

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.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	START DATE MM/YYYY	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	09/1988	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 15 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. 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.

1. 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. Uncoupling of the endocannabinoid signalling complex in a mouse model of fragile X syndrome. *Nat Commun.* 2012;3:1080. PubMed PMID: [23011134](#); PubMed Central PMCID: [PMC3657999](#).
2. 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. Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. *Nat Neurosci.* 2011 Mar;14(3):345-50. PubMed PMID: [21278728](#).
3. Kasanetz F, Deroche-Gamonet V, Berson N, Balado E, Lafourcade M, Manzoni O, Piazza PV. Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science.* 2010 Jun 25;328(5986):1709-12. PubMed PMID: [20576893](#).
4. Robbe D, Kopf M, Remaury A, Bockaert J, Manzoni OJ. Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. *Proc Natl Acad Sci U S A.* 2002 Jun 11;99(12):8384-8. PubMed PMID: [12060781](#); PubMed Central PMCID: [PMC123076](#).

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

C. Contribution to Science

- 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 cohabituate with short-term eCB plasticity (c). Recently we discovered that eCB-LTD in the accumbens is causally 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).
 - Bosch-Bouju C, Larrieu T, Linders L, Manzoni OJ, Layé S. Endocannabinoid-Mediated Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress. *Cell Rep.* 2016 Aug 2;16(5):1237-42. PubMed PMID: [27452462](#).
 - Puente N, Cui Y, Lassalle O, Lafourcade M, Georges F, Venance L, Grandes P, Manzoni OJ. Polymodal activation of the endocannabinoid system in the extended amygdala. *Nat Neurosci.* 2011 Nov 6;14(12):1542-7. PubMed PMID: [22057189](#).
 - Robbe D, Alonso G, Chaumont S, Bockaert J, Manzoni OJ. Role of p/q-Ca²⁺ channels in metabotropic glutamate receptor 2/3-dependent presynaptic long-term depression at nucleus accumbens synapses. *J Neurosci.* 2002 Jun 1;22(11):4346-56. PubMed PMID: [12040040](#).
 - Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ. Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. *J Neurosci.* 2001 Jan 1;21(1):109-16. PubMed PMID: [11150326](#).
- A single in-vivo exposure to delta 9THC blocks endocannabinoid-mediated synaptic plasticity.***
Mato S, Chevalayre V, Robbe D, Pazos A, Castillo PE, **Manzoni OJ. *Nat Neurosci.*** 2004 Jun;7(6):585-6. For this study we asked a simple question: Will cannabis alter the synaptic functions of endogenous cannabinoids? Our biochemical and electrophysiological approaches revealed that a single exposure to cannabis in vivo is sufficient to transiently abolish eCB-LTD in the accumbens and the hippocampus, two key regions implicated in the behavioral effects of marijuana. We introduced the

notion of functional tolerance of CB1R and provided new plausible neurobiological substrates of cannabis exposure. Subsequent work from our lab provided a new molecular mechanism for this phenomenon (c) and also showed that more sustained THC consumption triggers compensatory synaptic plasticity while leading to full desensitization/internalization of CB1R (b). We also found that nicotine induces CB1R-dependent synaptic plasticity in the bed nucleus of the stria terminalis (c) and that enhanced functional activity of CB1R mediates adolescent behavior. These studies illustrate how the endocannabinoid system participates to multiple behavioral traits and paved the way to the systematic search of synaptic adaptations in neuropsychiatric diseases.

- a. Schneider M, Kasanetz F, Lynch DL, Friemel CM, Lassalle O, Hurst DP, Steindel F, Monory K, Schäfer C, Miederer I, Leweke FM, Schreckenberger M, Lutz B, Reggio PH, Manzoni OJ, Spanagel R. Enhanced Functional Activity of the Cannabinoid Type-1 Receptor Mediates Adolescent Behavior. *J Neurosci*. 2015 Oct 14;35(41):13975-88. PubMed PMID: [26468198](#); PubMed Central PMCID: [PMC4604232](#).
- b. Reisinger AR, Kaufling J, Manzoni O, Cador M, Georges F, Caillé S. Nicotine self-administration induces CB1-dependent LTP in the bed nucleus of the stria terminalis. *J Neurosci*. 2014 Mar 19;34(12):4285-92. PubMed PMID: [24647948](#).
- c. Mikasova L, Groc L, Choquet D, Manzoni OJ. Altered surface trafficking of presynaptic cannabinoid type 1 receptor in and out synaptic terminals parallels receptor desensitization. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18596-601. PubMed PMID: [19015531](#); PubMed Central PMCID: [PMC2584146](#).
- d. Mato S, Robbe D, Puente N, Grandes P, Manzoni OJ. Presynaptic homeostatic plasticity rescues long-term depression after chronic Delta 9-tetrahydrocannabinol exposure. *J Neurosci*. 2005 Dec 14;25(50):11619-27. PubMed PMID: [16354920](#).

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.

- a. Manzoni O, Pujalte D, Williams J, Bockaert J. Decreased presynaptic sensitivity to adenosine after cocaine withdrawal. *J Neurosci*. 1998 Oct 1;18(19):7996-8002. PubMed PMID: [9742166](#).
- b. Williams JT, Christie MJ, Manzoni O. Cellular and synaptic adaptations mediating opioid dependence. *Physiol Rev*. 2001 Jan;81(1):299-343. PubMed PMID: [11152760](#).
- c. Harrison JM, Allen RG, Pellegrino MJ, Williams JT, Manzoni OJ. Chronic morphine treatment alters endogenous opioid control of hippocampal mossy fiber synaptic transmission. *J Neurophysiol*. 2002 May;87(5):2464-70. PubMed PMID: [11976383](#).
- d. Kasanetz F, Lafourcade M, Deroche-Gamonet V, Revest JM, Berson N, Balado E, Fiancette JF, Renault P, Piazza PV, Manzoni OJ. Prefrontal synaptic markers of cocaine addiction-like behavior in rats. *Mol Psychiatry*. 2013 Jun;18(6):729-37. PubMed PMID: [22584869](#).

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).

- a. Manduca A, Bara A, Larrieu T, Lassalle O, Joffre C, Layé S, Manzoni OJ. Amplification of mGlu₅-endocannabinoid signaling rescues behavioral and synaptic deficits in a mouse model of adolescent and adult dietary polyunsaturated fatty acids imbalance. *J Neurosci*. 2017 Jun 19; PubMed PMID: [28630250](#).
- b. Thomazeau A, Bosch-Bouju C, Manzoni O, Layé S. Nutritional n-3 PUFA Deficiency Abolishes Endocannabinoid Gating of Hippocampal Long-Term Potentiation. *Cereb Cortex*. 2017 Apr 1;27(4):2571-2579. PubMed PMID: [26946127](#).
- c. Bosch-Bouju C, Larrieu T, Linders L, Manzoni OJ, Layé S. Endocannabinoid-Mediated Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress. *Cell Rep*. 2016 Aug 2;16(5):1237-42. PubMed PMID: [27452462](#).
- d. Martin HGS, Lassalle O, Brown JT, Manzoni OJ. Age-Dependent Long-Term Potentiation Deficits in the Prefrontal Cortex of the Fmr1 Knockout Mouse Model of Fragile X Syndrome. *Cereb Cortex*. 2016 May;26(5):2084-2092. PubMed PMID: [25750254](#).

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 pharmacologically 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).

- a. Martin HG, Lassalle O, Manzoni OJ. Differential Adulthood Onset mGlu5 Signaling Saves Prefrontal Function in the Fragile X Mouse. *Cereb Cortex*. 2016 Oct 23; PubMed PMID: [27797833](#).
- b. Martin HGS, Lassalle O, Brown JT, Manzoni OJ. Age-Dependent Long-Term Potentiation Deficits in the Prefrontal Cortex of the Fmr1 Knockout Mouse Model of Fragile X Syndrome. *Cereb Cortex*. 2016 May;26(5):2084-2092. PubMed PMID: [25750254](#).
- c. Martin HG, Manzoni OJ. Late onset deficits in synaptic plasticity in the valproic acid rat model of autism. *Front Cell Neurosci*. 2014;8:23. PubMed PMID: [24550781](#); PubMed Central PMCID: [PMC3907704](#).
- d. Thomazeau A, Lassalle O, lafrati J, Souchet B, Guedj F, Janel N, Chavis P, Delabar J, Manzoni OJ. Prefrontal deficits in a murine model overexpressing the down syndrome candidate gene *dyrk1a*. *J Neurosci*. 2014 Jan 22;34(4):1138-47. PubMed PMID: [24453307](#); PubMed Central PMCID: [PMC3953590](#).

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

Ongoing Research Support

Equipe FRM 2015, Fondation pour la Recherche Médicale Manzoni, Olivier (PI) 12/31/15-12/31/18
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

Cannado, Agence Nationale pour la Recherche Pellissier, Anne-Laure (PI) 02/01/14-07/31/17
Pathophysiological correlates of adolescent cannabis use

In humans (schizophrenia patients) and in animal models of cannabis use, identify the molecular, synaptic and circuit substrates linking adolescent cannabis use to the vulnerability to develop schizophrenia symptoms.

Role: KP

Monoacylglycerol lipase inhibition for the treatment of multiple sclerosis, ARSEP Carlos Matute (PI)
12/01/14-11/30/17

Therapeutic potential of monoacylglycerol lipase inhibition for the treatment of multiple sclerosis
This project explores the therapeutic potential of MAGL inhibitors for the treatment of multiple sclerosis.

Role: CPI

Completed Research Support

CYFIP-Aut, Agence Nationale de la Recherche Barbara Bardoni (PI) 03/01/13-02/28/17
Role of CYFIP1 in physiopathology of autism and mental retardation

We will study the role of CYFIP1 in neuronal morphology, synaptic plasticity and behavior. At the molecular level, we will dissect the role of this protein in the Rac1-CYFIP1-FMRP pathway and to understand the functional significance of CYFIP1/FMRP interaction in different steps of RNA metabolism.

Role: CPI

Multiscale Down Syndrome, Fondation Jerome Lejeune Olivier Manzoni (PI) 12/09/14-12/08/16
Multiscale analysis of Down Syndrome Synaptopathies

Role: PI

MoodFood, Agence Nationale de la Recherche Olivier Manzoni (PI) 03/31/13-04/29/17
Depression and Nutrition

We want to elucidate the interactions between diet and the vulnerability to develop emotional disorders.

Role: PI

CortexCell, Agence Nationale de la Recherche Manzoni, Olivier (PI) 12/01/11-11/30/15
The cortical mechanisms of associative learning and of its deficits in Fragile X syndrome

Study the cortical mechanisms of associative learning and of its deficits in Fragile X syndrome in the mice barrel cortex.

Role: Co-Investigator