the networks they comprise have had on the understanding of motor behavior by working on the marine mollusk *Aplysia californica* under the mentorship of Professor Mark W. Miller (Univ. of Puerto Rico). During this time I started my formal training in neuroanatomy and neurophysiology while dissecting and performing electrophysiological experiments on *Aplysia*. I continued developing my training as a neurophysiologist and gained new knowledge on calcium imaging techniques as a postdoctoral fellow at Cornell University under the mentorship of Professor Ronald Harris-Warrick (Dept. of Neurobiology and Behavior) in collaboration with Professor Watt W. Webb (Dept. of Applied Physics and Engineering) where I studied locomotor behavior on a more clinically-relevant vertebrate model system (mouse spinal cord). Today, I can honestly say that I can attribute my scientific and academic approach, as well as my leadership style as a principal investigator, to the influence of these great mentors. Additionally, I was able to gain expertise in a range of methodological strategies and approaches, including neurophysiology, neuroanatomy, calcium imaging and molecular neurobiology.

I was hired to the department of Anatomy and Neurobiology at the University of Puerto Rico medical school in 2006 after 3 years as a post-doc at Cornell. Unfortunately, I arrived just after a severe financial crisis hit the United States and Puerto Rico which led to a significant delay in gaining access to my start-up funds (no significant support from 2006 to 2010). I focused my efforts on teaching and service (including community outreach initiatives which led to NSF funding for student support, see completed research support). This had a significant impact on my publication record but I have since published 6 publications within the last 5 years including one manuscript which is currently in review.

Currently our laboratory studies how does the thoracic spinal circuitry is organized and controls trunk-related movements in mammals. Additionally, we are interested in studying how does this network utilizes and processes sensory input in neonatal and adult mice. Studies regarding the control of movement in vertebrates have been mostly focused on limb-related neural circuits but the organization of trunk-related neural networks, important for the control of body posture/balance, have been largely unexplored. We use intracellular and extracellular recordings as well as calcium imaging to assess the basic organization of this spinal neural network and which are its component neurons. Identifying and characterizing the modular organization and neural components involved in trunk motor control and its interaction with limb-related networks and afferent inputs would provide fundamental information regarding sensory-motor integration relevant to mammals and other vertebrate systems. Additionally, these future studies will eventually be directed toward improving current rehabilitative

strategies, such as those following stroke or spinal cord injury (SCI) by including the process of regaining proper trunk stabilization and postural control, crucial factors for stability and propulsion during walking. Finally, we are interested in the study of the cellular effects of caffeine and other adenosine receptor antagonists and agonists on the spinal lumbar network controlling locomotion using the neonatal mouse spinal cord. Adenosine receptor have been shown to be powerful regulators of dopaminergic and glutamatergic neurotransmission in brain regions but little information has been provided within the spinal circuits controlling locomotion. We want to understand the cellular mechanisms by which adenosine receptor antagonists and agonist modulates the firing properties of neurons (including motoneurons) the spinal CPG network for locomotion since adenosine receptors have been related to the reduction of inflammation and neuroprotection after a SCI, and to the potential treatment of diseases related to increased neuronal excitability such as Restless Leg Syndrome.

Since my arrival to UPR, our lab has been highly committed in recruiting students underrepresented in science (including Hispanics and women) to a highly stimulating laboratory environment where electrophysiology and confocal imaging are used routinely by undergraduate and graduate participants. Four of the five last publications have included undergraduate (3) and graduate (4) students as contributing authors (names are underlined in recent publications included below).

B. Positions and Honors

Positions and Employment

- 1992 - 1994 Laboratory Assistant, Laboratory of Dr. Ned Fetcher, Department of Biology, Univ. of Puerto Rico, Rio Piedras campus, San Juan PR
- 1996 - 1997 Laboratory Assistant, Laboratory of Dr. Susan Corey, Department of Pharmacology, Univ. of Puerto Rico, Medical Sciences campus, San Juan, PR
- 1998 - 2003 Doctoral student, Laboratory of Dr. Mark W. Miller, Department of Anatomy and Neurobiology, Univ. of Puerto Rico, Institute of Neurobiology, San Juan PR
- 1999 - 2001 Assistant Instructor, Tropical Neuroethology Summer Course, Sponsored by NSF and the Univ. of Puerto Rico, San Juan, PR
- 2000 Teaching Assistant, Medical Neuroscience Course, Univ. of Puerto Rico, School of Medicine, San Juan, PR
- 2003 - 2006 Postdoctoral Fellow, Cornell University, NY
- 2006 - 2013 Assistant Professor, Dept. of Anatomy and Neurobiology, Univ. of Puerto Rico, School of Medicine, San Juan, PR
- 2013 - 2018 Associate Professor, Dept. of Anatomy and Neurobiology, Univ. of Puerto Rico, School of Medicine, San Juan, PR
- 2018 – today Professor, Dept. of Anatomy and Neurobiology, Univ. of Puerto Rico, School of Medicine, San Juan, PR

Other Experience and Professional Memberships

- 1999 - Society for Neuroscience
- 1999 - New York Academy of Sciences
- 2006 - Organizing Committee, Puerto Rico Neuroscience Meeting
- 2007 - Sigma XI, The Scientific Research Society
- 2007 - 2014 Mentor in the Neuroscience Scholars Program (NSP) – NIH NINDS
- 2008 - 2014 Mentor in program offered by the Society for Neuroscience's (SfN) Committee on Women in Neuroscience (C-WIN)
- 2008 - Participant in **Brain Awareness Week (BAW)** at the Univ. of Puerto Rico, Medical Sciences
- 2009 - 2015 Co-Principal investigator (Co-PI) – NSF Undergraduate Research and Mentoring (URM) Program, *Neural Circuits and Behavior*.
- 2010 - National Science Foundation Grant reviewer – Activation Panel (Washington, DC)
- 2010 - Reviewer for the following journals: PLOS Biology, J. Neuropharmacology, J. of Neurophysiology, BMC Medical Genetics, Pharmacological reports, Current Medicinal Chemistry, Life Sciences, Neuroscience Letters

Honors

- 2000 Recipient of the 1st Annual Society for Neuroscience Chapters Graduate Student Travel Award, 30th Annual Meeting for the Society of Neuroscience (New Orleans, LA)

- 2002 Fellow in the Summer Program in Neuroscience, Ethics and Survival (SPINES) at the Marine Biological Laboratory (Woods Hole, MA)
- 2001-2003 American Psychological Association (APA), Minority Fellowship Program (MFP) in Neuroscience Predoctoral Fellow (NIH)
- 2003- Award for excellence in academics (Honor role) and research given by the Associated Deanship for Biomedical Sciences, Univ. of Puerto Rico, Medical Sciences Campus, School of Medicine, at 2003 School of Medicine graduation ceremony, Guaynabo, PR
- 2004-2005 American Psychological Association (APA), Diversity Program in Neuroscience Post-doctoral Fellow (NIH, NRSA)
- 2006 Invited speaker at the 32nd Annual East Coast Nerve Net at the Marine Biological Laboratory, Woods Hole, MA
- 2008 Invited presenter of poster entitled: "Serotonin Modulation of Intrinsic Properties of Ascending Ipsilateral interneurons in the Neonatal Mouse Spinal Cord" at the Christopher and Dana Reeve Foundation Spinal Cord Symposium, Atlanta (GA).
- 2011 Invited speaker at Emory University School of Medicine, Department of Physiology Seminar Series. "Walking Without a Brain: Assessing the Role of Sensory Input to Locomotor Behavior" (Atlanta, GA)
- 2013 Invited panelist at NSF-funded workshop: "How Organisms Walk the Tightrope Between Stability and Change". Cold Spring Harbor, NY.
- 2016 Participant of the Grass Foundation Neuroscience workshop at the Marine Biological Laboratory (MBL; Woods Hole, MA)
- 2016 Invited speaker at Bowdoin College, Biology & Neuroscience Depts. Seminar: "Identification and Characterization of Trunk-controlling Neural Networks in Mammals" (Brunswick, ME)
- 2018 Invited speaker at University of Wisconsin-Madison, Dept. of Neuroscience; Seminar: "Adenosine A1-Dopamine D1 Receptor Heteromers in Spinal Motoneurons: Implications on Neurodegenerative Diseases" (Madison, WI)
- 2018 Invited speaker at East Carolina University, Dept. of Physiology; Seminar: "Adenosine A1-Dopamine D1 Receptor Heteromers in Spinal Motoneurons: Implications on Neurodegenerative Diseases" (Greenville, NC)

C. Contribution to Science

1. Anatomical and physiological characterization of feeding-related CPG neurons in *Aplysia californica*

My graduate studies focused on consummatory feeding behaviors in *Aplysia californica*, a marine mollusk whose patterns of motor activity are controlled by a polymorphic central pattern generator (CPG) circuit. Two key findings emerged regarding the localization and functional characterization of GABAergic and dopaminergic neurons within the feeding circuitry of *Aplysia*. First, using retrograde tracing techniques combined with immunohistochemistry, we found that GABA and dopamine were colocalized within two interneurons, B20 and B65, which participate in configuring the functional output of the feeding CPG network. We then used intracellular sharp electrode recordings combined with pharmacological manipulations to show that dopamine mediates divergent (B20 interneuron to B16 and B8 motoneurons) and convergent (B20 and B65 interneurons to B8 motoneurons) rapid excitatory effects from these two influential feeding-related CPG neurons.

- a) Díaz-Ríos M, Suess E, Miller MW. Localization of GABA-like immunoreactivity in the central nervous system of *Aplysia californica*. (1999) *J Comp Neurol* 413(2):255-70.
- b) Díaz-Ríos M, Oyola E, Miller MW. Colocalization of gamma-aminobutyric acid-like immunoreactivity and catecholamines in the feeding network of *Aplysia californica*. (2002) *J Comp Neurol* 445(1):29-46.
- c) Díaz-Ríos M., and Miller M.W. Rapid Dopaminergic Signaling by Interneurons that Contain Markers for catecholamines and GABA in the Feeding Circuitry of *Aplysia*. (2005) *J. Neurophysiol.* 93(4): 2142-56.
- d) Díaz-Ríos M., and Miller M.W. Target-specific regulation of synaptic efficacy in the feeding central pattern generator of *Aplysia*: Potential substrates for behavioral plasticity? (2006) *Biol Bull.* 210:215-29.

2. The Role of Commissural Interneurons in the Mouse Spinal Locomotor CPG Network

During my postdoctoral studies in the laboratory of Ronald Harris-Warrick, I continued pursuing my interests in motor systems working with the neonatal mouse lumbar spinal cord through the use patch clamp recordings and two-photon calcium imaging. We found that the application of serotonin, a key neurotransmitter known to activate locomotor behavior in mammals, was found to differentially modulate the intrinsic membrane properties of lumbar commissural interneurons (CINs) based on the their axonal projections with some being rhythmically active during locomotor behaviors suggesting that they may play important roles in the coordination of left–right movements during locomotion. The cellular targets and mechanisms of 5-HT actions were relatively unknown thus we investigated the possible role of serotonin in modifying dendritic calcium currents, using a combination of two-photon microscopy and patch clamp recordings, in identified CINs in the upper lumbar region. Our studies found that 5-HT reduced calcium currents while enhancing cell excitability suggesting that the possible reduction in I_{Ca} indirectly inhibits a calcium-activated potassium conductance to enhance CIN spiking.

- a. Zhong G., Díaz-Ríos M. and Harris-Warrick R.M. Serotonin modulates the properties of ascending commissural interneurons in the neonatal mouse spinal cord. (2006) *J Neurophysiol.* 95(3):1545-55.
- b. Zhong G., Díaz-Ríos M., and Harris-Warrick R.M. Intrinsic and functional differences among commissural interneurons in the central pattern generator for locomotion in the neonatal mouse. (2006) *J Neurosci* 26(24):6509-17.
- c. Wilson J, Dombeck D, Díaz-Ríos M, Harris-Warrick RM. and Brownstone RM. Two-photon calcium imaging of network activity in XFP expressing neurons in the mouse. (2007) *J Neurophysiol.* 97(4):3118-25.
- d. Díaz-Ríos M, Dombeck D, Webb WW, and Harris-Warrick RM. Serotonin modulates dendritic calcium influx in commissural interneurons in the mouse spinal locomotor network. (2007) *J Neurophysiol* 98(4):2157-67.

3. The Role of Neuromodulation and Sensory Input on Spinal Motor Network Function

We are currently interested in the sensory input and neuromodulation shapes the firing properties of neurons within the spinal neural network of mammals. We first used of a novel semi-intact preparation that included the thoracolumbar spinal cord connected to the hindlimbs of the neonatal mouse to assess the effects of sensory afferent feedback during early postnatal development. We found that removing sensory feedback coming from the hindlimbs by way of a lower lumbar transection or by ventral root denervation revealed a positive correlation in the ability of sensory input deprivation to disrupt ongoing locomotor activity on older versus younger animals. The differences in the motor responses as a function of age could be correlated with the loss of excitatory activity from sensory afferents. We are additionally assessing the effects of adenosine receptor antagonists (such as caffeine) and agonists on the function of lumbar network controlling locomotion. Our results support an indirect stimulant effect of caffeine on the lumbar spinal network controlling hindlimb locomotion through the inhibition of A1 adenosine receptors and subsequent activation of D1 dopamine receptors via a PKA-dependent intracellular mechanism. These effects have been recently linked to the presence of A1-D1 heteromers within spinal motoneurons and not interneurons within the lumbar spinal cord of mice. A₁-D₁ receptor heteromers play a significant control of the motoneuron excitability, represent main targets for the excitatory effects of caffeine in the spinal cord and can constitute a new target for the pharmacological therapy after spinal cord injury or by other neurodegenerative diseases.

Finally, and in accordance with our laboratory mission of public outreach and service, we conducted a study with two psychologists measuring the prevalence and frequency of energy drink (ED) consumption among college students according to gender, degree programs and specific university-related and social situations. Additionally, we were interested in assessing the frequency of consumption of ED mixed with alcoholic beverages. We found that the majority of students consumed EDs occasionally and while studying. Also, we found a high consumption of EDs and of EDs mixed with alcohol by students in graduate programs which could be explained by a higher and more complex study load requiring longer periods of wakefulness and concentration. Future studies looking at the consumption patterns of EDs in more competitive graduate programs such as medical and/or dentistry school should be considered.

- a. Acevedo J, Santana-Almansa A, Matos-Vergara N, Marrero-Cordero LR, Cabezas-Bou E, and Díaz-Ríos M. (2016) Caffeine stimulates locomotor activity in the mammalian spinal cord via adenosine A1 receptor-dopamine D1 receptor interaction and PKA-dependent mechanisms. *Neuropharmacology* 101:490-505.
- b. Díaz-Ríos M, Guertin PA, Rivera-Oliver M. (2017) Neuromodulation of spinal locomotor networks in rodents. *Curr Pharm Des* 23(12):1741-1752

- c. Ferré S, Quiroz C, Guitart X, Rea W, Seyedian A, Moreno E, Casadó-Anguera V, Díaz-Ríos M, Casadó V, Clemens S, Allen RP, Earley CJ and García-Borreguero D. (2018) Pivotal Role of Adenosine Neurotransmission in Restless Legs Syndrome. *Frontiers Neurosci* 8;11:722. eCollection 2017.
- d. Marla Rivera-Oliver M, Moreno E, Álvarez-Bagnarol Y, Ayala-Álvarez C, Cruz-Reyes N, Molina-Castro GC, Canela EI, Clemens S, Ferré S, Casadó V, and Díaz-Ríos M. (2018) Adenosine A1-Dopamine D1 Receptor Heteromers Control the Excitability of the Spinal Motoneuron. *Mol Neurobiol* 2018 May 24. [Epub ahead of print]

Complete list of publications in MyBibliography:

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Diaz-Rios+M>

D. Research Support

Ongoing Research Support:

4P20GM103642 PD: Jose Lasalde-Dominicci 07/01/18 – 06/30/23 3.6 cal. mo.

NIH/NIGMS \$10,642,657

Center for Neuroplasticity at the University of Puerto Rico

The major goal of this project is to increase the critical mass of competitive investigators in the area of Neuroscience at the University of Puerto Rico.

Role: Facility Director; no direct research support.

HRD-1736019 PD: M.W. Miller \$2,000,000 09/01/17 – 08/31/22 0.6 cal. mo.

NSF

Puerto Rico Center for Environmental Neuroscience (Cycle II)

The major goal of this project is to support the enhancement of research capabilities of minority-serving institutions through the establishment of centers that effectively integrate education and research.

Project title: "Impact of contaminants and temperature on central pattern generator neural circuits"

Role: Subproject Co-PI.