**DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO**

**39th CYCLE**

**Project proposal for a Sapienza PhD scholarship**

**Main research line**

**Title:** Neural stem cell properties and neurogenesis in a knock in mouse model expressing an autism-associated mutation

**Supervisor:**Emanuele Cacci

[emanuele.cacci@uniroma1.it](mailto:emanuele.cacci@uniroma1.it)

<https://corsidilaurea.uniroma1.it/it/users/emanuelecacciuniroma1it>

**Summary**

Adult hippocampal neurogenesis (AHN) impairment has been found associated with either physiological (e.g. aging) or pathological conditions, including neurological and neuropsychiatric diseases. Interestingly, AHN impairment has been recently reported in a few animal models of autism spectrum disorders (ASDs) by our and other research groups. Specifically, we studied AHN regulation in Neuroligin 3 knock in (Nlgn3 KI)mice, that expresses a previously identified human Nlgn3 mutation (the R451C Nlgn3 mutation) associated with a monogenic form of ASDs, and show behavioural alterations relevant to ASDs. We found that hippocampal adult-born neuron generation was impaired in Nlgn3 KI mice with respect to the wild-type animals; notably the neurogenic deficit could be rescued by prolonged treatment with the antidepressant fluoxetine, which also mitigated sociability alterations found in these mice. These data indicate a potential neurogenesis-mediated effect of FLX on the behaviour of these mice that, whether confirmed, might be relevant for the pharmacological treatment of ASDs.

However, further studies are required to fully uncover the relation between neurogenic impairment and the behavioural deficits observed in Nlgn3 KI mice and other mouse models carrying mutations in synaptic susceptibility genes associated to ASD.

The main goal of the current proposal is to gain insight into the cellular and molecular mechanisms underlying the neurogenic deficits observed in the Nlgn3 KI mouse and to deepen the knowledge about their contribution to the behavioural disturbances observed.

**Pertinent Publications of the proponent (last 5 years)**

1) [Roberta Gioia](https://pubmed.ncbi.nlm.nih.gov/?term=Gioia+R&cauthor_id=36583243), [Tommaso Seri](https://pubmed.ncbi.nlm.nih.gov/?term=Seri+T&cauthor_id=36583243), [Tamara Diamanti](https://pubmed.ncbi.nlm.nih.gov/?term=Diamanti+T&cauthor_id=36583243), [Stefania Fimmanò](https://pubmed.ncbi.nlm.nih.gov/?term=Fimman%C3%B2+S&cauthor_id=36583243), [Marina Vitale](https://pubmed.ncbi.nlm.nih.gov/?term=Vitale+M&cauthor_id=36583243), [Henrik Ahlenius](https://pubmed.ncbi.nlm.nih.gov/?term=Ahlenius+H&cauthor_id=36583243), [ZaalKokaia](https://pubmed.ncbi.nlm.nih.gov/?term=Kokaia+Z&cauthor_id=36583243), [Felice Tirone](https://pubmed.ncbi.nlm.nih.gov/?term=Tirone+F&cauthor_id=36583243), [Laura Micheli](https://pubmed.ncbi.nlm.nih.gov/?term=Micheli+L&cauthor_id=36583243), [Stefano Biagioni](https://pubmed.ncbi.nlm.nih.gov/?term=Biagioni+S&cauthor_id=36583243), [Giuseppe Lupo](https://pubmed.ncbi.nlm.nih.gov/?term=Lupo+G&cauthor_id=36583243), [Arianna Rinaldi](https://pubmed.ncbi.nlm.nih.gov/?term=Rinaldi+A&cauthor_id=36583243), [Antonella De Jaco](https://pubmed.ncbi.nlm.nih.gov/?term=De+Jaco+A&cauthor_id=36583243), [Emanuele Cacci](https://pubmed.ncbi.nlm.nih.gov/?term=Cacci+E&cauthor_id=36583243). Adult hippocampal neurogenesis and social behavioural deficits in the R451C Neuroligin3 mouse model of autism are reverted by the antidepressant fluoxetine. J. Neurochememistry. 2022; doi: 10.1111/jnc.15753.

2) Quaresima S, Istiaq A, Jono H, Cacci E, Ohta K, Lupo G. [Assessing the Role of Ependymal and Vascular Cells as Sources of Extracellular Cues Regulating the Mouse Ventricular-Subventricular Zone Neurogenic Niche.](https://pubmed.ncbi.nlm.nih.gov/35450289/)  Front Cell Dev Biol. 2022 Apr 5;10:845567. doi: 10.3389/fcell.2022.845567.

3) Wang W, Di Nisio E, Licursi V, Cacci E, Lupo G, Kokaia Z, Galanti S, Degan P, D'Angelo S, Castagnola P, Tavella S, Negri R. [Simulated Microgravity Modulates Focal Adhesion Gene Expression in Human Neural Stem Progenitor Cells.](https://pubmed.ncbi.nlm.nih.gov/36362982/)

Life (Basel). 2022 Nov 9;12(11):1827. doi: 10.3390/life12111827.

4) Morandell J, Schwarz LA, Basilico B, Tasciyan S, Dimchev G, Nicolas A, Sommer C, Kreuzinger C, Dotter CP, Knaus LS, Dobler Z, Cacci E, Schur FKM, Danzl JG, Novarino G. [Cul3 regulates cytoskeleton protein homeostasis and cell migration during a critical window of brain development.](https://pubmed.ncbi.nlm.nih.gov/34031387/) NatCommun. 2021 May 24;12(1):3058. doi: 10.1038/s41467-021-23123-x.

5) Stronati E, Biagioni S, Fiore M, Giorgi M, Poiana G, Toselli C, Cacci E. [Wild-Type and Mutant FUS Expression Reduce Proliferation and Neuronal Differentiation Properties of Neural Stem Progenitor Cells.](https://pubmed.ncbi.nlm.nih.gov/34299185/) Int J Mol Sci. 2021 Jul 15;22(14):7566. doi: 10.3390/ijms22147566.

6) Sacco R, Cacci E, Novarino G. [Neural stem cells in neuropsychiatric disorders.](https://pubmed.ncbi.nlm.nih.gov/29287246/)

CurrOpinNeurobiol. 2018 Feb;48:131-138. doi: 10.1016/j.conb.2017.12.005.

7) Poiana G, Gioia R, Sineri S, Cardarelli S, Lupo G, Cacci E. [Transcriptional regulation of adult neural stem/progenitor cells: tales from the subventricular zone.](https://pubmed.ncbi.nlm.nih.gov/32246617/) Neural Regen Res. 2020 Oct;15(10):1773-1783. doi: 10.4103/1673-5374.280301.

8) Licursi V, Anzellotti S, Favaro J, Sineri S, Carucci N, Cundari E, Fiore M, Guarguaglini G, Pippa S, Nisi PS, Vernì F, Biagioni S, Cacci E, Amendola R, Lupo G, Negri R. [X-ray irradiated cultures of mouse cortical neural stem/progenitor cells recover cell viability and proliferation with dose-dependent kinetics.](https://pubmed.ncbi.nlm.nih.gov/32300147/)  Sci Rep. 2020 Apr 16;10(1):6562. doi: 10.1038/s41598-020-63348-2.

9) Ajmone-Cat MA, Onori A, Toselli C, Stronati E, Morlando M, Bozzoni I, Monni E, Kokaia Z, Lupo G, Minghetti L, Biagioni S, Cacci E. [Increased FUS levels in astrocytes leads to astrocyte and microglia activation and neuronal death.](https://pubmed.ncbi.nlm.nih.gov/30872738/)  Sci Rep. 2019 Mar 14;9(1):4572. doi: 10.1038/s41598-019-41040-4.

10) Lupo G, Gioia R, Nisi PS, Biagioni S, Cacci E. [Molecular Mechanisms of Neurogenic Aging in the Adult Mouse Subventricular Zone.](https://pubmed.ncbi.nlm.nih.gov/30814846/)  J ExpNeurosci. 2019 Feb19;13:1179069519829040. doi: 10.1177/1179069519829040.

11) Stronati E, Conti R, Cacci E, Cardarelli S, Biagioni S, Poiana G. [Extracellular Vesicle-Induced Differentiation of Neural Stem Progenitor Cells.](https://pubmed.ncbi.nlm.nih.gov/31357666/) Int J Mol Sci. 2019 Jul 27;20(15):3691. doi: 10.3390/ijms20153691.

12) Lupo G, Nisi PS, Esteve P, Paul YL, Novo CL, Sidders B, Khan MA, Biagioni S, Liu HK, Bovolenta P, Cacci E, Rugg-Gunn PJ. [Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline.](https://pubmed.ncbi.nlm.nih.gov/29504228/) Aging Cell. 2018 Jun;17(3):e12745. doi: 10.1111/acel.12745.

**REFERENCES**

1. Anacker, et al. Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. Nature, 2018; 559(7712), 98–102.
2. Bonaguidi, et al. A unifying hypothesis on mammalian neural stem cell properties in the adult hippocampus. *Current opinion in neurobiology***22**, 754 (Oct, 2012).
3. Cope et al. Immature neurons and radial glia, but not astrocytes or microglia, are altered in adult cntnap2 and shank3 mice, models of autism. eNeuro, 3(5), 1–15.
4. De Jaco *et al.* Neuroligin trafficking deficiencies arising from mutations in the alpha/beta-hydrolase fold protein family. *The Journal of biological chemistry***285**, 28674 (Sep 10, 2010).
5. Ellegood, J., & Crawley, J. N. (2015). Behavioral and neuroanatomical phenotypes in mouse models of autism. Neurotherapeutics, 12(3), 521–533
6. Gioia et al. *Adult hippocampal neurogenesis and social behavioural deficits in the R451C Neuroligin3 mouse model of autism are reverted by the antidepressant fluoxetine*. *J. Neurochememistry. 2022;doi: 10.1111/jnc.15753.*
7. Goncalves et al. Adult Neurogenesis in the Hippocampus: From Stem Cells to Behavior. *Cell***167**, 897 (Nov 03, 2016).
8. Kempermann. Activity Dependency and Aging in the Regulation of Adult Neurogenesis. *Cold Spring Harbor perspectives in biology***7**, (Nov 02, 2015).
9. Lupo et al. [Molecular Mechanisms of Neurogenic Aging in the Adult Mouse Subventricular Zone.](https://pubmed.ncbi.nlm.nih.gov/30814846/) J Exp Neurosci. 2019 Feb 19;13:1179069519829040. doi: 10.1177/1179069519829040.
10. Opendak *et al.*, Lasting Adaptations in Social Behavior Produced by Social Disruption and Inhibition of Adult Neurogenesis. *The Journal of neuroscience : the official journal of the Society for Neuroscience***36**, 7027 (Jun 29, 2016).
11. *Snyder, et al. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature, 2011; 476(7361), 458–461.*
12. Tunc-Ozcan et al. Activating newborn neurons suppresses depression and anxiety-like behaviors. Nature Communications, 2019; 10(1), 3768.