

BIOGRAPHICAL SKETCH

NAME: Matteo Fossati

POSITION TITLE: Junior Group Leader

EDUCATION/TRAINING: PhD

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Milan, Milano, Italy	B.S	07/2007	Medical Biotechnology
University of Milan, Milano, Italy	M.S	10/2009	Molecular and Cellular Medical Biotechnology
University of Milan & National Research Council of Italy (CNR), Milano, Italy	Ph.D.	01/2013	PhD in Medical Pharmacology
University of Milan & National Research Council of Italy (CNR), Milano, Italy	Postdoctoral	02/2014	Molecular Biology of the Cell
INSERM & Institut de Biologie de l'École Normale Supérieure, Paris, France	Postdoctoral	12/2018	Molecular Neuroscience

A. Personal Statement

I'm a tenured researcher at the Institute of Neuroscience of the CNR and Junior Group Leader at the Humanitas Research Hospital, where I lead the "Cell Biology of the Synapse" laboratory. My mainstream research is focused on investigating cellular and molecular mechanisms underlying the development and function of synapses, the basic functional units of the nervous system, whose impairment is linked to pathological conditions (e.g. autism spectrum disorders, intellectual disability, epilepsy and schizophrenia). After a PhD in cellular and molecular biology, where I also came in contact with biophysics of biological membranes (Fossati et al, 2014 *EMBO J.* and *Cell. Logist.*), my career evolved in the field of neuroscience, where I applied my knowledge on cellular logistics to interrogate the function of nervous system. As postdoctoral fellow at the ENS (Paris, France), I developed an extensive expertise in neurobiology and acquired *in vivo* molecular tools to study the development of neuronal circuits. My research led to uncover fundamental roles of novel proteins in the regulation of synapse physiology and in setting a proper E/I ratio in the brain (Fossati et al, 2016 and 2019 *Neuron*). In 2019, I was recruited as independent investigator at the CNR – Institute of Neuroscience. As group leader, I'm developing different innovative research lines in the field of molecular neuroscience. The main goal of my laboratory is to understand the molecular processes underlying the functional organization of synapses up to the nanometer scale and how their alteration leads to brain disorders. My lab has currently several on-going projects on the pathogenic mechanisms of the Angelman syndrome. To this aim, we exploit an interdisciplinary approach that integrates a range of *in vivo* molecular tools with advanced optical microscopy (including super-resolution), proteomics and biochemistry. Our research is supported by private and public funding agencies. I'm currently leading a laboratory with 1 postdoctoral fellow, 3 PhD student and 1 predoctoral fellow and 1 master student.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – present	Junior Group Leader, IRCCS – Humanitas Clinical and Research Hospital, Rozzano (MI), Italy (https://www.humanitas-research.com/groups/matteo-fossati-group/)
2021 – present	Adjunct Teaching Professor, Open Faculty member, Humanitas University, Pieve Emanuele (MI), Italy
2021 – present	Member, Italian Society of Neuroscience (SINS)

2019 – present	Research group leader, “Cell Biology of the Synapse” laboratory, Institute of Neuroscience, CNR, Rozzano (MI), Italy (http://www.in.cnr.it/index.php/it/people-it/302-matteo-fossati)
2019 – present	Editorial Board of Cellular Neurophysiology as Review Editor for <i>Frontiers in Cellular Neuroscience</i>
2019 – present	Editorial Board of Neurodevelopment as Review Editor for <i>Frontiers in Neuroscience</i>
2019 – present	Ad hoc research grant referee for Cariplo Foundation (Italy), Fondation pour la Recherche Médicale (France) and Agence Nationale de la Recherche (ANR, France)
2019 – present	Member, recruitment committee for postdoctoral fellows and technician positions at the Institute of Neuroscience – CNR, Italy
2018 – present	Ad hoc reviewer for international journals (Scientific Reports, Molecular Psychiatry, Frontiers, Brain)
2016 – 2020	Member, French Society of Neuroscience
2010 – 2015	Member, Italian Society of Cellular, Molecular and Developmental Biology (ABCD)

Honors

2024	Scientific award in “Molecular and Cellular Biology and Pathology”, Dept. of Biomedical Sciences, CNR (Italy)
2024	invited talk – bi-annual Angelman Syndrome Alliance conference, Coventry (UK)
2024	invited talk – FENS Forum 2024, Vienna (Austria)
2023	invited talk – Italian Society for Neuroscience meeting, Torino (Italy)
2023	invited seminar – Human Technopole, Milano (Italy)
2022	invited talk – FENS-Kavli Network of Excellence (FKNE) meeting, Milano (Italy)
2021	invited seminar – PhD Retreat, University of Milano (Italy)
2019	invited talk (keynote speaker) – Network of Young Researcher (NYR), Paris (France)
2019	Fossati et al. 2019 Neuron selected among the most relevant publications of the year 2019 from the French Society of Neuroscience (https://indd.adobe.com/view/166a8f90-8f47-4208-9427-697a16ed8b86)
2013	Postdoctoral fellowship from “Fratelli Confalonieri” Foundation
2012	Travel grant to attend the five-week intensive lecture and practical course “Molecular biology of the cell” jointly organized by Institut Pasteur and Institut Curie, Paris, France
2010	EMBO Short-Term Fellowship to support a scientific collaboration with Bruno Goud’s lab, Institut Curie, Paris, France
2010	Graduate Scholarship, University of Milan, Milano, Italy

C. Contributions to Science

Research unique identifiers: ORCID: 0000-0002-9210-5242
Scopus author ID: 36089941600

1. Mechanisms of protein transport at the ER-Golgi interface

My PhD studies focused on the transport of newly synthesized membrane proteins from the endoplasmic reticulum (ER) to the Golgi Apparatus (GA), the early station of the secretory pathway. In particular, we investigated two key, yet poorly characterized issues: *i*) whether the geometry and composition of the ER membranes contributes to sort protein cargoes into transport carriers to enter the secretory pathway, and *ii*) how secretory proteins escape from the Golgi-to-ER retrograde transport to ensure efficient delivery to their final destination. To study the role of membrane curvature and composition to protein trafficking, I was visiting PhD student (supported by an EMBO short-term fellowship) in Bruno Goud’s laboratory (Institut Curie, France). We used a model system consisting of Giant Unilamellar Vesicles (GUVs) from which highly curved domains

were pulled out by micromanipulation (optical tweezers and molecular motors) and reported that membrane curvature alone is not sufficient to sort membrane proteins at the ER-Golgi interface (Fossati et al. Cell Logist). Concerning the first topic, we analyzed the behavior of several membrane cargoes using advanced optical microscopy (Fossati et al. JoVE 2014) and found that positive signals, in addition to mediate cargo export from the ER efficiently exclude cargo proteins from being recycled back to the ER via a Rab6-dependent retrograde transport (Fossati et al. EMBO J 2014). The data resulting from this work uncover novel mechanisms regulating the efficiency of cargo proteins to their final destination and modify current views of cargo transport along the secretory pathway.

Fossati et al. An investigation of the effect of membrane curvature on transmembrane domain-dependent protein sorting in lipid bilayers. 2014 Cell Logist. 4 (2): e29087 doi: [10.4161/cl.29087](https://doi.org/10.4161/cl.29087)

Fossati et al. Visualization of endoplasmic reticulum sub-domains in cultured cells. 2014 J. Vis. Exp. (84): e50985. doi: [10.3791/50985](https://doi.org/10.3791/50985)

Fossati et al. A positive signal prevents secretory cargoes from recycling between the Golgi and the ER. 2014 EMBO J. 33 (18): 2080-2097 doi: [10.15252/emboj.201488367](https://doi.org/10.15252/emboj.201488367)

2. Mechanisms coordinating excitatory and inhibitory synapse development

The proper function of the brain requires balanced excitation and inhibition. However, the molecular basis underlying the formation and maturation of excitatory (E) and inhibitory (I) synapses are largely unknown. As postdoctoral fellow, I identified that SRGAP2 coordinates the development of E and I synapses in the neocortex through the interaction with key components of E and I postsynaptic densities (Fossati et al. 2019 Neuron). SRGAP2 is one of the few genes that is specifically duplicated in humans. The introduction of the human-specific paralog SRGAP2C in the mouse brain promotes the emergence of human features of E synapses (neoteny and increased complexity). Here, we demonstrate that SRGAP2C also controls the number, maturation and complexity (number of I synapses located in dendritic spines, also referred to as dually innervated spines, Gemin et al. Plos Biol 2021) of I synapses to ensure an optimal E/I ratio. Together, these results uncover a novel molecular mechanism coordinating critical features of synaptic development and suggest that human-specific duplication of SRGAP2 might have contributed to the emergence of unique traits of human neurons while preserving the E/I balance.

Fossati et al. SRGAP2 and Its Human-Specific Paralog Co-Regulate the Development of Excitatory and Inhibitory Synapses. 2016 Neuron 91 (2): 356-369 doi: [10.1016/j.neuron.2016.06.013](https://doi.org/10.1016/j.neuron.2016.06.013)

Gemin et al. Unique properties of dually innervated dendritic spines in pyramidal neurons of the somatosensory cortex uncovered by 3D correlative light and electron microscopy. 2021 Plos Biol. 19(8):e3001375. doi: [10.1371/journal.pbio.3001375](https://doi.org/10.1371/journal.pbio.3001375)

3. Non-ionotropic functions of glutamate receptors

During the second part of my postdoctoral training I investigated the molecular function of the poorly characterized glutamate receptor delta 1 (GluD1). In the somatosensory cortex, GluD1, which is expressed on the post-synaptic membrane of pyramidal neurons forms a *trans*-synaptic complex with cerebellin 4 (Cbln4) and pre-synaptic Neurexins (Nrxn). Using proteomics and an *in vivo* structure-function analysis, we show that GluD1 specifies the formation of synapses between pyramidal neurons and somatostatin-positive interneurons through a post-synaptic signaling that requires the activation of GluD1 by glycine/D-serine, but does not depend on the ion flux through the pore (Fossati et al. 2019). Altogether, we find that GluD1 engages in a *trans*-synaptic interaction with Cbln4 and Nrxn and serves as a hub for post-synaptic molecules that are required for the proper establishment of inhibitory connectivity in the neocortex. Recent evidence indicates that other members of the ionotropic glutamate receptor family may engage in *trans*-synaptic adhesion and that this function is crucial for the development of different subtypes of synapses (Fossati & Charrier 2021 Curr Opin Neurobiol). Our work *i)* further expanded the repertoire of glutamate receptors involved in this, and *ii)* provide the first demonstration *in vivo* on the function of a ionotropic glutamate receptor mediating the assembly and the specification of inhibitory synapses via *trans*-synaptic signaling.

Fossati et al. Trans-synaptic signaling through the glutamate receptor delta-1 mediates inhibitory synapse formation in cortical pyramidal neurons. 2019 Neuron 104 (6): 1081-1094e7 doi: [10.1016/j.neuron.2019.09.027](https://doi.org/10.1016/j.neuron.2019.09.027)

Fossati and Charrier* Trans-synaptic interactions of ionotropic glutamate receptors. 2021 Curr. Opin. Neurobiol. 66:85-92. doi: [10.1016/j.conb.2020.09.001](https://doi.org/10.1016/j.conb.2020.09.001). *corresponding authors*

Assendorp N, Fossati M, Libé-Philippot B, Christopoulou E, Depp M, Rapone R, Dingli F, Loew D, Vanderhaeghen P, Charrier C. CTNND2 moderates the pace of synaptic maturation and links human evolution to synaptic neoteny. 2024 Cell Rep Oct 22;43(10):114797. doi: 10.1016/j.celrep.2024.114797

4. Pathogenic mechanisms of neurodevelopmental disorders

Neurodevelopmental disorders have multifactorial origins, with genetic and environmental factors contributing to deviating developmental trajectories of synaptic connections and neuronal circuits. As group leader of the “Cell biology of the synapse” team, we investigate cellular and molecular mechanisms underlying the onset of neurodevelopmental disorders. To this aim, we combine in vivo and in vitro manipulation of gene function with advanced imaging, biochemistry and proteomics to understand how genetic and early life adversities lead to alterations of synapse developmental, ultimately resulting in cognitive and behavioral deficits. Several ongoing studies are focused on UBE3A gene, whose mutations are causative of the Angelman syndrome and autism.

Biagioni M, Baronchelli F and Fossati M. Multiscale spatio-temporal dynamics of UBE3A gene in brain physiology and neurodevelopmental disorders. 2024 Neurobiol Dis Oct 15:201:106669. doi: 10.1016/j.nbd.2024.106669.

van Esbroeck ACM, Verhagen FM, Biagioni M, Fossati M, Distel B, Elgersma Y. Localization of Human UBE3A Isoform 3 is Highly Sensitive to Amino Acid Substitutions at p.Met21 Position. 2024 BioRxiv doi: 10.1101/2024.02.05.578859. (currently in revision in Human Molecular Genetics)

Folci A.*, Mirabella F., Fossati M.* Ubiquitin and ubiquitin-like proteins in the critical equilibrium between synapse physiology and intellectual disability. 2020 eNeuro 7 (4): ENEURO.0137-20.2020

D. Relevant publications (10)

- Matteoli M., Pozzi D, **Fossati M.** and Menna E. Immune synaptopathies: how materna immune activation impacts synaptic function during development. 2022 **EMBO J.** Jul 3;42(13):e113796. [10.15252/embj.2023113796](https://doi.org/10.15252/embj.2023113796)
- Gemin O., Serna P., Zamith J., Assendorp N., **Fossati M.**, Rostaing P., Triller A. and Charrier C. Unique properties of dually innervated dendritic spines in pyramidal neurons of the somatosensory cortex uncovered by 3D correlative light and electron microscopy. 2021 **Plos Biol.** 19(8):e3001375. doi: [10.1371/journal.pbio.3001375](https://doi.org/10.1371/journal.pbio.3001375).
- **Fossati M.***, Charrier C.* Trans-synaptic interactions of ionotropic glutamate receptors. 2021 **Curr. Opin. Neurobiol.** 66:85-92. doi: [10.1016/j.conb.2020.09.001](https://doi.org/10.1016/j.conb.2020.09.001). *corresponding authors
- Folci A.*, Mirabella F., **Fossati M.*** Ubiquitin and ubiquitin-like proteins in the critical equilibrium between synapse physiology and intellectual disability. 2020 **eNeuro** 7 (4): [10.1523/ENEURO.0137-20.2020](https://doi.org/10.1523/ENEURO.0137-20.2020). *corresponding authors
- **Fossati M.**, Assendorp A., Gemin O., Colasse S., Dingli F., Arras G., Loew D., Charrier C. Trans-synaptic signaling through the glutamate receptor delta-1 mediates inhibitory synapse formation in cortical pyramidal neurons. 2019 **Neuron** 104 (6): 1081-1094e7 doi: [10.1016/j.neuron.2019.09.027](https://doi.org/10.1016/j.neuron.2019.09.027).
- Zapata J, Moretto E, Hannan S, Murru L, Longatti A, Mazza D, Benedetti L, **Fossati M**, Heise C, Ponzoni L, Valnegri P, Braida D, Sala M, Francolini M, Hildebrand J, Kalscheuer V, Fanelli F, Sala C, Bettler C, Bassani S, Smart TG and Passafaro M. Epilepsy and intellectual disability linked protein Shrm4 interaction with GABABRs shapes inhibitory neurotransmission. 2017 **Nat. Commun.** 8: 14536. doi: [10.1038/ncomms14536](https://doi.org/10.1038/ncomms14536).
- **Fossati M.**, Pizzarelli R., Schmidt E.R., Kupferman J.V., Stroebel D., Polleux F., Charrier C. SRGAP2 and Its Human-Specific Paralog Co-Regulate the Development of Excitatory and Inhibitory Synapses. 2016 **Neuron** 91 (2): 356-369 doi: [10.1016/j.neuron.2016.06.013](https://doi.org/10.1016/j.neuron.2016.06.013).
- **Fossati M.**, Colombo S.F., Borgese N. A positive signal prevents secretory cargoes from recycling between the Golgi and the ER. 2014 **EMBO J.** 33 (18): 2080-2097 doi: [10.15252/embj.201488367](https://doi.org/10.15252/embj.201488367). *Recommended on F1000 Prime*
- **Fossati M.**, Goud B., Borgese N., Manneville J.B. An investigation of the effect of membrane curvature on transmembrane domain-dependent protein sorting in lipid bilayers. 2014 **Cell Logist.** 4 (2): e29087 doi: [10.4161/cl.29087](https://doi.org/10.4161/cl.29087).

- Fasana E., **Fossati M.**, Brambillasca S., Francolini M. and Borgese N. A VAP-B mutant linked to Amyotrophic Lateral Sclerosis generates a novel form of Organized Smooth Endoplasmic Reticulum. 2010 ***FASEB J.*** 24(5): 1419-30. doi: [10.1096/fj.09-147850](https://doi.org/10.1096/fj.09-147850).

Complete list of published work:

<https://pubmed.ncbi.nlm.nih.gov/?term=fossati+matteo>