BIOGRAPHICAL SKETCH

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NAME: Manzoni, Olivier

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

POSITION TITLE: Research Director DR1

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)	END DATE MM/YYYY	FIELD OF STUDY
J. Fourier Science & Technology University, Grenoble	BS	06/1982	Cellular Biology and Physiology
J. Fourier Science & Technology University, Grenoble	MS	06/1986	Physiology
Université Montpellier II, Montpellier	PHD	10/1992	Neuroscience

A. Personal Statement

My entire scientific career has been devoted to the study of synaptic pathophysiology. I initially combined biochemical and imaging methods to discover new second messengers produced by two essential classes of receptors expressed at excitatory central synapses: NMDAR and mGluRs. I learned electrophysiology during two post-doctoral fellowships at the University of California San Francisco (P.I. Dr. R.A. Nicoll) and the Vollum Institute (P.I. Dr. J.T. Williams. For the past 20 years I have lead an independent group studying synaptopathies. Early on, we discovered that the endocannabinoid system underlies long lasting synaptic plasticity in the accumbens. Endocannabinoid-synaptic depression has since proven to be one of the most common forms of synaptic plasticity in the CNS and a synaptic correlate of neuropsychiatric diseases. Notably, we discovered that endocannabinoid synaptic plasticity is altered in mice models of social-defeat stress and nutrition induced depression, Fragile X and drugs of abuse including cocaine and cannabis. In recent years our work has focused on sex-differences and the effects of cannabis in lifetime. Our strategy is to elaborate structural and functional portraits of normal and diseased synapse in order to identify new endophenotypes of neuropsychiatric diseases and design innovative therapeutic strategies.

B. Positions and Honors

Positions and Employment

1993 - 1997 Chargé de recherches CR2, INSERM, Montpellier
1997 - 2002 Chargé de recherches CR1, INSERM, Montpellier
2002 - 2010 Research Director DR2, INSERM, Bordeaux
2010 - Research Director DR1, INSERM, Marseille

Other Experience and Professional Memberships

- Member, Society for Neuroscience, USA
- Member, Société des Neurosciences, France

Honors

1997 NIDA/INVEST fellowship, NIDA
2010 Independent Investigator Award, NARSAD
2015 Equipe FRM, Fondation pour la Recherche Médicale

2017 - 2021 Director Cannabinoids Neuroscience Research Laboratory INMED-Indiana University, International Associated Laboratory INSERM

C. Contribution to Science

1. ***Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens***. Robbe D, Kopf M, Remaury A, Bockaert J, ***Manzoni OJ. Proc Natl Acad Sci U S A.*** 2002 Jun 11;99(12):8384-8. When this study was undertaken, CB1 receptors had been described at CNS synapses, endogenous cannabinoids (eCB) had been discovered but evidence of synaptic release of eCBs was scarce. It was known that postsynaptic neurons produced eCBs in response to postsynaptic depolarization (e.g., Wilson & Nicoll Nature. 2001) but there was no evidence for eCB-mediated long-term synaptic plasticity. Based on our original description of CB1R at accumbens synapses (a) we discovered that alpha-wave stimulation induces a mGluR/eCB-mediated long-term depression. We determined the transduction pathways of this plasticity and found that it intersects with mGluR2/3 LTD (b) and can cohabitate with short-term eCB plasticity (c). Recently we discovered that eCB-LTD in the accumbens is causaly related to anxious behavior in a naturalistic model of depression (d). “eCB-LTD” has since been observed at most central synapses. This paper has made a significant impact on the research community and has been extensively cited (over 460 times Google scholar).

2. **Sex-dependent effects of in utero cannabinoid exposure on cortical function**. Bara A, Manduca A, Bernabeu A, Borsoi M, Serviado M, Lassalle O, Murphy M, Wager-Miller J, Mackie K, Pelissier-Alicot AL, Trezza V, **Manzoni OJ. Elife** 2018 Sep 11;7 The main component in marijuana, delta 9-tetrahydrocannabinol (THC), is able to cross the placental barrier and enter the fetal bloodstream so thousands of infants are exposed to cannabis before birth. This means that the consumption of the drug during pregnancy is a major public health concern.We found that prenatal cannabinoid exposure decreased social interactions and reduced play behavior in adult males but not in adult females. Based on these results and qPCR analysis we designed and validated new drug based therapies and fully restored synaptic plasticity and normalized social interaction in male rats exposed to cannabinoids in the womb. This work is part of past and ongoing investigations on the effects of cannabis in lifetime (a,b,c,d).

3. ***Transition to addiction is associated with a persistent impairment in synaptic plasticity.*** Kasanetz F, Deroche-Gamonet V, Berson N, Balado E, Lafourcade M, ***Manzoni* O, Piazza PV. Science.*** 2010 Jun 25;328(5986):1709-12. ***co-senior author.*** My group has had a constant interest in drug addiction research (e.g. a, b, c). To uncover the biological basis of the shift from controlled drug use to compulsive drug taking in cocaine addiction we studied accumbens synapses in an anthropomorphic rat model of addiction. We found that animals that develop the behavioral hallmarks of addiction have permanently impaired NMDAR-mediated long-term depression (LTD), whereas LTD recovers in non-addicted rats. We recently discovered the synaptic markers of addiction at prefrontal synapses in this model (d). This work indicates that the development of cocaine addiction might be due to the inability to reverse drug-induced neuroadaptations in vulnerable individuals.

4. ***Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions.*** Lafourcade M, Larrieu T, Mato S, Duffaud A, Sepers M, Matias I, De Smedt-Peyrusse V, Labrousse VF, Bretillon L, Matute C, Rodríguez-Puertas R, Layé S, ***Manzoni OJ. Nat Neurosci.*** 2011;14(3):345-50.. Despite their high-caloric content, western diets are poor in essential nutrients and notorious for their low levels of n-3 and high levels of n-6 polyunsaturated fatty acids. Dietary insufficiency in omega-3 fatty acid has been implicated in many disorders. We studied mice fed a diet low in omega-3 fatty acid from gestation onwards and discovered that low levels of omega-3 had deleterious consequences on the brain levels of polyunsaturated fatty acids, synaptic functions and emotional behaviors. Our results show a major deregulation of the endogenous cannabinoid system, similar to other pathological models of neuropsychiatric disease (a,b,c). This was the first paper providing a plausible substrate for the effect of food on mood and it generated immense interest in the general public. Along the same line we also reported that perinatal omega-3 deficiency abolishes

hippocampal LTP (c), eCB-LTD in the accumbens underlies anxious-type depression (b) and that omega-3 deficiency at adolescence induces anxiety and reduces cognition at adulthood (d).

5. ***Uncoupling of the endocannabinoid signalling complex in a mouse model of fragile X syndrome***. Jung KM, Sepers M, Henstridge CM, Lassalle O, Neuhofer D, Martin H, Ginger M, Frick A, DiPatrizio NV, Mackie K, Katona I, Piomelli D, ***Manzoni OJ. Nat Commun***. 2012;3:1080. Fragile X syndrome (FRAX) is the most common identified genetic cause of autism and is due to under expression of a translational repressor called FMRP. mGlu5-LTD in the hippocampus is altered in FMRP-deficient (fmr1−/−) mice. We found that endocannabinoid (eCB)-LTD in the accumbens is absent in fmr1−/− mice. In collaboration with the Mackie, Piomelli and Katona groups we found that the mGlu5/eCB macromolecular complex is disrupted in these mice. We discovered that pharmacological enhancement of eCB signaling normalizes this synaptic defect and corrects behavioral abnormalities in fmr1−/− mice. The results identify the mGlu5-eCB signalosome as a molecular substrate for fragile X syndrome, which might be targeted by therapy. Our most recent results show how mGlu5 signaling can be pharmacologcally modulated during aging to restore aberrant LTP (c) and LTD (d) in the mouse prefrontal cortex. This study forms the basis for ongoing work in the lab focusing on the synaptic aberrations in genetic and environmental models of autisms and mental retardation (a,b,c,d).

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

Ongoing Research Support

1R01DA046196-01, NIDA Olivier Manzoni (PI) 08/01/18-06/30/23
Perinatal cannabinoids delay KCC2 expression and lead to neurodevelopmental abnormalities
Cannabis is the most frequently used illicit drug. Maternal perinatal cannabis use has been associated with a range of adverse neurodevelopmental consequences in the offspring. The underlying mechanism(s) remain incompletely understood, but are consistent with impaired cortical neuronal circuit formation. The proposed work will address three specific aims. Aim 1. Identify the early molecular, functional and behavioral consequences of exposing dams to THC ± CBD during lactation on the progeny of both sexes. These experiments will characterize the early consequences on neuronal circuits in the PFC, determine THC's mechanism (and possible antagonism by cannabidiol (CBD)) to delay KCC2 expression, examine the localization and levels of components of the PFC endocannabinoid system and measure ecologically-relevant pup behaviors (ultrasonic vocalizations and homing following maternal separation) after maternal exposure to cannabinoids. Aim 2. Determine the long-term consequences of THC ± CBD exposure during lactation. These experiments will determine if THC ± CBD exposure during lactation has enduring effects on synaptic plasticity in adolescent and adult, on levels or localization of PFC endocannabinoid components, on naturalistic social behaviors, and cognitive function. Aim 3. Strategies to ameliorate the long-term deleterious consequences of THC exposure during lactation. These experiments will test the hypothesis that enhancing endocannabinoid signaling (CB1 positive allosteric modulators or inhibitors of eCB degradation) will rescue the behavioral and physiological deficits that are a consequence of PCE. Completion of these experiments will reveal the underpinnings of the impact of perinatal THC exposure on neuronal functions and behavior and provide new therapeutic strategies to ameliorate associated behavioral deficits.
Role: CPI

1R01DA043982-01A1, NIDA Manzoni, Olivier (PI) 08/01/17-05/31/22
Sex-specific critical periods determine the effects of cannabinoids on the mesocorticolimbic system
We want to define new structural, molecular and functional synaptic substrates of the sex-specific effects of adolescent cannabis use on ECS function and behavior. Thus we will: 1/ Characterize and compare the normal functional development of neuronal and synaptic responses in the mesocorticoloimbic system

(MCS) between male and female rats from pre-adolescence to adulthood. 2/ Establish the developmental patterns of expression and localization of key components of the endocannabinoid system (ECS) in the rat MCS in a sex and age-specific fashion. 3/ Determine the sex-specific functional (molecular, synaptic, and behavioral) consequences of THC exposure during critical periods of adolescence and adulthood.
Role: CPI

Equipe FRM 2015, Fondation pour la Recherche Medicale Manzoni, Olivier (PI) 12/31/15-05/31/19
Multi scale study of inutero cannabis exposure
The general purpose of this proposal is to decipher how exposure to cannabis during fetal life cause protracted changes in synaptic functions, brain circuits, in vivo neuronal ensembles activity and associated behaviors.
Role: PI