BIOGRAPHICAL SKETCH

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NAME: Ricardo M. Pautassi, Ph.D.

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

POSITION TITLE: Independent Researcher, National Council of Scientific Research (CONICET, Argentina)

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
National University of Cordoba Cordoba, Argentina	Licenciate (M.S.)	12/1999	Psychobiology
National University of Cordoba Cordoba, Argentina	Ph.D.	04/2005	Biological Sciences
State University of New York (SUNY), Binghamton, New York, USA	Post-doc	12/2008	Behavioral Neuroscience

A. Personal Statement

I have always been interested in understanding the psychobiology of drug disorders. Over the course of my career, I became more and more focused on how early experiences with drugs, well before adulthood, can determine life-long trajectories of involvement in alcohol and other drugs. Although my original training mainly led to the mastering of behavioral techniques (including the thorough and painstaking acquisition of skills for analyzing operant-self administration of ethanol in immature rats), subsequent experiences have enabled me to develop considerable expertise in performing epidemiological, pharmacological and molecular studies involving human subjects or animal models. While my primary interests have stayed within the realm of addictive disorders, I am also highly interested in understanding the acquisition of early taste and food preferences, and have spent a considerable amount of time investigating personality and cognitive factors involved in pathological (e.g., addiction) and normal, including educational, processes. In the last years I have begun working in cooperation with Dr. Paul Meyer. He and I examined the conditions leading to the simultaneous emergence of alcohol-mediated conditioned preference and aversion in the rat, and the modulation of these effects by nicotine. My role in the proposed grant will be co-PI, in charge of the production of lines of rats selected for high- or low alcohol drinking during adolescence. I will also conduct a significant part of the neurobehavioral assays and direct the statistical analyses of these data. I have extensive experience performing all of these tasks in various publications and supervisions of Ph. D thesis from my own lab, as well as in publications from other groups that I have served as a primary data analyst and consultant for. In summary, I look forward to contributing to the ongoing success of this exciting line of work, which will untap the still unknown mechanisms leading to heightened vulnerability for alcohol escalation during adolescence and will delineate candidate genes and new biological pathways for these phenomena.

B. Positions and Honors

1999 Academic Award, Dept. of Psychology, National University of Cordoba
1999 Awarded Distinction for Excellence in Undergraduate studies, National University of Cordoba
2000-2001 National Agency of Science, Argentina, Predoctoral Fellowship (Argentina)
2001-2005 CONICET Predoctoral Fellow, Instituto de Inv. Medicas M. y M. Ferreyra, Cordoba, Argentina
2003-2005 Assistant Professor, Dept. of Psychology, National University of Cordoba, Argentina
2006-2008 Research Associate/ Postdoctoral Fellow, Dept. Psychology, SUNY Binghamton, NY.

2009-2016 Editor-in-chief, Argentinian Journal of Behavioral Sciences (AJBS)
2009-Present Independent Researcher at CONICET, Cordoba, Argentina
2009-2011 Vice-President, Argentinian Association for Behavioral Sciences (IUPSyS member)
2009-2016 Associate Professor, Dept. of Psychology, National University of Cordoba, Argentina
2010-2017 Vice-President, Latin-American Society for Biomedical Research on Alcoholism (LASBRA)
2010 Young Investigator Award 2010, International Society for Biomedical Research on Alcoholism
2010-2015 Vice-Director, Ph.D Program in Neurosciences, National University of Cordoba, Argentina
2011-2013 President, Argentinian Association for Behavioral Sciences (AACC, IUPSyS member)
2012 Fulbright Fellow (Visiting Scholar) at SUNY Binghamton, Department of State of the US.
2013-present Member of National University of Cordoba, in-house grants Committee, basic sciences
2015-2018 Vice-Director, Ph.D Program in Psychology, National University of Cordoba, Argentina
2016-present Full Professor, Dept. of Psychology, National University of Cordoba, Argentina
2017-present Co-coordinator of grant selection study section, National Agency of Science, Social Sciences
2017-2019 President, Latin-American Society for Biomedical Research on Alcoholism (LASBRA).

C. Contributions to Science

Link to published work: www.ncbi.nlm.nih.gov/sites/myncbi/ricardo.pautassi.1/bibliography/40608254/public

1. Characterization of motivational reactivity to ethanol during infancy.

I have a long-standing interest in understanding the motivational processing of drugs, this is the appetitive, aversive and anxiolytic effects implicated in the transition from regular to problematic drug use. I completed my Ph.D. with Dr. Juan Molina, who played a major role in establishing that infancy is a developmental stage in which early experiences with alcohol can shape, via associative and non-associative mechanisms, subsequent alcohol-mediated learning and intake. Together with Dr. Juan Molina, we confirmed the hypothesis of high sensitivity to alcohol reinforcement in infancy and revealed that alcohol-mediated operant learning in infancy leads to increased alcohol intake during adolescence. The completion of these achievements was possible thanks to the development of novel preparations (e.g., revaluation procedures, age-specific operant procedures, second-order conditioning procedure, a conditioned place preference alternative used in infant rats) that overcame the well-known difficulties of translating behavioral procedures designed for adults to developing organisms. These preparations have been valuable assets and have been since employed in several studies. The finding themselves (reviewed in Pautassi et al., 2009) provided the basis for my more recent studies in humans, in which we established the surprisingly highly prevalent alcohol initiation in children aged 8-12 years (Pilatti et al, 2012).

a) **Pautassi RM,** Godoy JC, Spear NE, Molina JC. (2002) Early responsiveness to stimuli paired with different stages within the state of alcohol intoxication. Alcohol Clin Exp Res. 26:644-54. PMID: 12045472
b) **Pautassi RM,** Sanders S, Miller S, Spear N, Molina JC. (2006) Early ethanol's anxiolytic effects assessed through an unconditional stimulus revaluation procedure. Alcohol Clin Exp Res 30:448-59. PMID: 16499485
c) Molina JC, **Pautassi RM**, Truxell E, Spear NE (2007) Differential motivational properties of ethanol during early ontogeny as a function of dose and postadministration time. Alcohol 41, 41-55. PMID: 17452298
d) **Pautassi RM,** Nizhnikov M, Spear NE (2009) Assessing appetitive, aversive, and negative ethanol-mediated reinforcement through an immature rat model. Neurosci Biobehav Rev. 33:953-74 PMID: 19428502

2. Characterization of age-related effects of ethanol.

Building on my experience using novel biobehavioral tools to analyze motivational responsivity to alcohol, I then sought out a postdoctoral training experience that would enable me to analyze the pharmacological underpinnings of this phenomenon and to establish how this motivational reactivity explains propensity to drink during adolescence, the developmental stage in which alcohol drinking usually begins. I first joined the laboratory of Dr. Norman Spear, and then the laboratory of Dr. Linda Spear, both at the State University of New York at Binghamton. During these post-docs I established for the first time in the literature that appetitive conditioning

by ethanol can be reliably established in infant and adolescent, but not in adult, rats. The finding, indicative of a developmental window of increased vulnerability for ethanol's effects on behavior, provided the basis for more recent studies conducted in my lab, in which we kept finding greater sensitivity to ethanol's rewarding effects and to ethanol-stress interactions in adolescent than in adults. We also found that environmental enrichment, a non-pharmacological treatment that reduces alcohol seeking in adults, actually seems to increase ethanol seeking and intake in adolescents, and reported on the vulnerability of the adolescent brain to binge drinking (i.e., the young but not the adult rats accumulate Delta-Fos-B, an addition linked protein, after ethanol intake). The implications of the work is that adolescent seem to exhibit an idiosyncratic pattern of response to ethanol, which may put them at risk for quickly escalating into abuse and dependence.

a) **Pautassi RM**, Myers M, Spear LP, Molina JC & Spear NE. (2008). Adolescent, but not adult, rats exhibit ethanol-mediated appetitive second-order conditioning. Alcoholism, Clinical and Experimental Research, 32, 2016-2027. PMID: 18782343
b) R Camarini, A.B. Suárez, L.B. Hofmann, A.V. Rueda, M.B. Rae, P Marianno, **R.M. Pautassi**. (2017). Effects of environmental enrichment upon ethanol-induced conditioned place preference and pre-frontal BDNF levels in adolescent and adult mice. Scientific Reports 7: 8574. PMID: 28819238
c) Wille-Bille, A., Ferreyra A, Sciangula M, Chiner F, Nizhnikov ME and **Pautassi RM** (2017). Restraint stress enhances alcohol intake in adolescent female rats but reduces alcohol intake in adolescent male and adult female rats. Behavioural Brain Research 332, pp. 269-279. PMID: 28606631
d) Wille-Bille A., De Olmos S., Marengo L., Chiner F., **Pautassi RM** (2017) Long-term ethanol self-administration induces Delta-Fos B in male and female adolescent, but not in adult, Wistar rats. Progress in Neuropsychopharmacology & Biological Psychiatry 74, 6, pp.15–30. PMID: 27919738

3. Neurobiological alterations leading to exacerbated adolescent ethanol intake, in an animal model of fetal alcohol syndrome.

After completing my postdoctoral training, I was recruited by the National Council of Scientific and Technical Research of Argentina to establish my own independent lab at one of their best intramural research institutes (Instituto de Investigaciones Médicas M. y M. Ferreyra, INIMEC-CONICET-UNC). After successfully obtaining funding from national and international sources, I began some of the first systematic studies of the neurobiological mechanisms underlying the promoting effect of moderate gestational ethanol exposure (1.0-2.0 g/kg, gestational days 17-20) on adolescent alcohol consumption. This work not only identified a critical biological pathway of the prenatal exposure (i.e., enhanced sensibility to the reinforcing effect of ethanol), but also indicated brain changes in the mesocorticolimbic pathway after this treatment. Moreover, some of the findings clearly implicated neuroadaptations in the functionality of the kappa opioid system. We are currently exploring epigenetic changes associated, and likely responsible, for these effects.

a) Fabio MC, March SM, Molina JC, Nizhnikov ME, Spear NE, **Pautassi RM.** (2013) Prenatal ethanol exposure increases ethanol intake and reduces c-Fos expression in infralimbic cortex of adolescent rats. Pharmacol Biochem Behav. 103:842-52. PMID: 23266368
b) Nizhnikov ME, **Pautassi RM**, Carter JM, Landin JD, Varlinskaya EI, Bordner KA, Werner DF, Spear NE (2014) Brief prenatal ethanol exposure alters behavioral sensitivity to the kappa opioid receptor agonist (U62,066E) and antagonist (Nor-BNI) and reduces kappa opioid receptor expression. Alcohol Clin Exp Res. 38:1630-8. PMID: 24796820
c) Fabio MC, Macchione AF, Nizhnikov ME, **Pautassi RM.** (2015) Prenatal ethanol increases ethanol intake throughout adolescence, alters ethanol-mediated aversive learning, and affects μ but not δ or κ opioid receptor mRNA expression. Eur J Neurosci 41:1569-79. PMID: 25865037
d) Fabio MC, Vivas LM, **Pautassi RM** (2015) Prenatal ethanol exposure alters ethanol-induced Fos immunoreactivity and dopaminergic activity in the mesocorticolimbic pathway of the adolescent brain. Neuroscience 20:221-34.PMID: 26057446

4. Prediction of ethanol drinking during adolescence.

The study of factors predisposing adolescents to drink ethanol, as shown via animal models, experienced a significant surge during the last decade. My lab was among the first to utilize multivariate models to predict ethanol intake in heterogeneous, rats. We were guided by studies in which we found that those preweanling or

adolescent rats exhibiting high response to novelty, or exacerbated response to ethanol's psychostimulant effects, are more likely to ingest ethanol. We employed this information to create and test a multivariate prediction model, in which novelty seeking and anxiety response traits combined to explain a significant fraction of alcohol ingestion in adolescent rats. We also devised an animal model that confirmed the "early debut" effect, i.e., the greater prevalence of alcohol disorders among those that began drinking earlier in life, as compared to those that began after the legal age limit. The causality between these events has not been completely confirmed, yet our studies provide convincing pre-clinical evidence for it, as well as empirical support for public policies that aim at delaying the first contact with ethanol. In another approach to predict alcohol intake during adolescence, we have recently conducted a short-breeding program that selected for high or low ethanol intake during adolescence. The offspring of the high-drinker rats exhibited enhanced sensitivity to stimulant effects of ethanol yet blunted sensitivity to the aversive effects of the drug, in conjunction with increases innate anxiety with translated into greater neural activation at brain areas involved in processing of fear-related stimuli.

a)Fabio MC, Nizhnikov ME, Spear NE, **Pautassi RM.** (2014) Binge ethanol intoxication heightens subsequent ethanol intake in adolescent, but not adult, rats. Dev Psychobiol. 56:574-83. PMID: 23341340

b) Acevedo MB, Nizhnikov ME, Molina JC, **Pautassi RM** (2014) Relationship between ethanol-induced activity and anxiolysis in the open field, elevated plus maze, light-dark box, and ethanol intake in adolescent rats. Behav Brain Res. 265:203-15 PMID 24583190

c) Acevedo MB, Fabio MC, Fernandez M, **Pautassi R.** (2016) Anxiety response and restraint-induced stress differentially affect ethanol intake in female adolescent rats. Neuroscience 334:259-274. PMID: 27531856

d) Fernandez M., Baez B., Bordon A., Fernandez L., Martinez E., **Pautassi R.M.** (2017). Short-term selection for high and low ethanol intake yields differential sensitivity to ethanol's motivational effects and anxiety-like responses in adolescent Wistar rats. Progress in Neuropsychopharmacology & Biological Psychiatry 27, 220-233. PMID: 28663116.

5. Epidemiological analyses of addictive disorders.

A major part of my research has focused on the use of brain and behavioral measures, derived from animal models, to gain insight into changes in the brain that have been caused by, or predispose to, exposure to drugs of abuse. Yet a significant section of my latest research has used the knowledge derived from these highly analytical animal models to test hypotheses about the etiology of drug disorders in human populations. In total congruency with our earlier rat studies, we found that alcohol initiation in children aged 8-12 years has far-reaching implications: those with greater motivational reactivity for the drug during the first drinking experience are more likely to keep up drinking than those who disliked their first drug experience. Also in agreement with our pre-clinical data, greater impulsivity and novelty seeking (in conjunction with exaggerated expectations about the effects of alcohol on social and sexual function) predicted greater engagement in alcohol and other drugs, in adolescents and young adults. These studies also underscored the synergic interplay between environmental and genetic factors: our research helped established the notion that a family history of alcohol problems, which we found to be associated with enhanced sensitivity to ethanol-induced HR and risk-taking, exacerbates the promoting effect of the "early alcohol debut" upon later prevalence of alcohol-related problems. These studies add to a growing body of research that has changed the conception of alcohol abuse disorders, which are now considered developmental conditions, with etiological roots in early development, including childhood and adolescence. Our more recent and longitudinal ELSA study, conducted in a large sample of Argentinean college freshmen (n = 4083) also underscored the significant role that the perception (and approval) of drinking behaviors on significant others exert on alcohol drinking. Our research indicates that many of the developmental factors or events leading to increased likelihood of alcohol-related problems appear to be reversible through specific interventional strategies (e.g., educational interventions to dispel erroneous beliefs on the effects of alcohol on social or sexual function).

a) Pilatti A, Godoy JC, Brussino S, **Pautassi RM.** (2013) Underage drinking: prevalence and risk factors associated with drinking experiences among Argentinean children. Alcohol 47:323-31 PMID: 23591270

b) Pilatti A, Caneto F, Garimaldi JA, Vera Bdel V, **Pautassi RM**. (2014) Contribution of time of drinking onset and family history of alcohol problems in alcohol and drug use behaviors in Argentinean college students.. Alcohol Alcohol 49:128-37.PMID: 24322673

c) Pilatti A, Read JP, **Pautassi RM**. (2017) ELSA 2016 Cohort: Alcohol, Tobacco, and Marijuana Use and Their Association with Age of Drug Use Onset, Risk Perception, and Social Norms in Argentinean College Freshmen. Front Psychol. 25; 8:1452. PMID: 28890707

d) Caneto F, **Pautassi RM**, Pilatti A (2018) Ethanol-induced autonomic responses and risk taking increase in young adults with a positive family history of alcohol problems. Addict Behav. 76:174-181. PMID: 28843731

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE (All as PI)

- PIP CONICET

National Council of Scientific and Technical Research of Argentina 03/13-06/18

Title: Behavioral, Pharmacological and neurochemical mechanisms underlying the facilitative effect of prenatal lead or ethanol on ethanol consumption later on life. The focus is to investigate the behavioral and cellular consequences effects of adolescent alcohol exposure, alone or in combination with lead. Overlap: None

- PICT-2015-0325 01/17-01/20

National Agency for the Promotion of Science and Technology of Argentina, (ANPCyT)
Title: Interaction between factors of vulnerability for alcohol consumption during adolescence. The focus is to investigate, via animal rat models, neurobiological factors, including exposure to aversive events, which affect ethanol intake during adolescence. Overlap: None

- SECYT UNC 2016-2017 (intramural university funding) 04/16-04/18

Secretary of Science, National University of Cordoba, Argentina
Title: Assessment of vulnerability factors for alcohol consumption. Overlap: None. The focus is to investigate, via animal rat models, behavioral traits associated with heightened ethanol intake during adolescence. Overlap: None

COMPLETED IN PAST 3 YEARS (All as PI)

- PICT-2012-0436 03/12-12/16

National Agency for the Promotion of Science and Technology of Argentina, (ANPCyT) Type D Projects
Title: Ethanol intake and reinforcement in the adolescent rat: vulnerability factors associated with the occurrence of ethanol-related problems. The focus is to investigate, via animal rat models, how early alcohol exposure and stress affect age-related effects of ethanol that in turn increase the probability of alcohol disorders later in life. Overlap: None

- SECYT UNC 2014-2015 (intramural university funding) 03/14-03/16

Secretary of Science, National University of Cordoba, Argentina
Title: Functional and Neurochemical characterization of vulnerability factors associated with ethanol intake during adolescence. The focus is to investigate the effects of adolescent ethanol exposure and ingestion on early gene expression and functionality of the endogenous opioid system. Overlap: None

- PID MINCyT 03/11-10/16

Ministry of Science and Technology of the Province of Córdoba. Title: Development of a predictive model of adolescent ethanol drinking. The focus is to generate, via multivariate statistics, a model that allows predicting adolescents at risk for problematic alcohol drinking. Role PI. Overlap: None