

MicroRNAs in stress response: form brain to periphery.

Luisa Lo Iacono, PhD

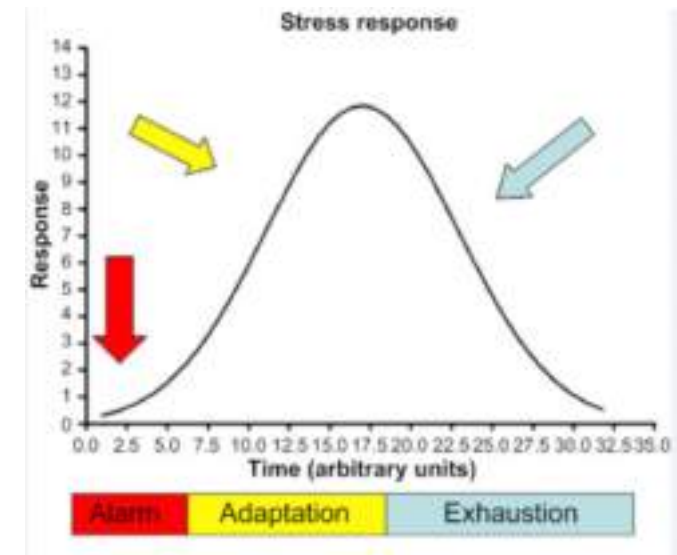
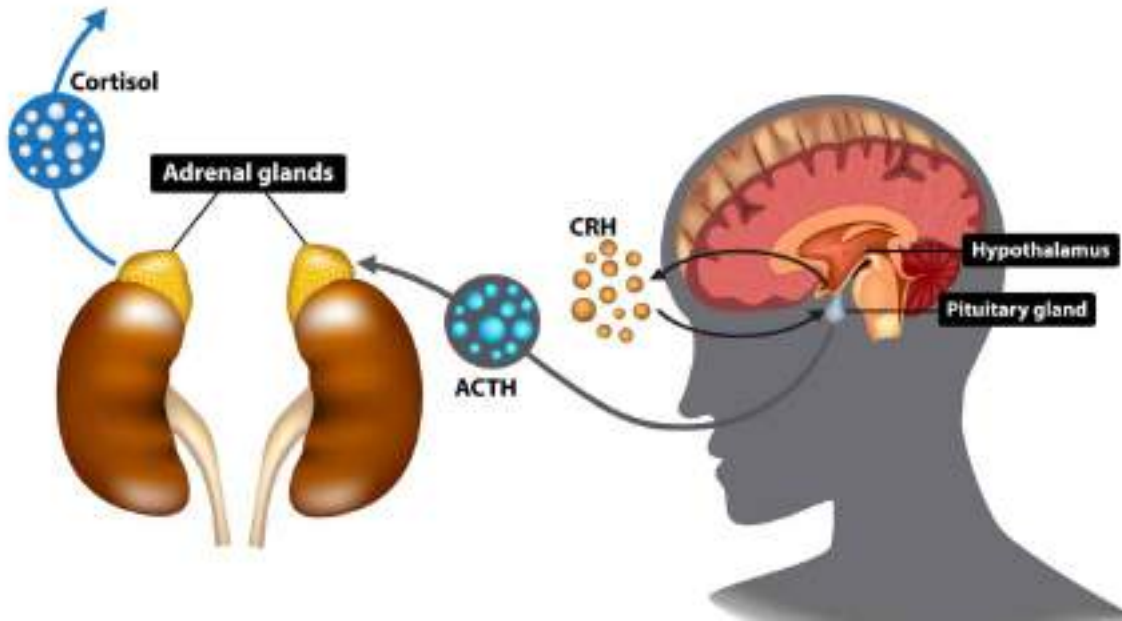
Luisa.loiacono@unipi.it



Stress

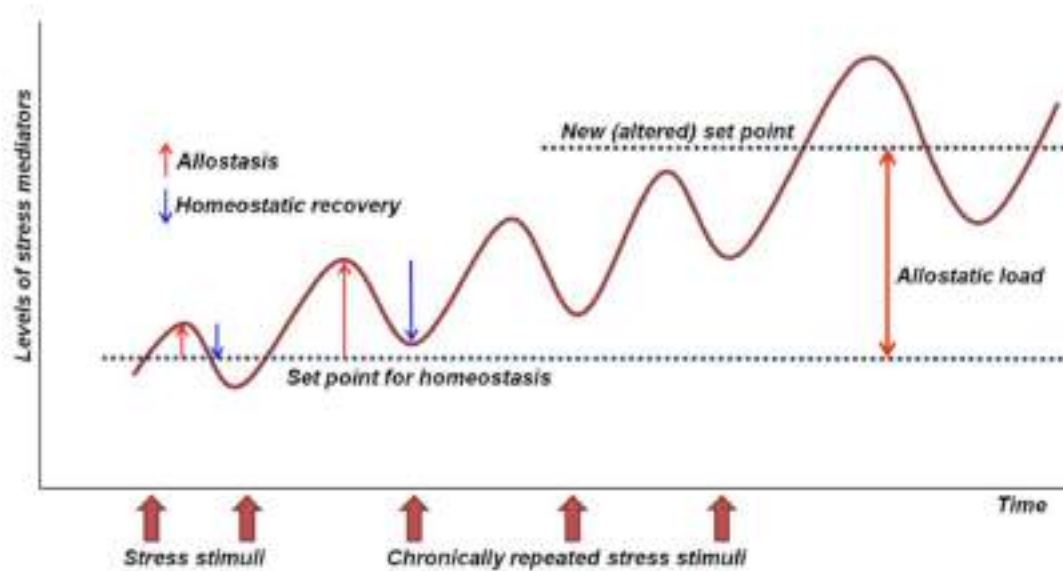


Stress response



- Suppress immune function
- Suppress digestive physiology
- Suppress reproductive physiology
- Increase energy mobilization
- Increase heart rate

Chronic stress



75-90% of diseases has stress as risk factor



Stress and research



Open questions regard the neurobiology underlying:

- stimuli encoding
- coping strategies
- circuits mal-adaptation to chronic stress
- circuits mal-adaptation to traumatic childhood
- Vulnerability and resilience

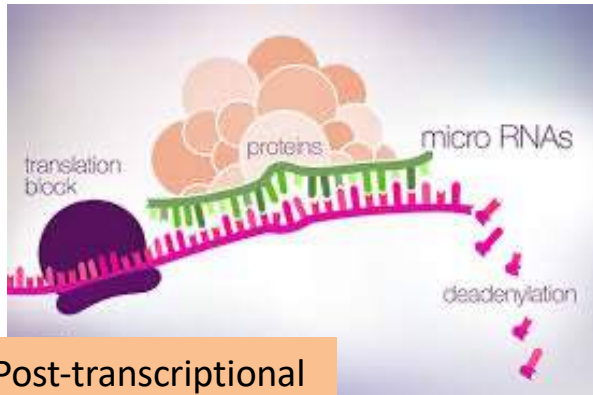
MicroRNAs



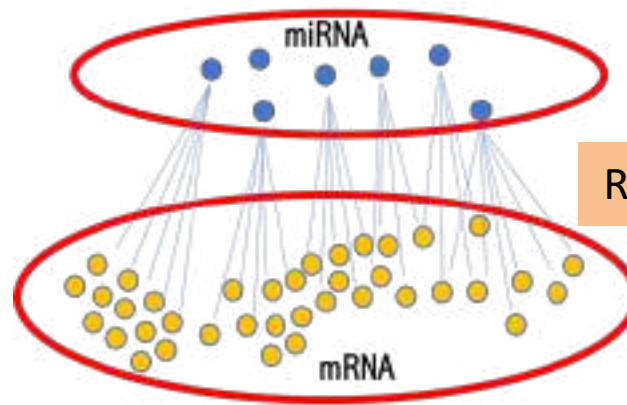
Victor Ambros
Gary Ruvkun



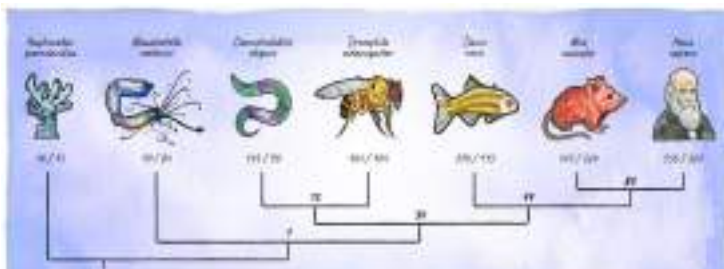
Nobel prize Medicine 2024



Post-transcriptional regulators of gene expression

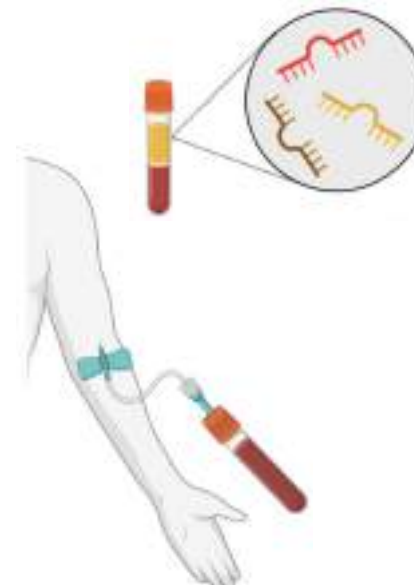


Regulate thousands of targets



Ancient and conserved across species

Dexheimer et al., Front.Cell Dev. Biol. 2020

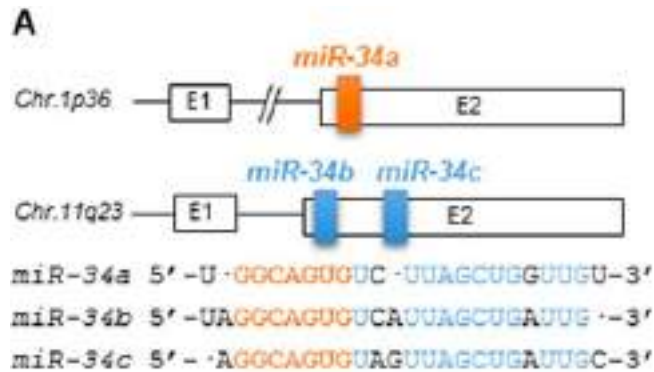


Circulant in blood plasma

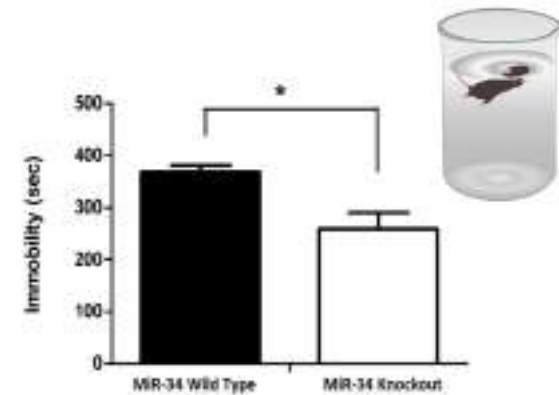
miR-34 family



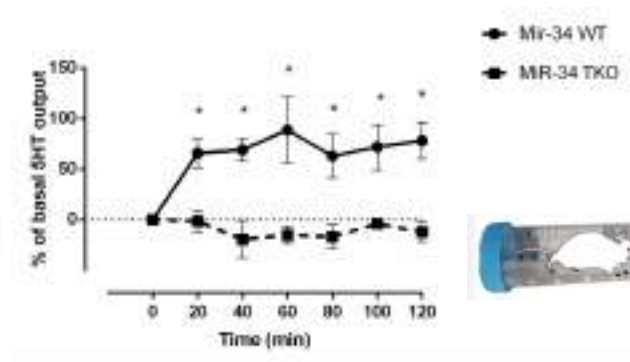
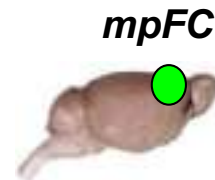
miR-34 KO mice



- miR-34a
- miR-34b
- miR-34c

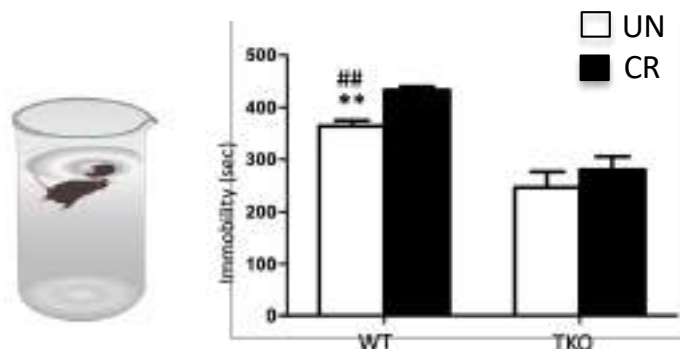
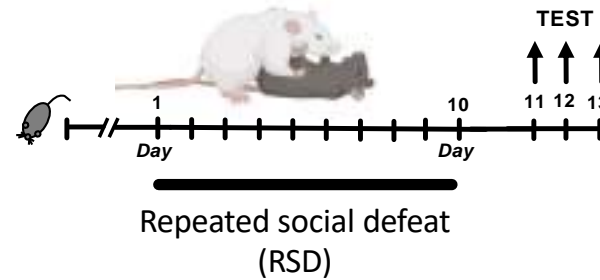
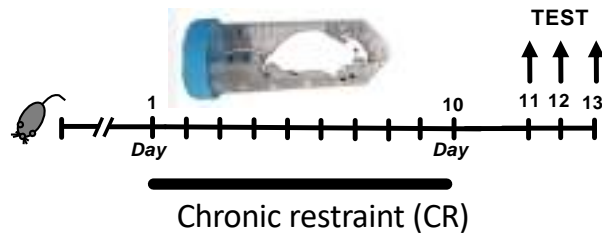


In miR-34 KO mice,
serotonin release under
stress is prevented

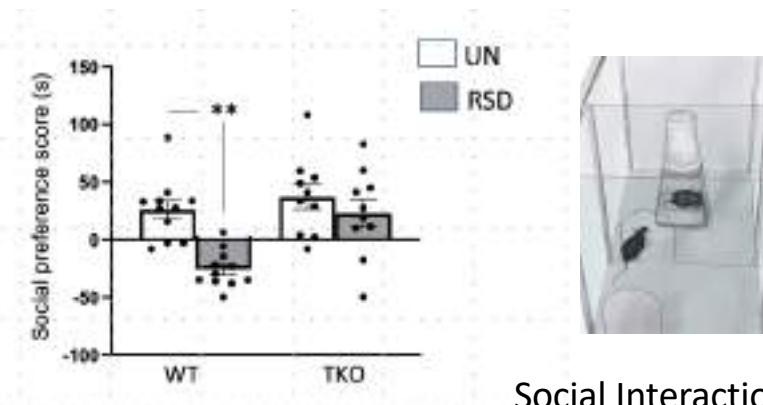


(Andolina et al., 2013, *Neuropsychopharmacology*)

Mice lacking miR-34 do not adapt to chronic stress



Forced swimming test

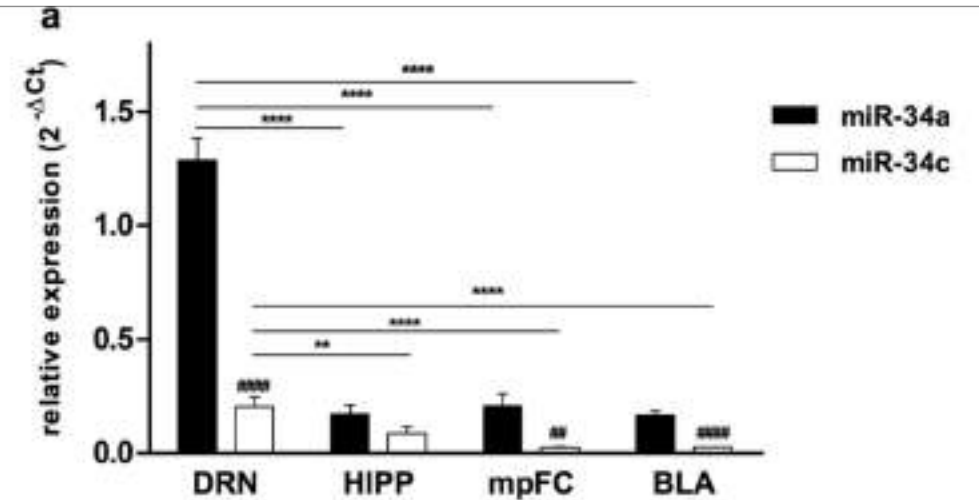
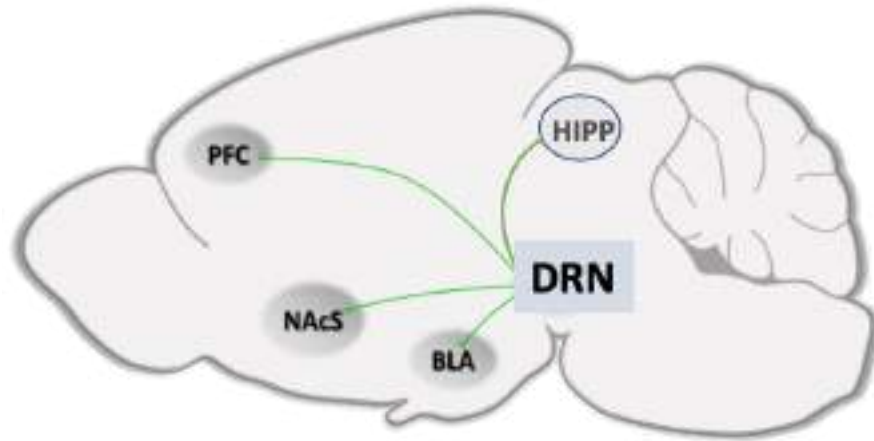


Social Interaction test

Lo Iacono et al., Mol Neurobiol 2019

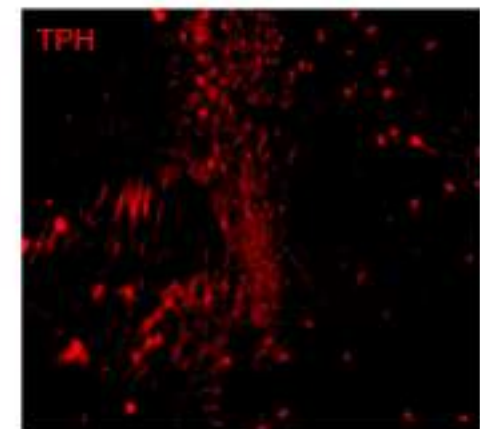
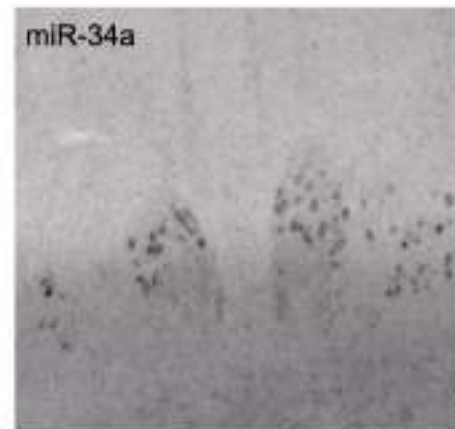
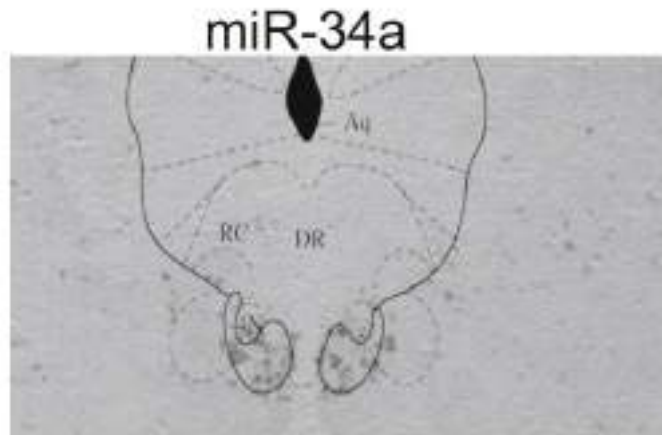
Ielpo et al., Phys Behav 2025

miR-34a is highly expressed in the Dorsal Raphe nuclei



Andolina et al., Mol Neurob 2016

.. In a restricted ventrolateral area

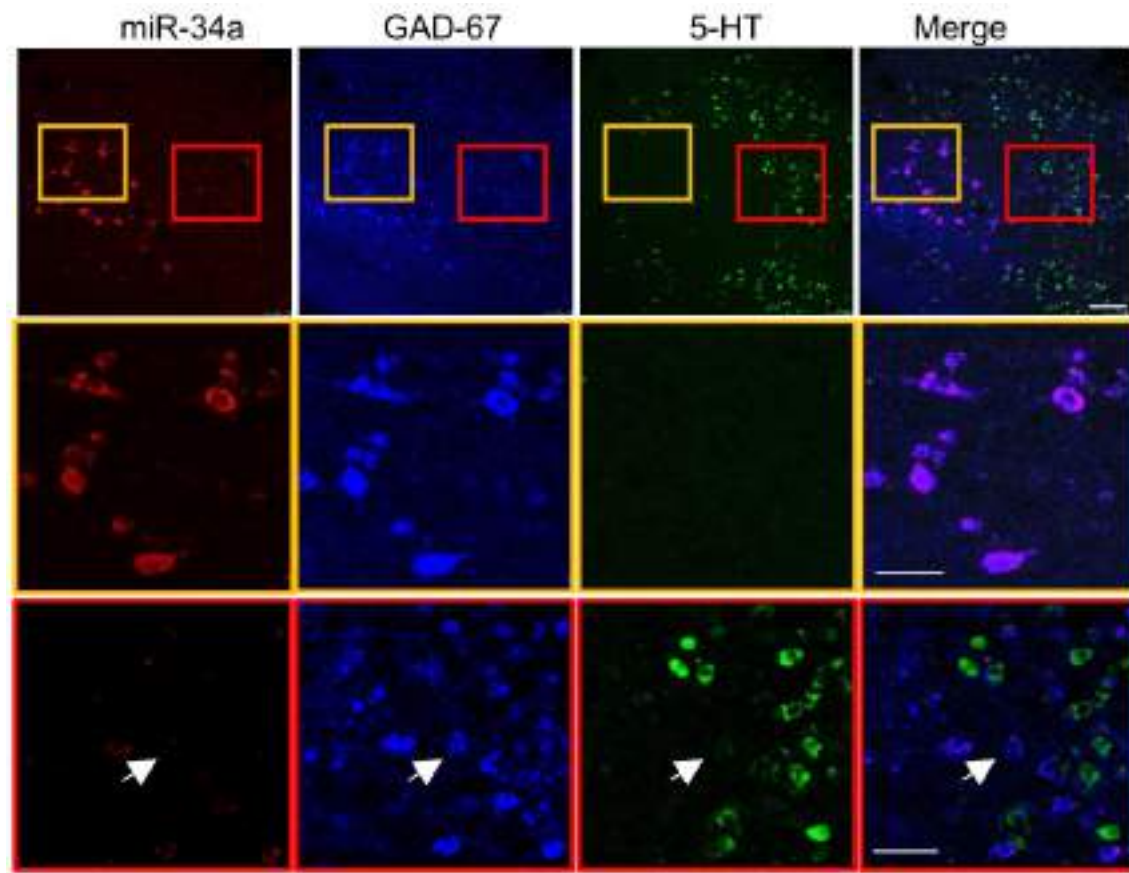
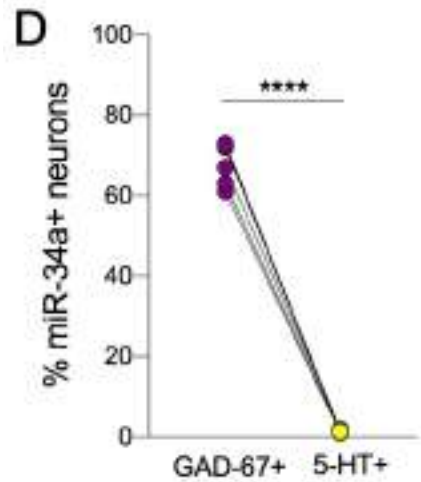
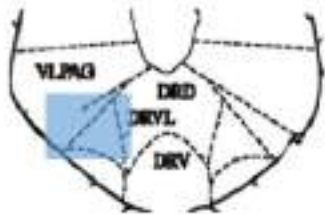


.. Mir-34a is expressed selectively on GABAergic neurons



Donald Ielpo

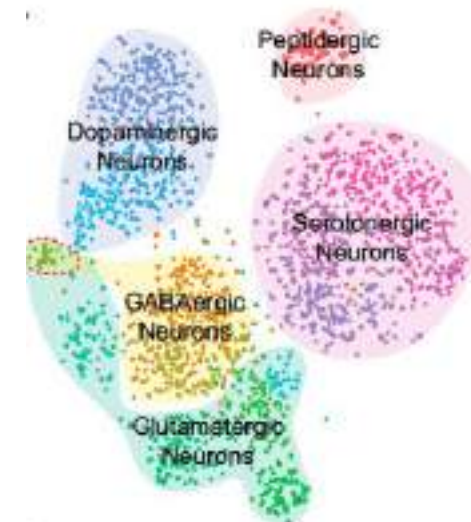
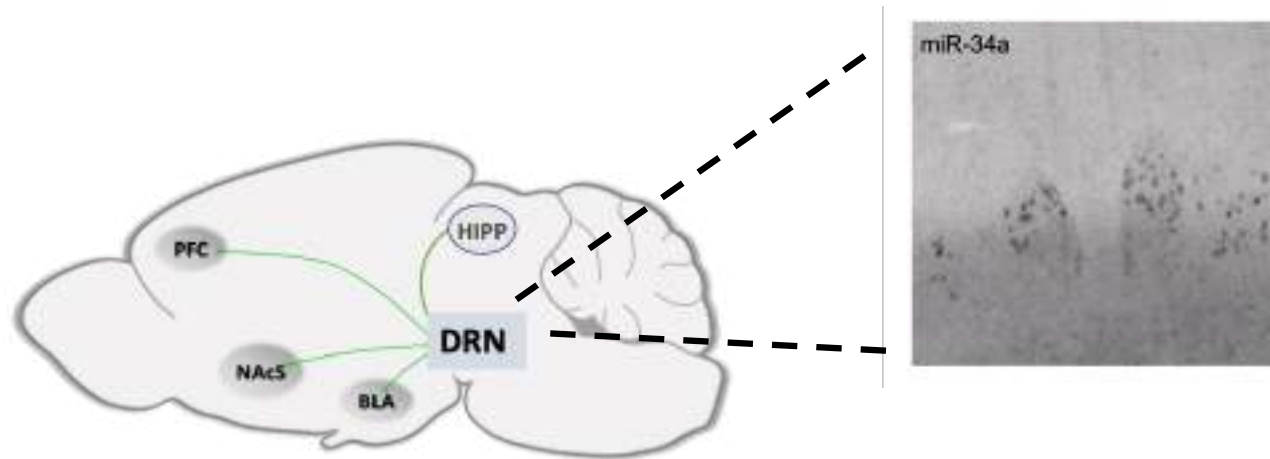
MiRNA scope



Ielpo et al., PNAS 2023



miR-34a identifies a subpopulation of GABAergic neurons in the Raphe



Huang et al, elife 2019

Local GABA neurotransmission was studied through:

In vivo microdialysis



Patch clamp recording



Stimuli:

NEGATIVE

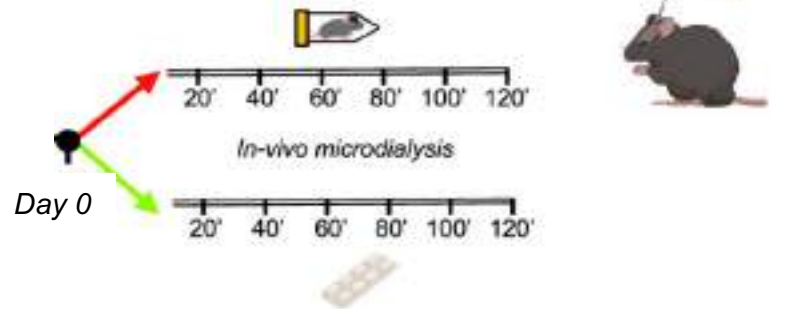


POSITIVE

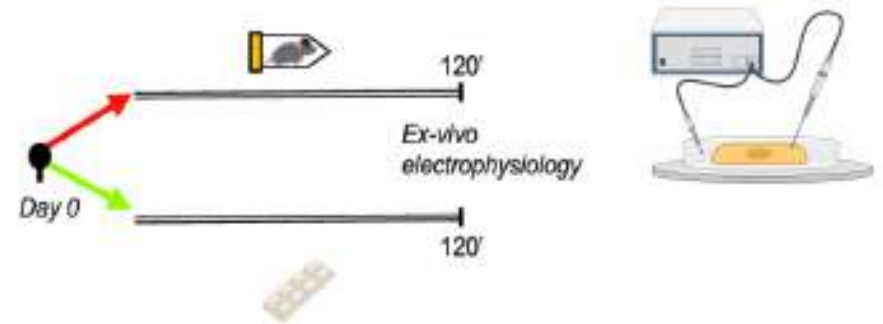


GABAergic response to different stimuli in the DRN

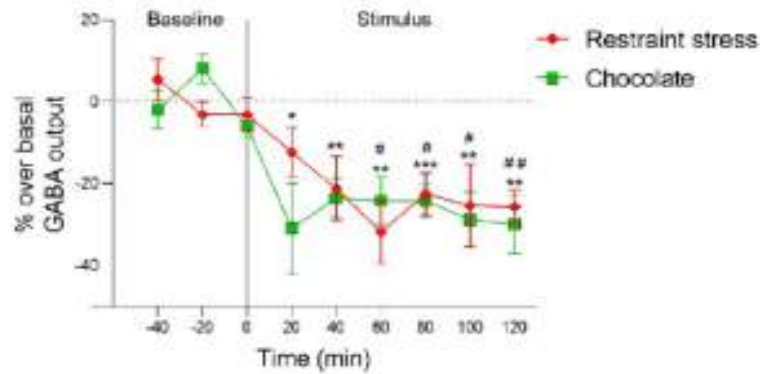
In vivo microdialysis



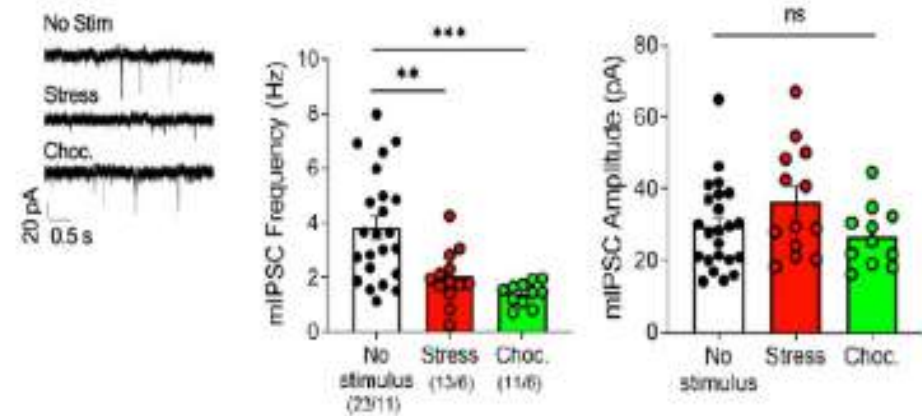
Patch clamp recording



C



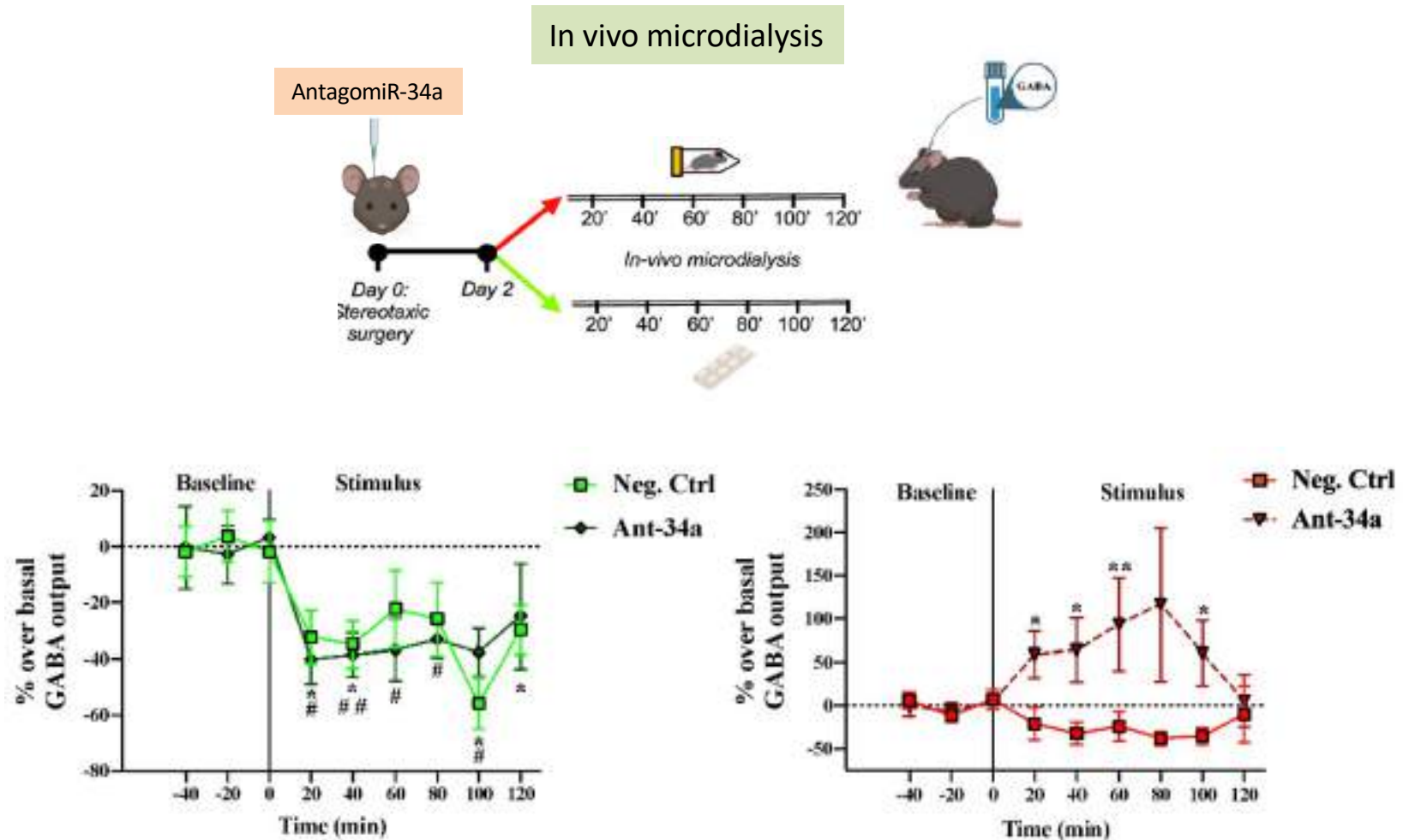
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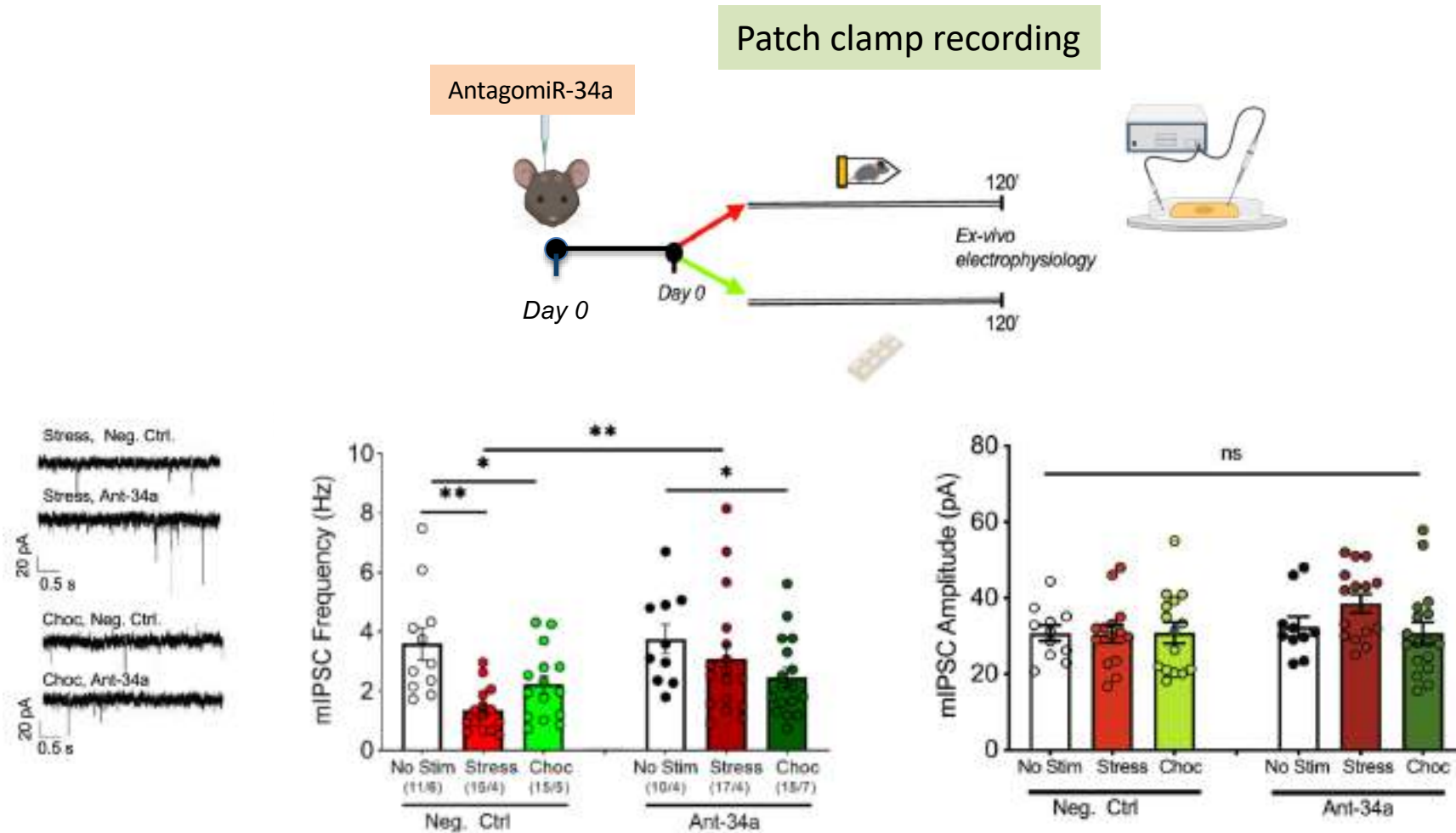
GABAergic transmission in the DRN is reduced in response to Pos or Neg stimuli

(Ielpo et al., 2023, PNAS)

miR-34a regulates GABAergic activity in the DRN in response to aversive stimuli



miR-34a regulates GABAergic activity in the DRN in response to aversive stimuli

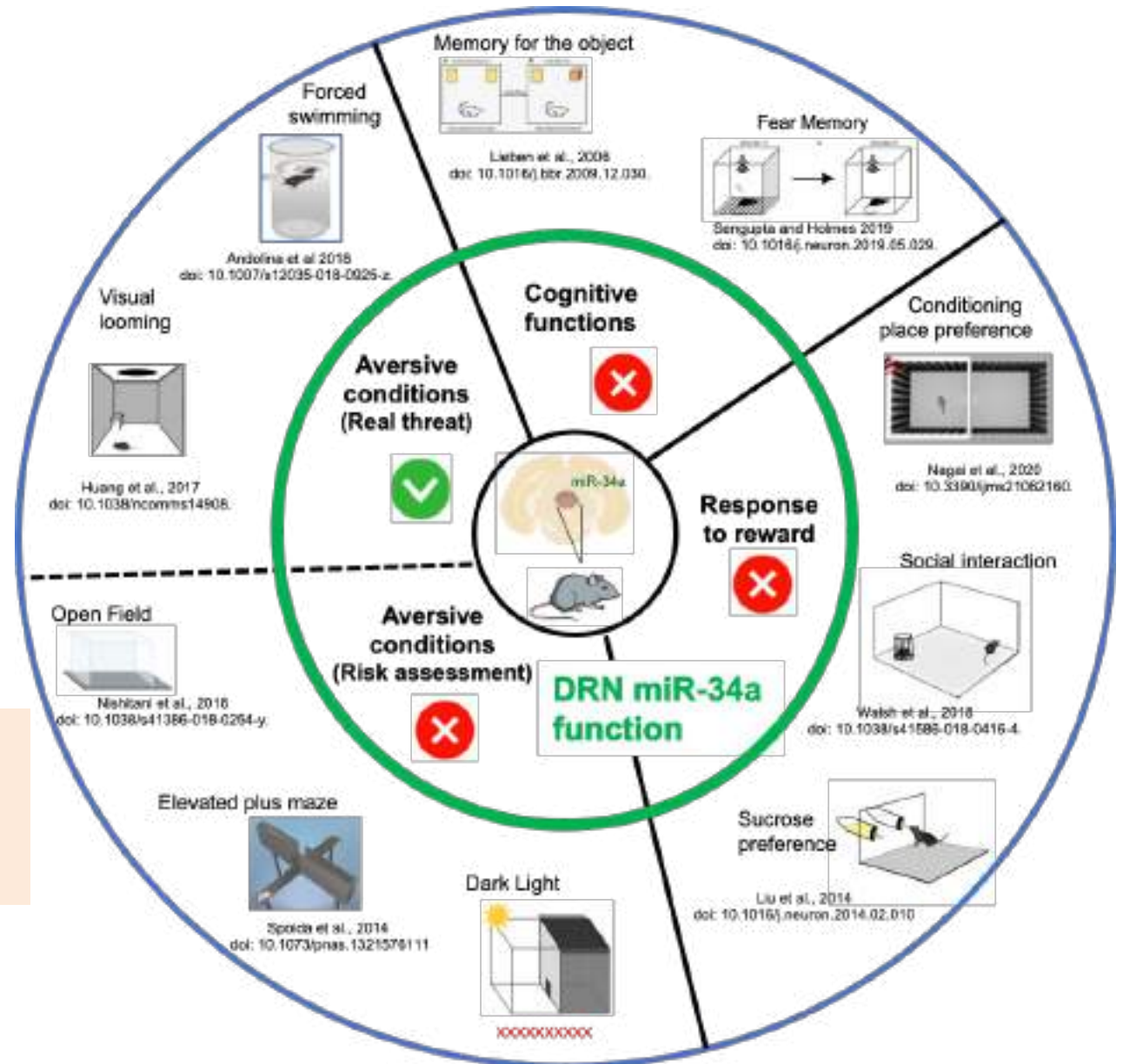


miR-34a

AntagomiR-34a



Mice lacking miR-34a do not respond properly to threatening conditions

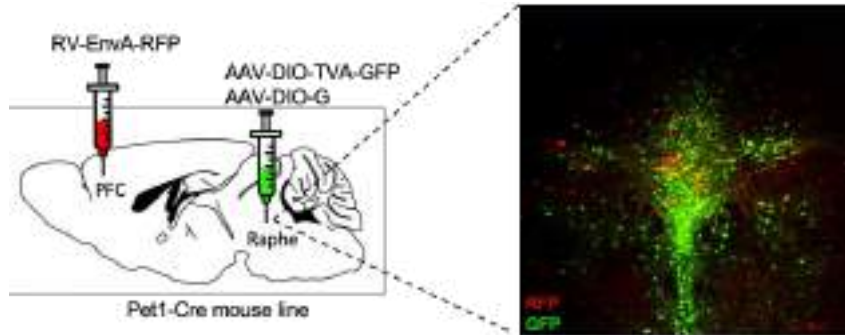


The miRcuit



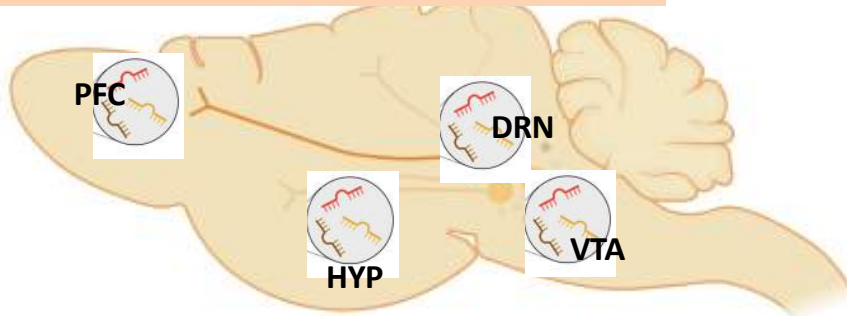
Massimo Pasqualetti

Anatomical definition

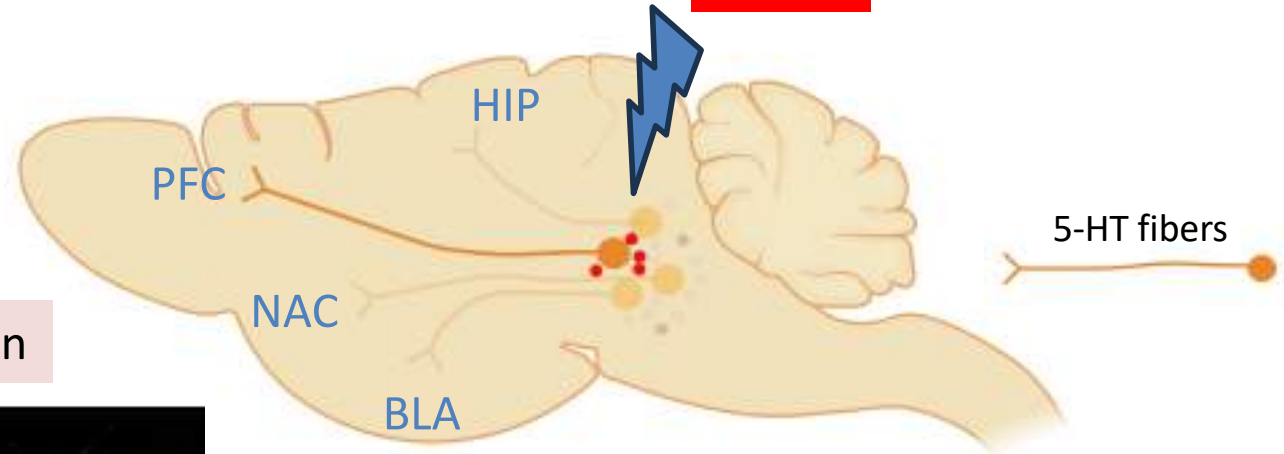


Monosynaptic retrograde tracers

MiRNA profiles in other regions



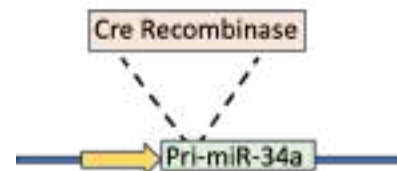
Threat



Functional definition

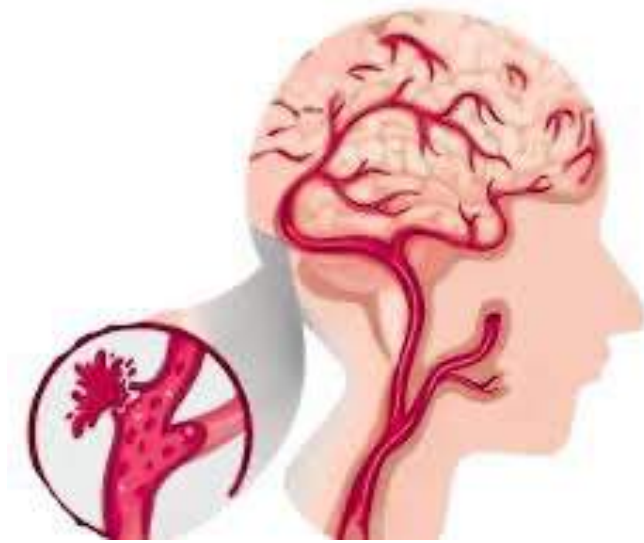


Cornelius Gross

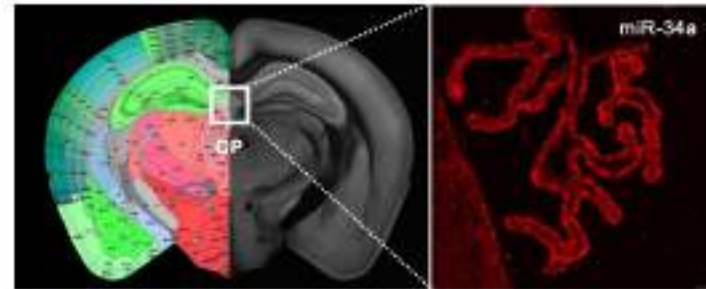
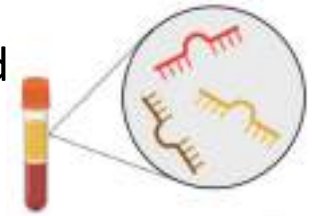


miR-34a^{Cre} mouse

Brain/Blood communication through microRNAs



miR-34a is found in choroid plexus and in plasma



Does DRN contribute to plasmatic miR-34a?

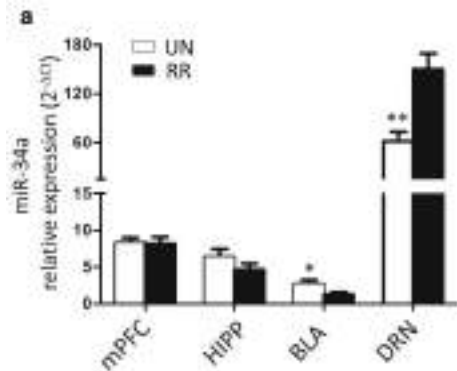
Chronic stimulations of the Dorsal Raphe Nuclei increase miR-34a expression in the DRN and in plasma



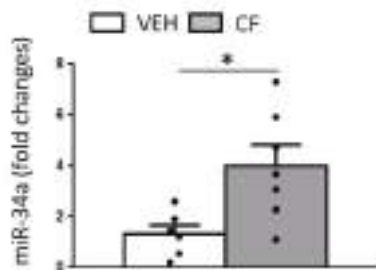
Serafina Manila Guzzo



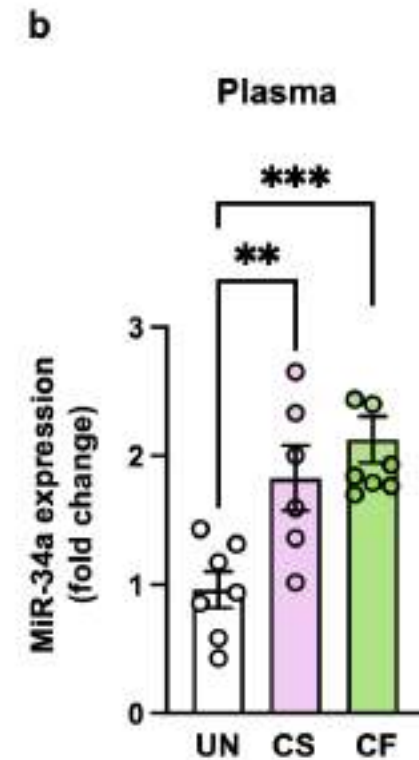
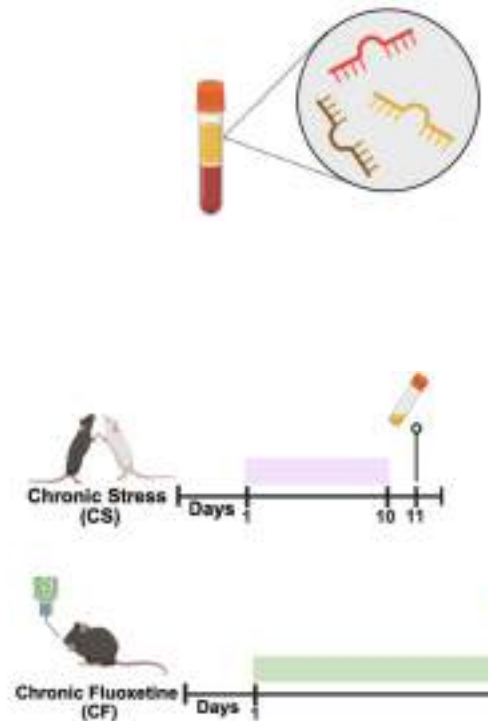
miR-34a increases in DRN after chronic stress or Chronic Fluoxetine



Lo Iacono et al., Mol Neurobiol 2019



Lo Iacono et al., Neuropharmacology 2021



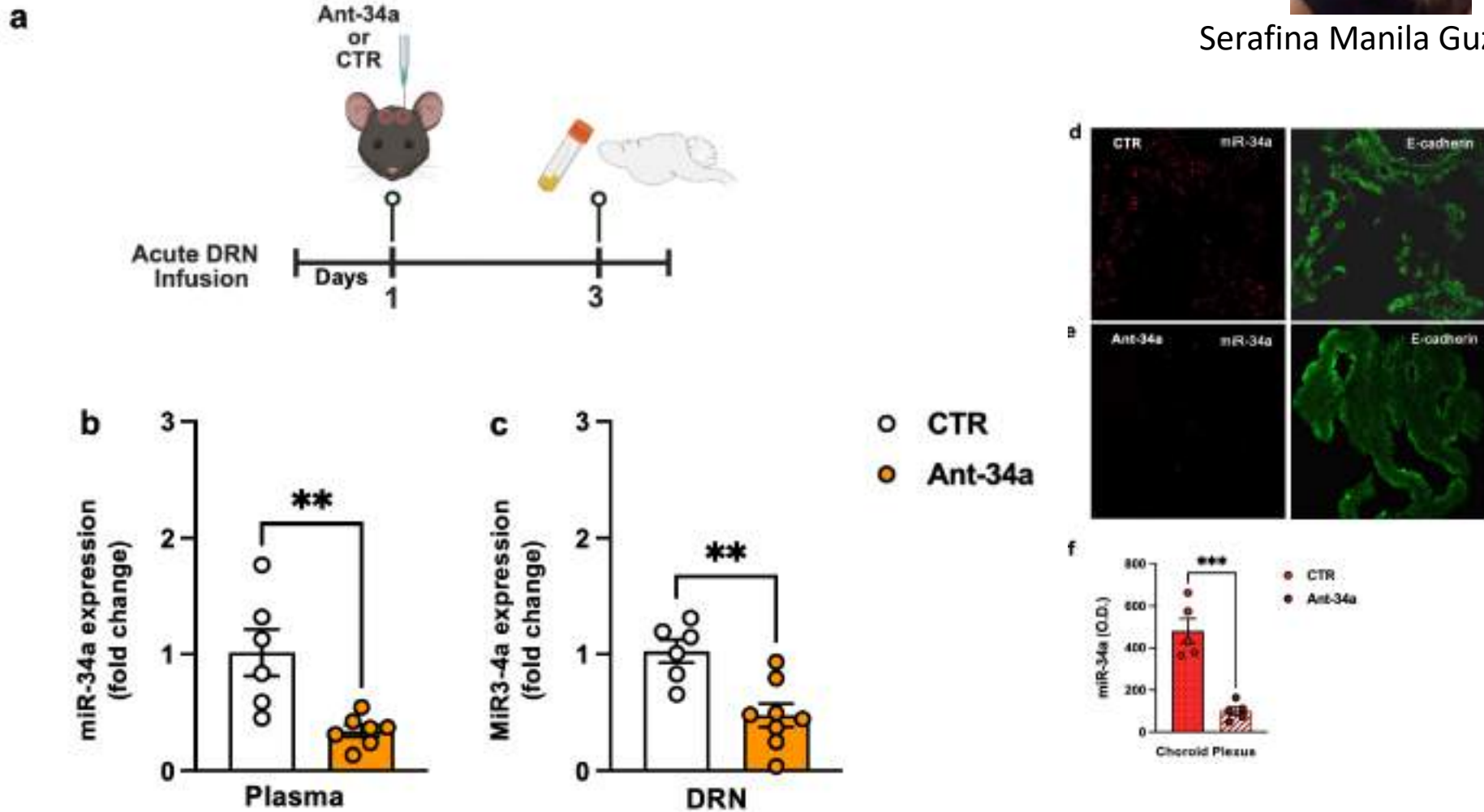
Guzzo et al., Molecular Neurobiology in press



Inhibition of miR-34a in the DRN reduces miR-34a in plasma



Serafina Manila Guzzo

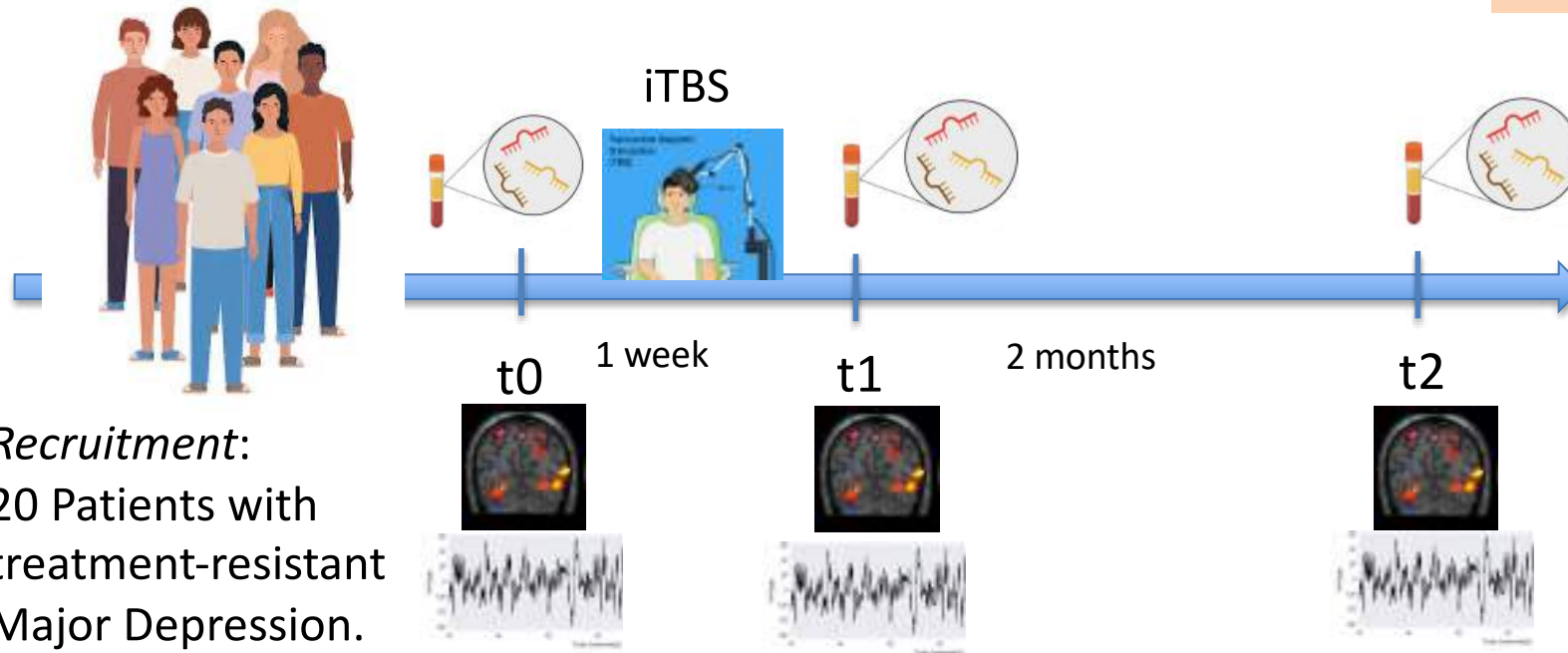


The effect of TMS on plasmatic microRNAs

Objective: evaluate the efficacy of iTBS on treatment-resistant depression



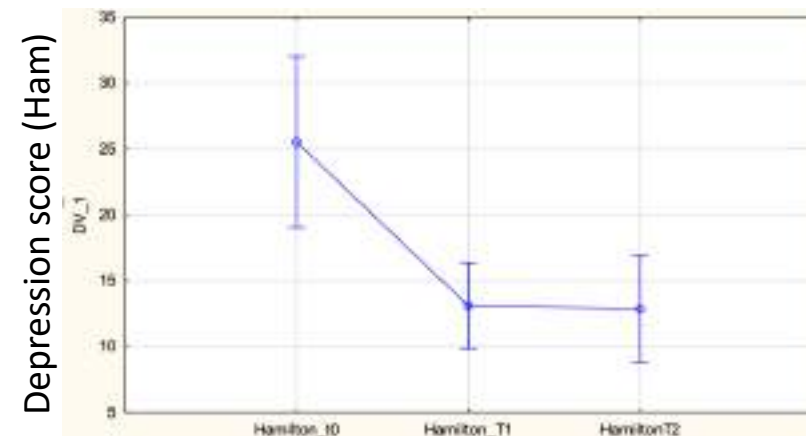
Diego Andolina



Recruitment:
20 Patients with
treatment-resistant
Major Depression.

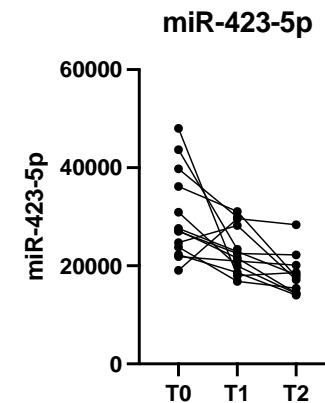
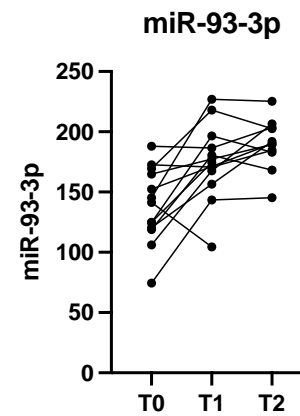
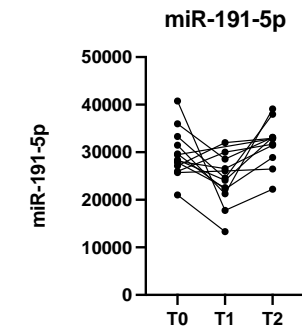
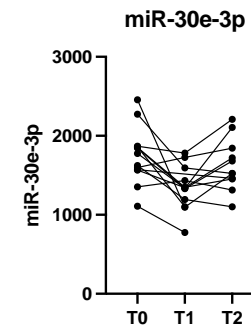
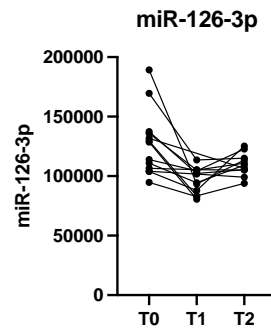
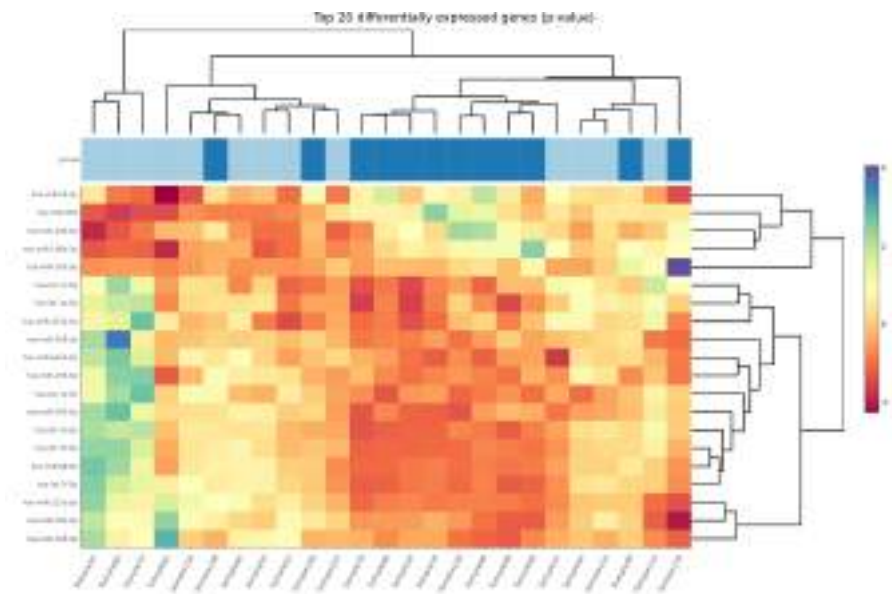
Clinical Assessment

- Childhood Trauma Questionnaire -**
- Hamilton scale**
- Beck Depression Inventory – II**
- General anxiety disorder 7**



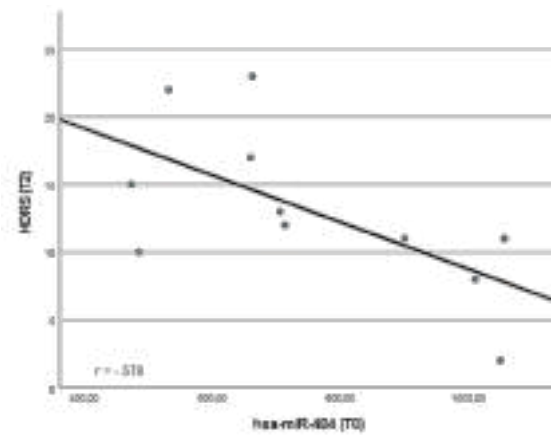
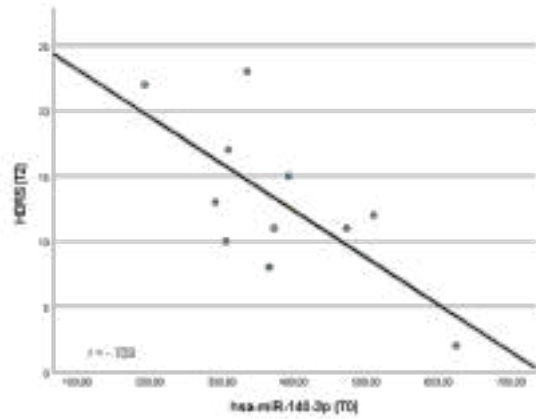
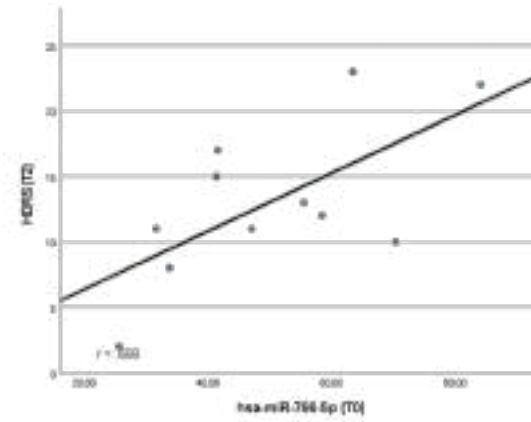
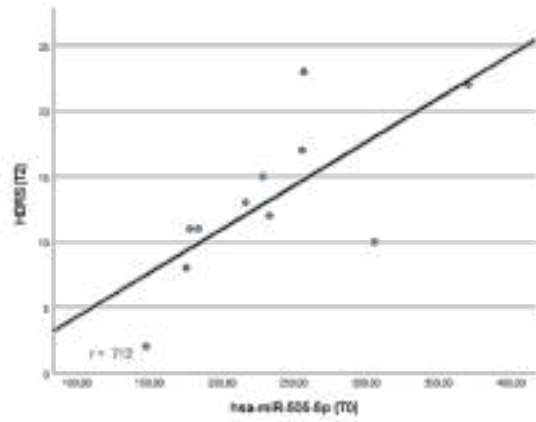
Plasmatic miRNAs are modulated by transcranial stimulation

In short- and long term



Plasmatic miRNA levels can predict TMS response

Depressive score (Hamilton)



Thank you!



Diego Andolina



Valeria Carola



Cornelius Gross



Simona Cabib



Massimo Pasqualetti



Maria Teresa Viscomi



Vincenzo Leuzzi



Alfonso Troisi



Luca Carnevali



Cristina Marchetti



Marcello D'Amelio



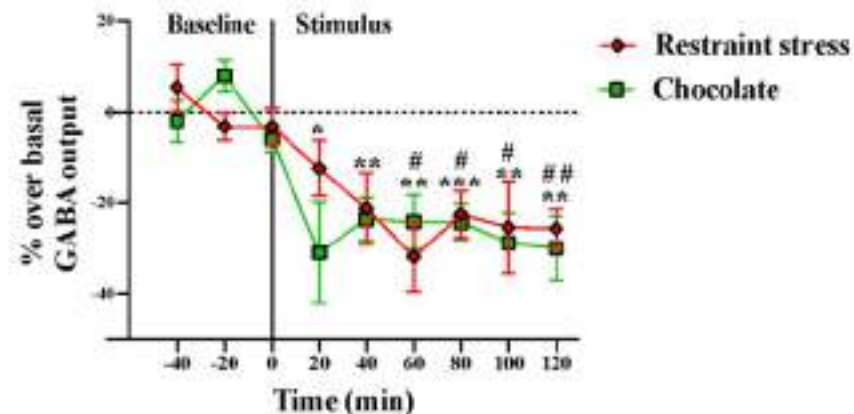
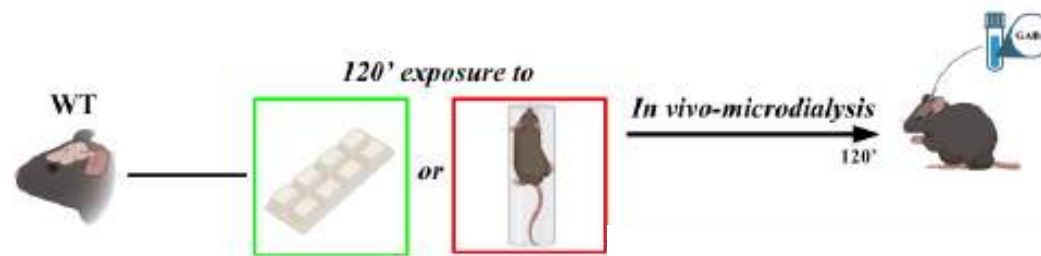
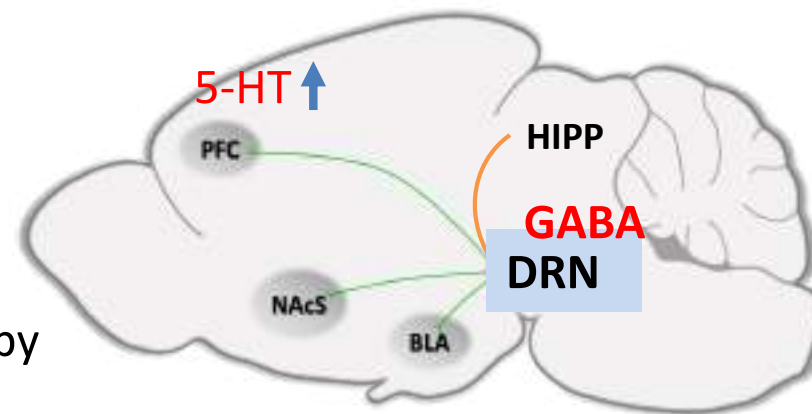
*Buone
Feste*

GABAergic transmission in the Dorsal Raphe Nuclei

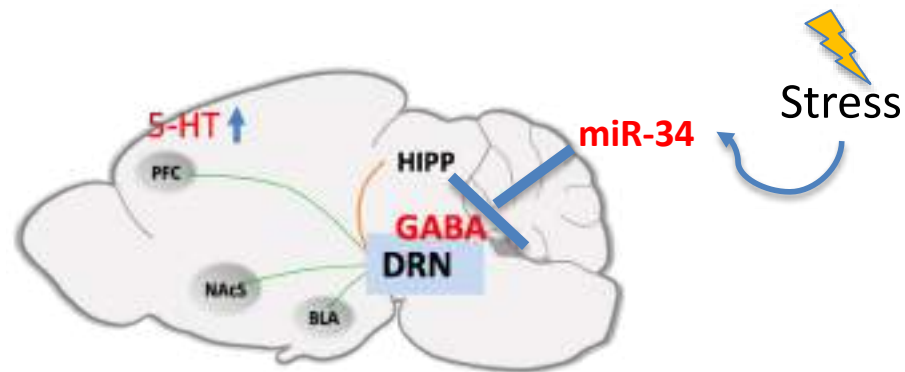
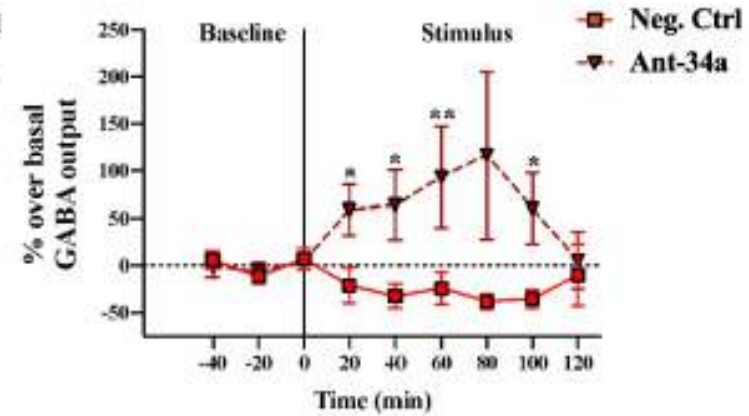
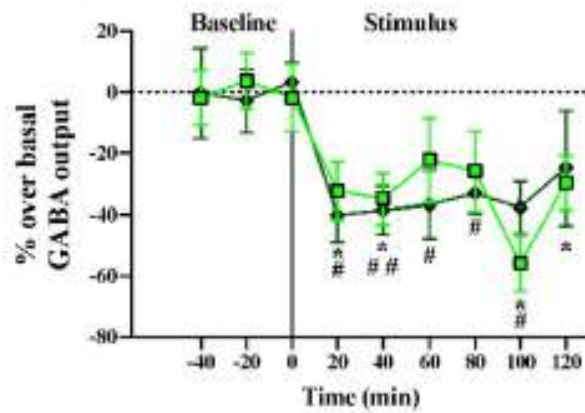
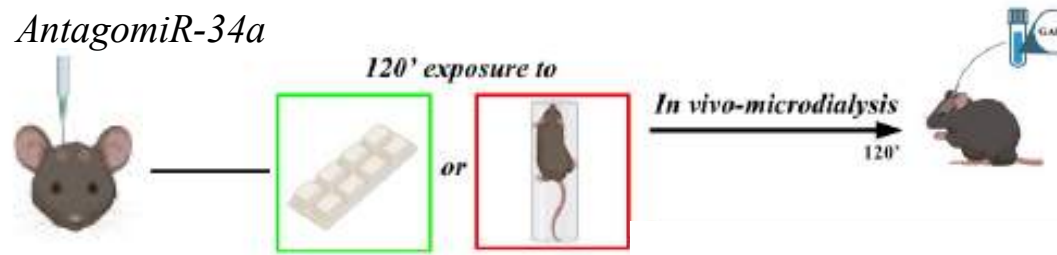
DRN is involved in the encoding of specific stimuli

DRN provides 5-HT to several brain regions

Release of 5-HT is finely controlled by local GABAergic circuits



miR-34a regulates GABAergic activity in the DRN in response to aversive stimuli



lelpo et al., PNAS 2023