ALBATROS International Congress of Addictology

Prevention or Treatment: Do We Have to Choose?

Alcohol Use Disorders: a neurobiological evolution and revolution

Recurrent stress during adolescence may trigger an allostatic load not only contributing to a functional arrest of adolescent brain development but promoting alcohol use disorder

The author declares no competing interests

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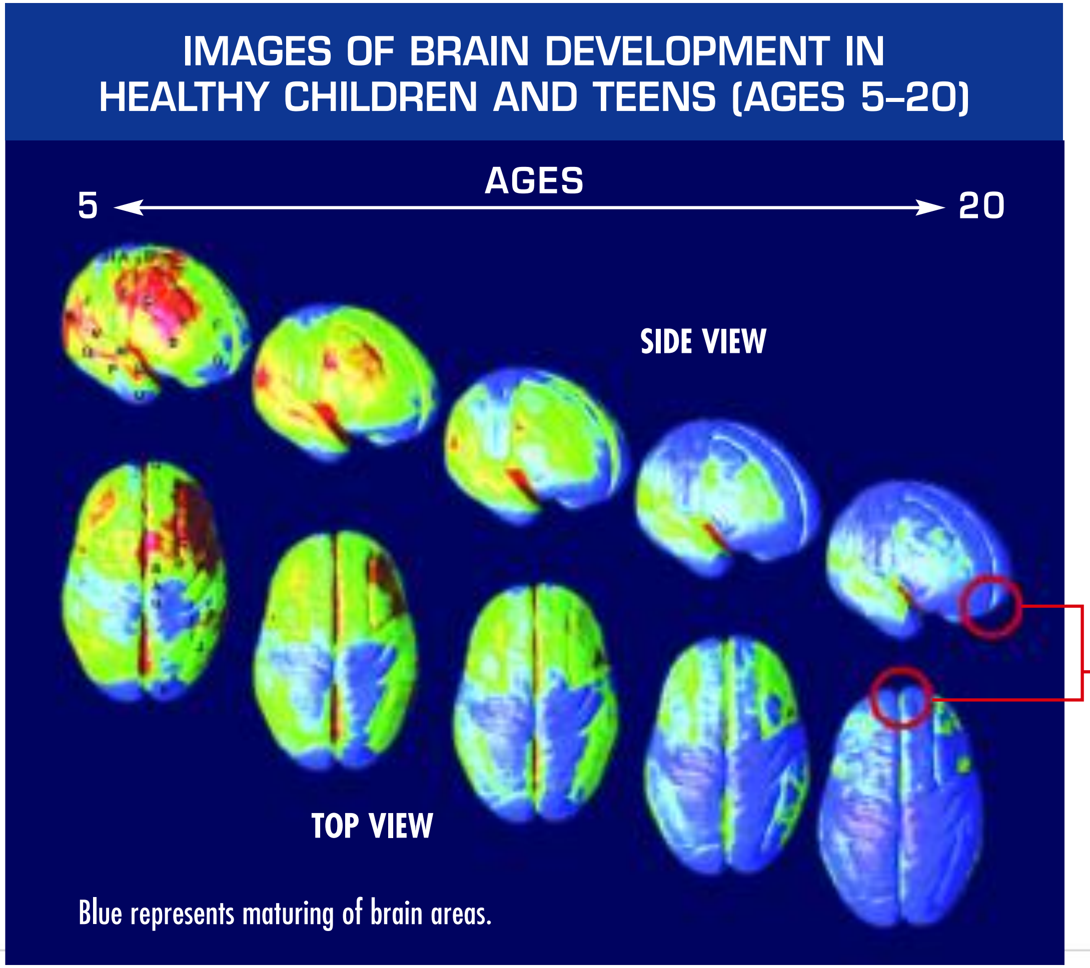
Addiction is a developmental disease— it typically begins in childhood or adolescence.



Source: PNAS 101:8174–8179, 2004.

The brain continues to develop into adulthood and undergoes dramatic changes during adolescence.

One of the brain areas still maturing during adolescence is the prefrontal cortex—the part of the brain that enables us to assess situations, make sound decisions, and keep our emotions and desires under control. The fact that this critical part of an adolescent's brain is still a work-in-progress puts them at increased risk for poor decisions (such as trying drugs or continued abuse). Also, introducing drugs while the brain is still developing may have profound and long-lasting consequences.

NIH, NIDA: Drugs, Brains, and Behavior, The Science of Addiction (2014)

PNAS

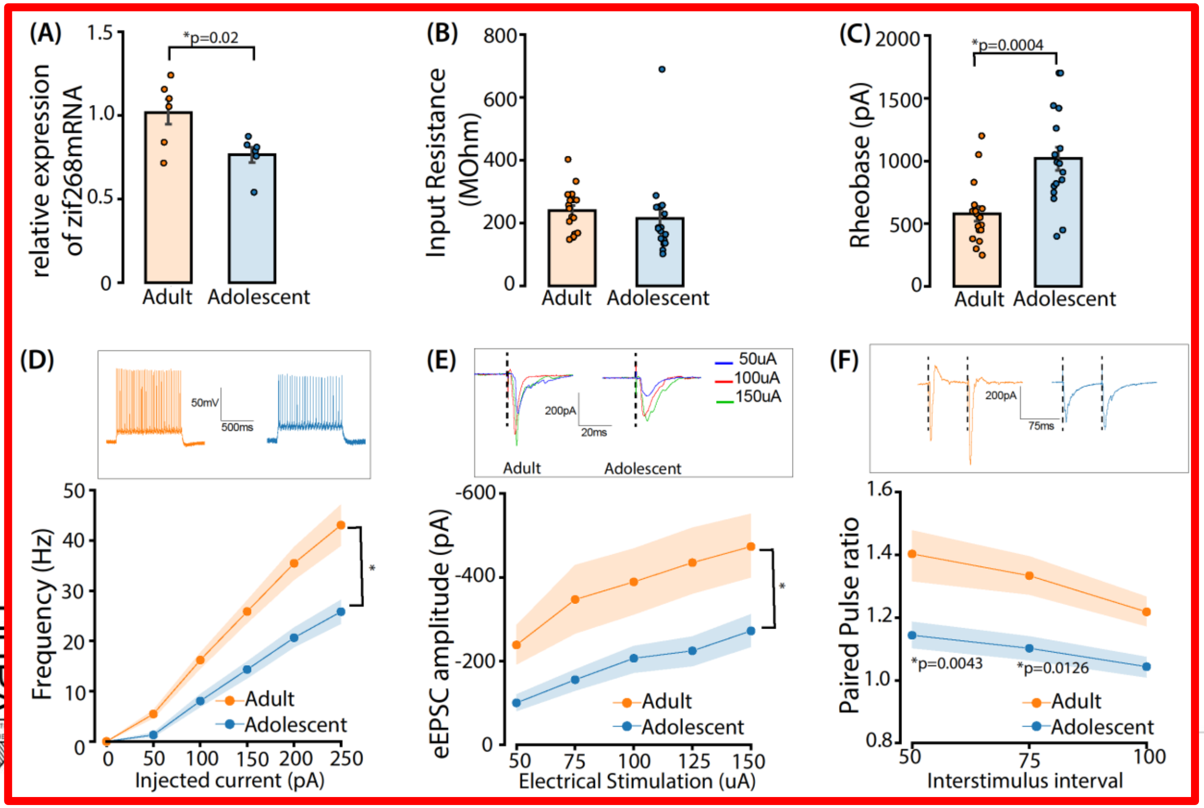
RESEARCH ARTICLE | NEUROSCIENCE

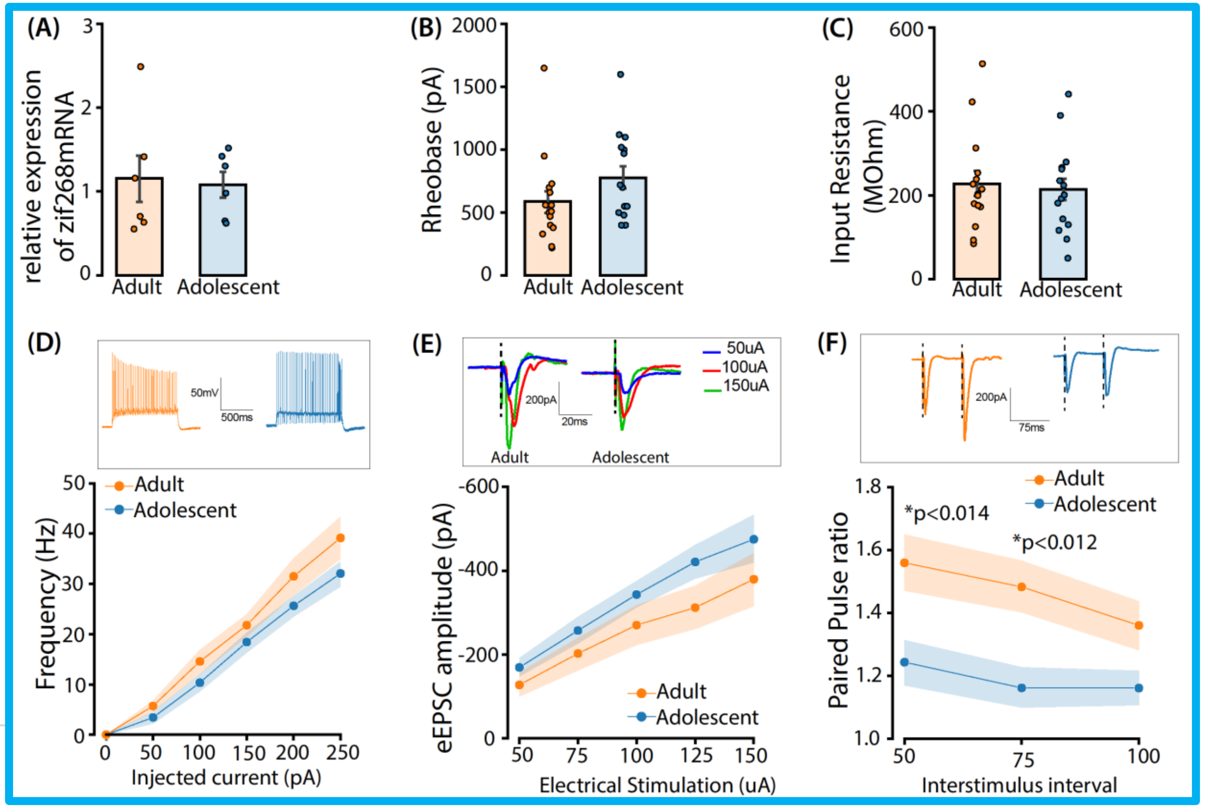
Reversing anterior insular cortex neuronal hypoexcitability attenuates compulsive behavior in adolescent rats

Kshitij S. Jadhav[a], Aurélien P. Bernheim[a], Léa Aeschlimann[a], Guylène Kirschmann[b], Isabelle Decosterd[b], Alexander F. Hoffman[c], Carl R. Lupica[c], and Benjamin Boutrel[a,d,1]

Edited by Huda Akil, University of Michigan-Ann Arbor, Ann Arbor, MI; received November 22, 2021; accepted March 29, 2022

Lower excitability of layer 5 pyramidal neurons in the anterior insular cortex of adolescent rats and smaller synaptic glutamatergic inputs to these cells but no difference in layer 5 prefrontal cortex pyramidal neurons





THE AMERICAN JOURNAL OF PSYCHIATRY

The Self-Medication Hypothesis of Addictive Disorders: Focus on Heroin and Cocaine Dependence

Edward J. Khantzian, M.D.

Recent clinical observations and psychiatric diagnostic findings of drug-dependent individuals suggest that they are predisposed to addiction because they suffer with painful affect states and related psychiatric disorders. The drugs that addicts select are not chosen randomly. Their drug of choice is the result of an interaction between the psychopharmacologic action of the drug and the dominant painful feelings with which they struggle. Narcotic addicts prefer opiates because of their powerful muting action on the disorganizing and threatening affects of rage and aggression. Cocaine has its appeal because of its ability to relieve distress associated with depression, hypomania, and hyperactivity.

(Am J Psychiatry 142:1259–1264, 1985)

Developments in psychoanalysis and psychiatry over the past 50 years have provided enabling new insights and approaches in understanding mental life and in treating its aberrations. In psychoanalysis, there has been a shift from a focus on drives and conflict to a greater emphasis on the importance of ego and self structures in regulating emotions, self-esteem, behavior, and adaptation to reality. In psychiatry, we have witnessed the advent of psychotropic medications, a more precise understanding of the neurobiology of the brain, and the development of standardized diagnostic approaches for identifying and classifying psychiatric disorders. Such developments have had implications for understanding and treating addictions, especially given the recent dramatic rise in drug abuse in all sectors of our society and our growing inclination to treat our drug-dependent patients through private practice, in community mental health centers, and in methadone-maintenance or self-help programs, in close proximity to the surroundings in which their addictions evolved.

Popular or simplistic formulations in the early 1970s emphasized peer group pressure, escape, euphoria, or self-destructive themes to explain the compelling nature of drug dependency. In contrast, the work of a number of psychoanalysts in the 1960s and 1970s has led to observations, theoretical formulations, and subsequent studies representing a significant departure from these previous approaches and explanations. On the basis of a modern psychodynamic perspective, these analysts succeeded in better identifying the nature of the psychological vulnerabilities, disturbances, and pain that predispose certain individuals to drug dependence. This perspective, which has spawned a series of diagnostic studies over the past decade, emphasizes that heavy reliance on and continuous use of illicit drugs (i.e., individuals who become and remain addicted) are associated with severe and significant psychopathology. Moreover, the drug of choice that individuals come upon is not a random phenomenon.

On the basis of recent psychodynamic and psychiatric perspectives and findings, I will elaborate on a self-medication hypothesis of addictive disorders, emphasizing problems with heroin and cocaine dependence. This point of view suggests that the specific psychotropic effects of these drugs interact with psychiatric disturbances and painful affect states to make them compelling in susceptible individuals.

Received Oct. 9, 1984; revised Jan. 28, 1985; accepted Feb. 27, 1985. From Harvard Medical School at the Cambridge Hospital. Address reprint requests to Dr. Khantzian, Department of Psychiatry, the Cambridge Hospital, 1493 Cambridge St., Cambridge, MA 02139.

Supported in part by contract 271-77-3431 and grant DA-01828 from the National Institute on Drug Abuse.

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I base this conclusion on observations of over 200 addicts whose histories reveal lifelong difficulties with rage and violent behavior predating their addiction, often linked to intense and unusual exposure to extreme aggression and violence in their early family life and the environment outside their homes. These experiences included being both the subject and the perpetrator of physical abuse, brutality, violent fights, and sadism. In the course of their evaluation and treatment these patients repeatedly described how opiates helped them to feel normal, calm, mellow, soothed, and relaxed.

For some, the energizing properties of stimulants are compelling because they help to overcome fatigue and depletion states associated with depression. In other cases, the use of stimulants leads to increased feelings of assertiveness, self-esteem, and frustration tolerance and the riddance of feelings of boredom and emptiness.
More recently, we have considered from a psychiatric diagnostic perspective a number of factors that might predispose an individual to become and remain dependent on cocaine : 1) preexistent chronic depression; 2) cocaine abstinence depression; 3) hyperactive, restless syndrome or attention deficit disorder; and 4) cyclothymic or bipolar illness.

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On the basis of recent psychodynamic and psychiatric perspectives and findings, I will elaborate on a self-medication hypothesis of addictive disorders, emphasizing problems with heroin and cocaine dependence. This point of view suggests that the specific psychotropic effects of these drugs interact with psychiatric disturbances and painful affect states to make them compelling in susceptible individuals.

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Clearly, there are other determinants of addiction, but I believe a self-medication motive is one of the more compelling reasons for overuse of and dependency on drugs.

Rather than simply seeking escape, euphoria, or self-destruction, addicts are attempting to medicate themselves for a range of psychiatric problems and painful emotional states.

Although most such efforts at self-treatment are eventually doomed, given the hazards and complications of long term, unstable drug use patterns, addicts discover that the short-term effects of their drugs of choice help them to cope with distressful subjective states and an external reality otherwise experienced as unmanageable or overwhelming.

The heuristic value of this self-medication hypothesis might help us to understand better the nature of compulsive drug use and may provide a useful rationale in considering treatment alternatives.

- Adolescence, defined as a transition phase towards autonomy and independence, is a natural time of learning and adjustment, particularly in the setting of long-term goals and personal aspirations.
- The development of self-regulatory competences is a normative process, that depends on brain maturation and social experiences, at the end of which young adults have acquired the aptitude to better regulate their emotions and impulsiveness (Spear, 2000; Foulkes & Blakemore, 2018; Jadhav and Boutrel, 2019).

- The construction of identity and the self-image ensures essential functions for the individual life of the child and the construction of self-esteem.
- If the maternal environment is good enough and the mother is sufficiently attentive to her child, the separation process and the psychological maturation will allow the construction of self-secure/self-confident ego. (what D. WINNICOTT refers as "good enough mother")

- Jacques LACAN defined the stage of the mirror as formator of the function of the I: structuring of the identity and the personality.
- Real or symbolic, the mirror image breaks the fusional existence linking the child to his mother.
- Narcissism will allow the teenager to ensure his identity and to support his investment towards the outside of the family unit, it is the construction of the autonomy. It is the feeling of internal security that will give access to autonomy.

- The history of drug abusers systematically reveals a pre-existing family conflict.
- Most of the suffering and risk behaviors in adolescence (anorexia, bulimia, scarification, suicide attempts and addictive behaviors) can be called: psychopathologies of the bond. This shows the difficult link that the adolescent has with the other and his parents, the problem of the separation of the link.
- The addictive strategy would be a way to avoid the experience of a solitude that would not be lived as serene and structured.
- Early emotional deficiencies and/or traumatic experiences in childhood lead clinically to a devalued self-image, a lack of self-confidence, in other words to a narcissistic failure. It is during childhood that these flaws are created, particularly during the phase that, C. OLIVENSTEIN calls the stage of the broken mirror.
- The addictive behavior, and in particular the use of psychotropic products, reflects the socio-affective immaturity which determines the impossibility of building a true and solid psychosocial identity. This immaturity generates a feeling of personal non-value, of non-recognition. The addictive behavior constitutes a psychic economy permitting to deal with intra psychic conflicts and to remain in life or in survival.

Let's focus on vulnerable individuals

- Alcohol use is one of the world's leading causes of death and disease, *although only a small proportion of individuals develop persistent alcohol use disorder (AUD).*

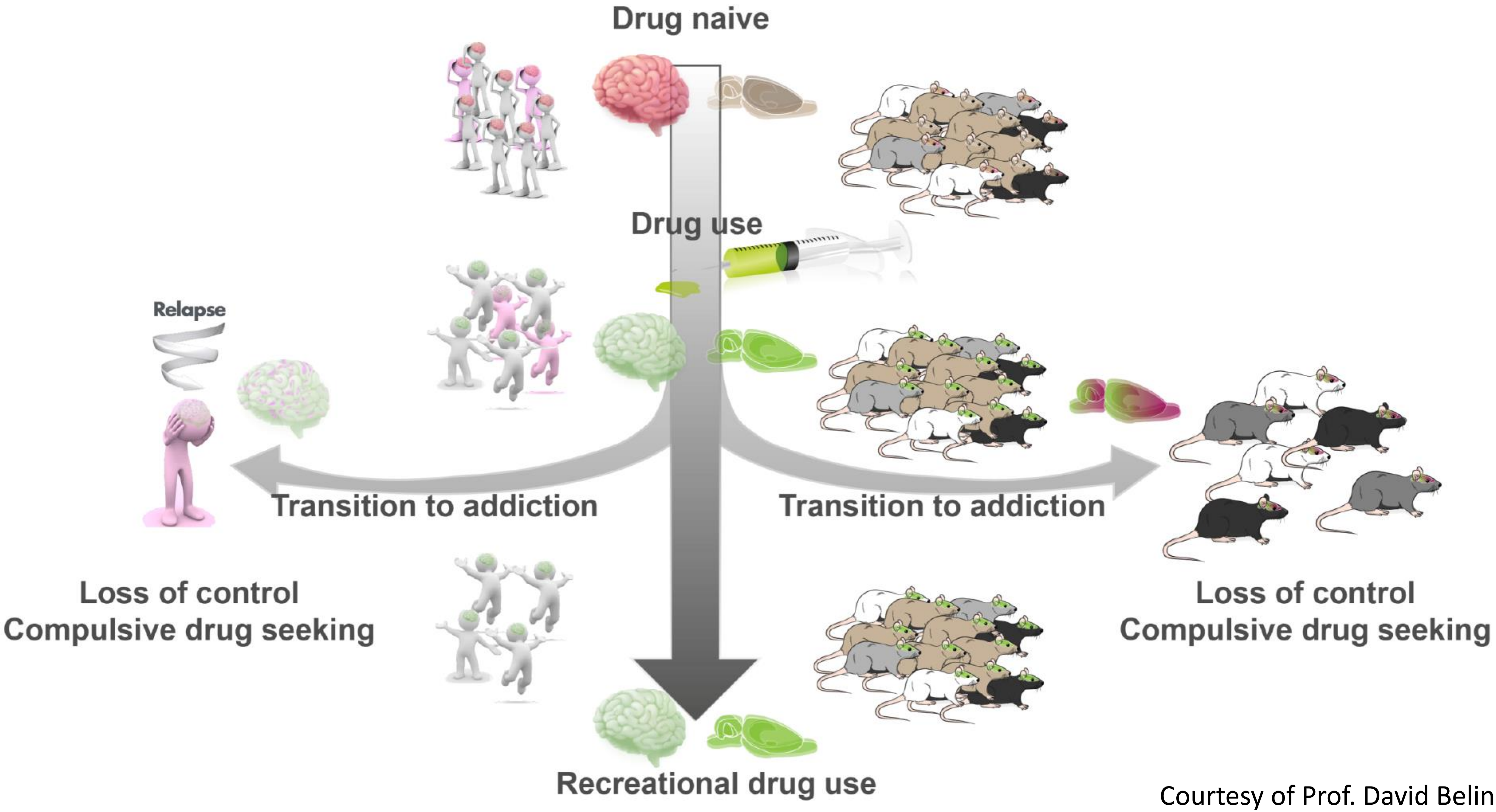
- The identification of vulnerable individuals prior to their chronic intoxication remains of highest importance.

- Individuals prone to attribute incentive salience to reward cues will have particular difficulty to resist them.

- In such individuals, reward cues may become maladaptively attractive, "wanted" and spur behavior to obtain the associated reward, and when combined with poor inhibitory control, this may promote excessive behaviors, be it food or drug, and may thus confer vulnerability for various impulse control disorders

(Robinson *et al.*, 2014)

Defining Vulnerable (to loss of control) versus Resilient (recreational user) rats



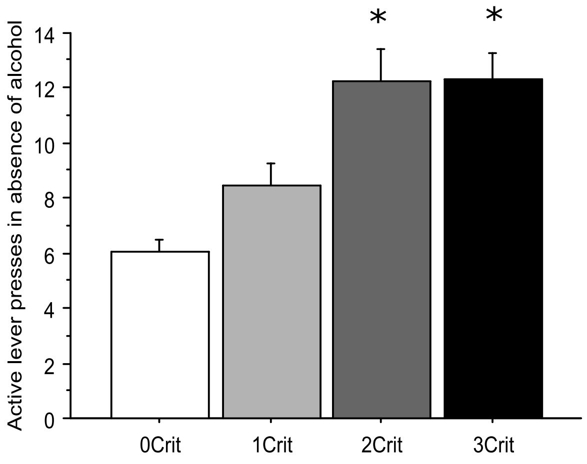
Courtesy of Prof. David Belin

Defining Vulnerable (to loss of control) versus Resilient (recreational user) rats

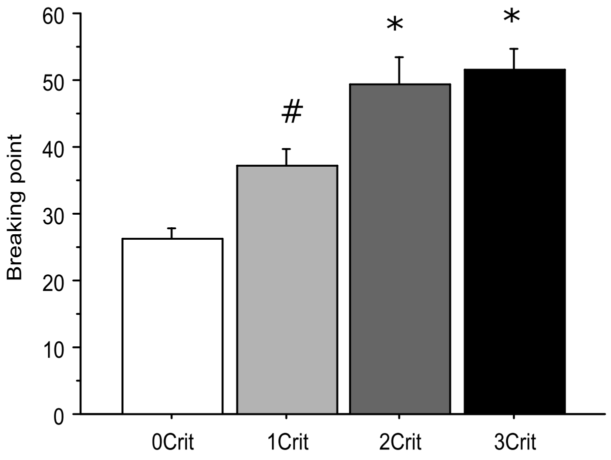
After <u>80 daily sessions</u> of alcohol self-administration

Positive Criterium : score for the addiction-like behavior in the 66th to 99th percentile of the distribution

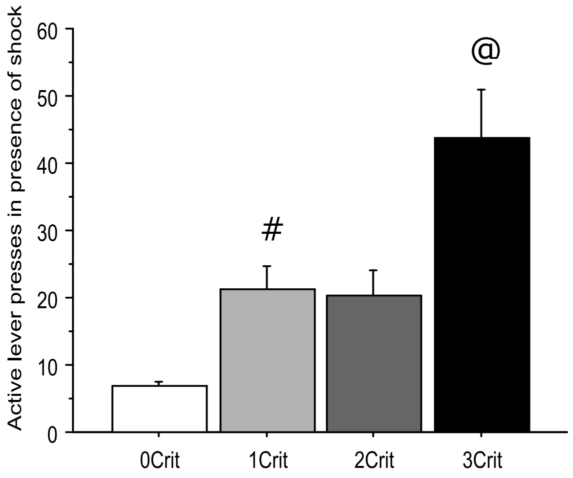
Persistance in lever pressing during no drug period



Motivation on progressive ratio paradigm



Lever pressing in presence of shock

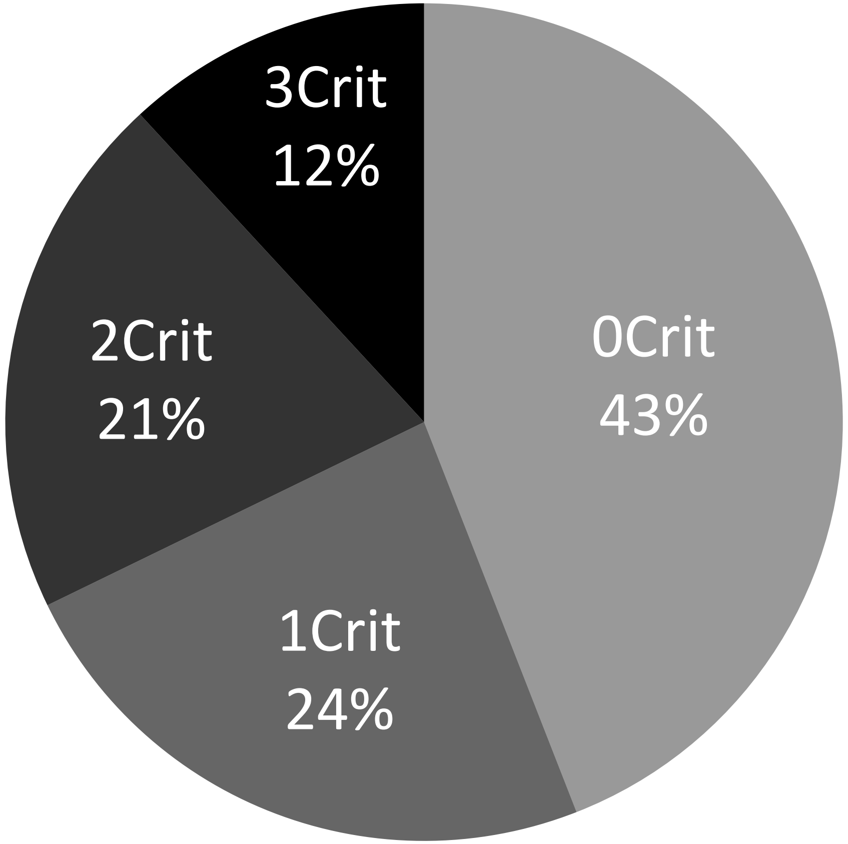


* Significant compared to 0Crit and 1Crit rats, # Significant compared to 0Crit rats, @ Significant compared to 0Crit, 1Crit and 2Crit rats

One way ANOVA (<u>**n=118**</u>)

Jadhav et al., 2017, 2018 (adapted from Deroche-Gamonet et al., 2004)

Defining Vulnerable
(to lose control)
versus
Resilient
(recreational user)
rats



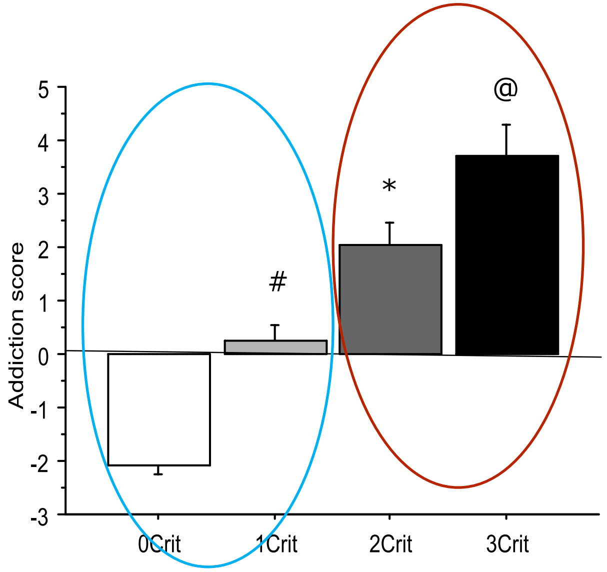
(n=118 rats)

Kshitij S. Jadhav, MD PhD.

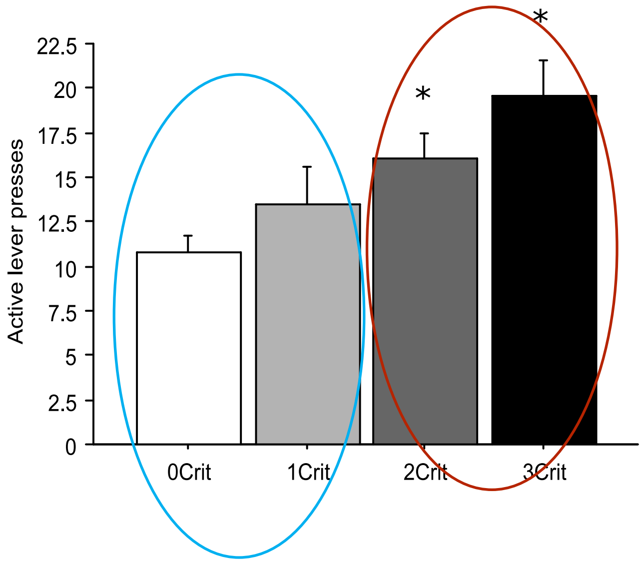
Jadhav et al., 2017, 2018 (adapted from Deroche-Gamonet et al., 2004)

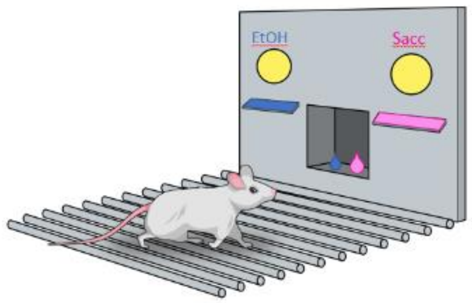
Defining Vulnerable (to lose control) versus Resilient (recreational user) rats

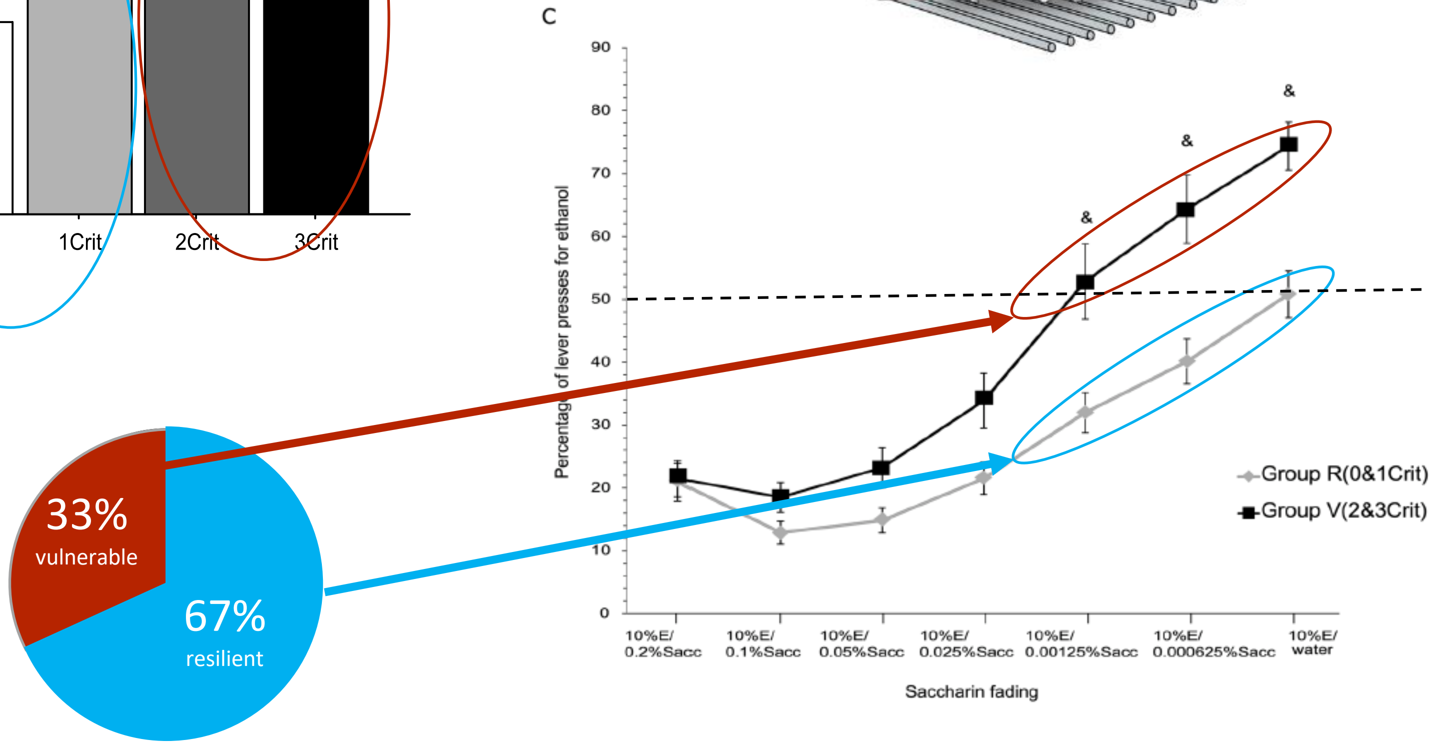
Addiction score:
(sum of the standardized scores of each of the addiction-like criteria)



Reinstatement







compared to 0Crit rats
* compared to 0Crit and 1Crit rats
@ compared to 0Crit, 1Crit and 2Crit rats

Jadhav et al., 2017, 2018

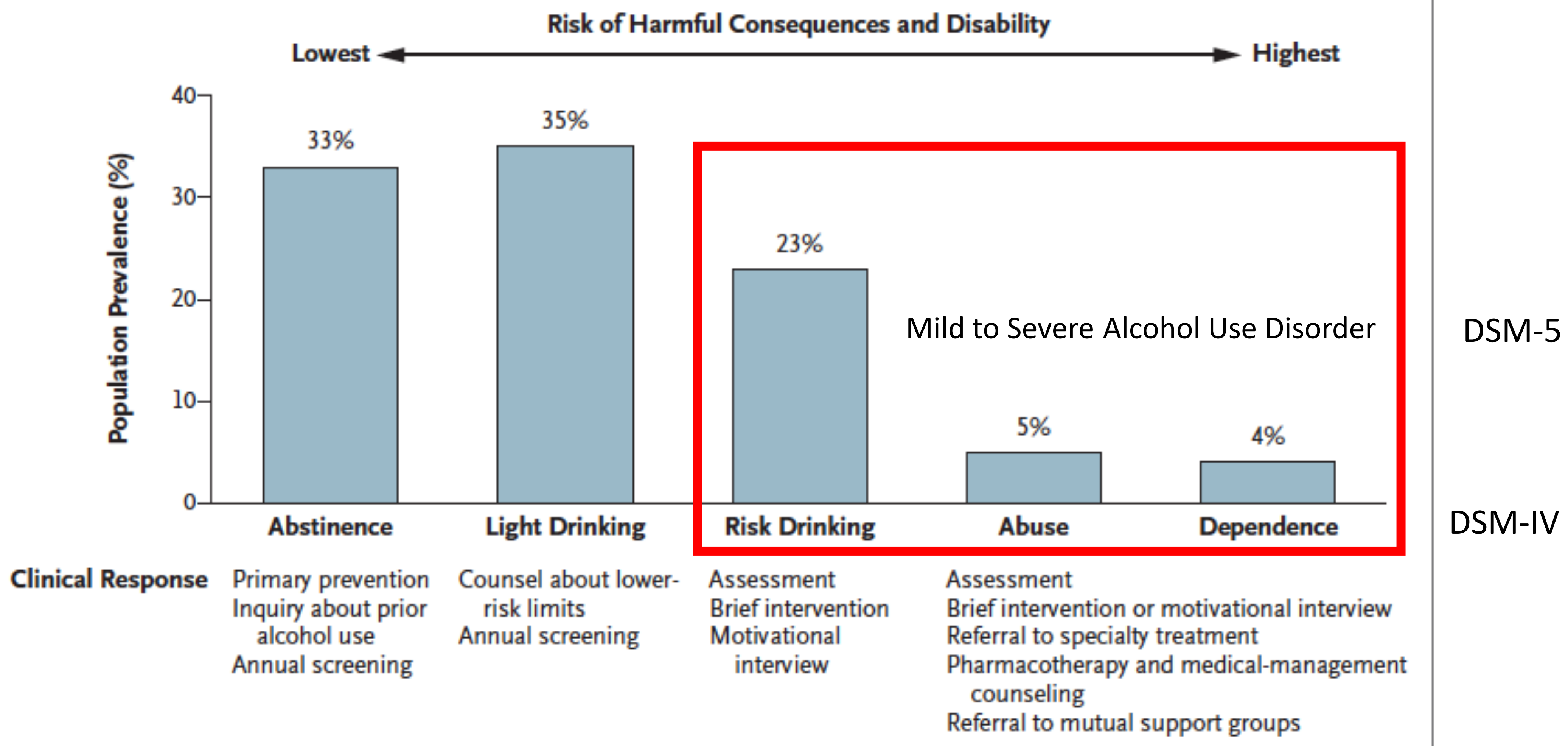
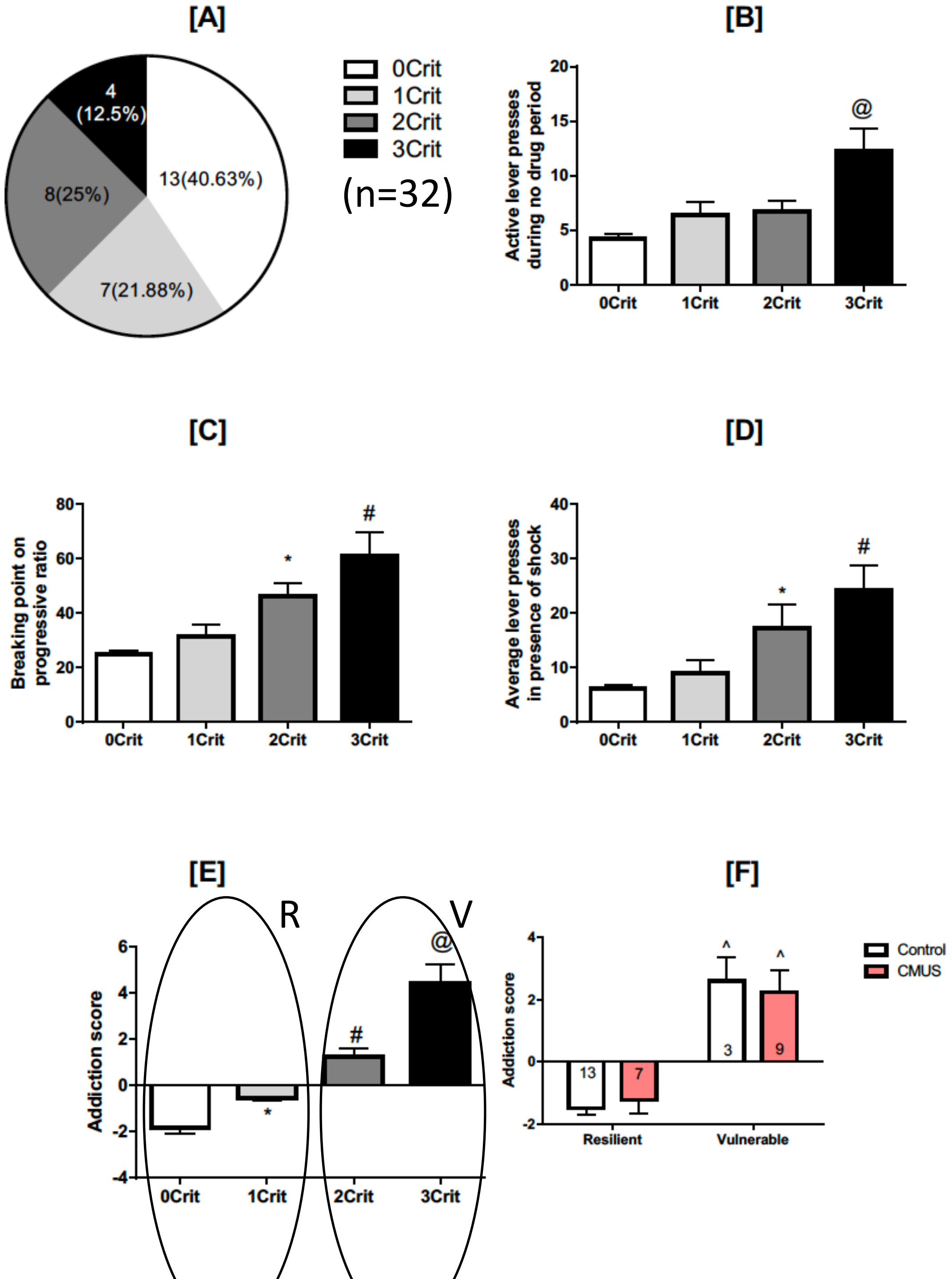


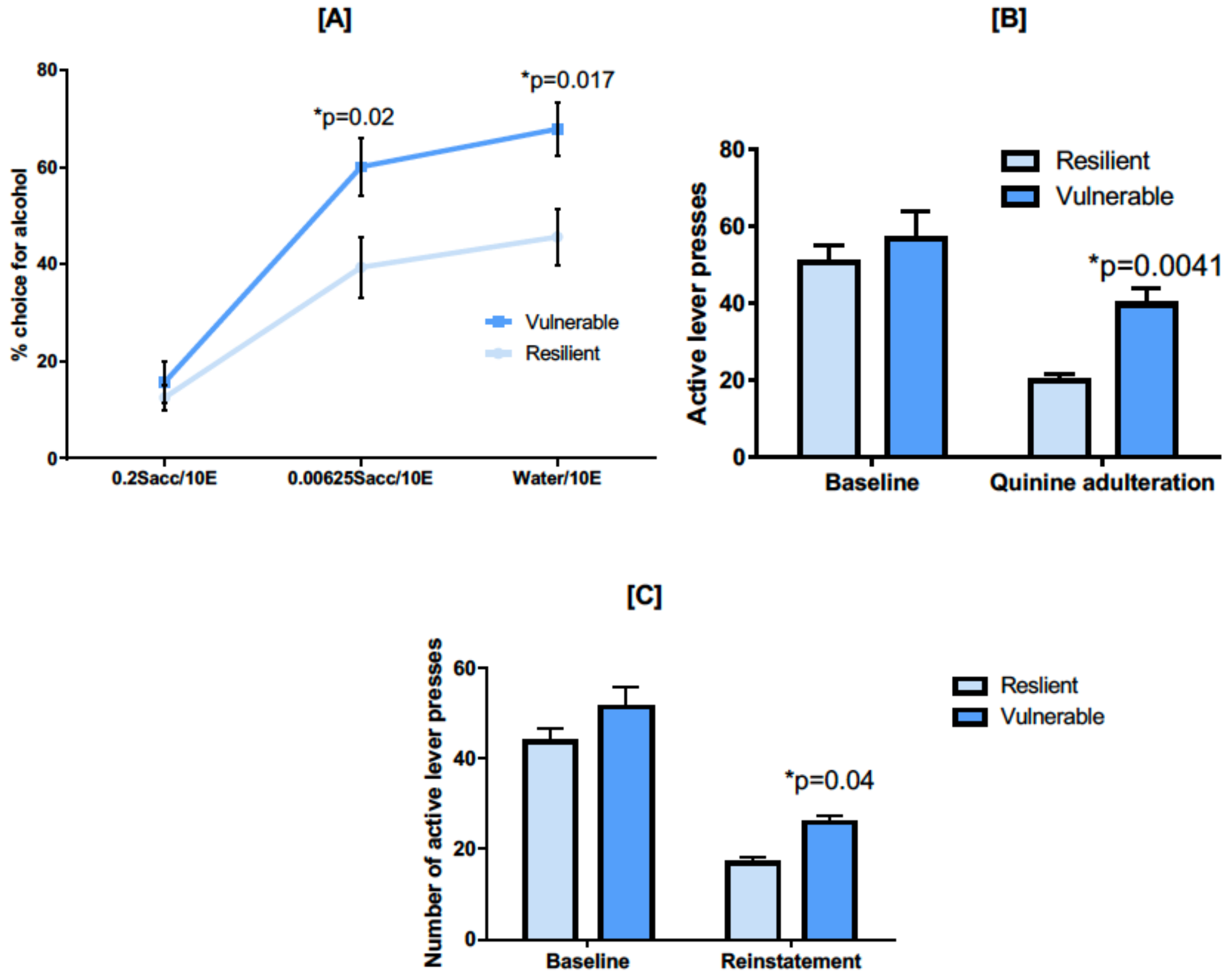
Figure 1. Continuum of Risk Associated with Alcohol Use and Possible Clinical Responses.

Risk drinking is defined as an average of 15 or more standard drinks per week or 5 or more on an occasion for men and 8 or more drinks weekly or 4 or more on an occasion for women and people older than 65 years of age.[5] Persons in remission from an alcohol-use disorder remain at risk for recurrent drinking and adverse consequences.

Friedmann, The New England Journal of Medicine, 2013



Early stress triggers enhanced vulnerability to lose control over alcohol seeking



Chronic Mild Unpredictable Stress (CMUS) in adolescence

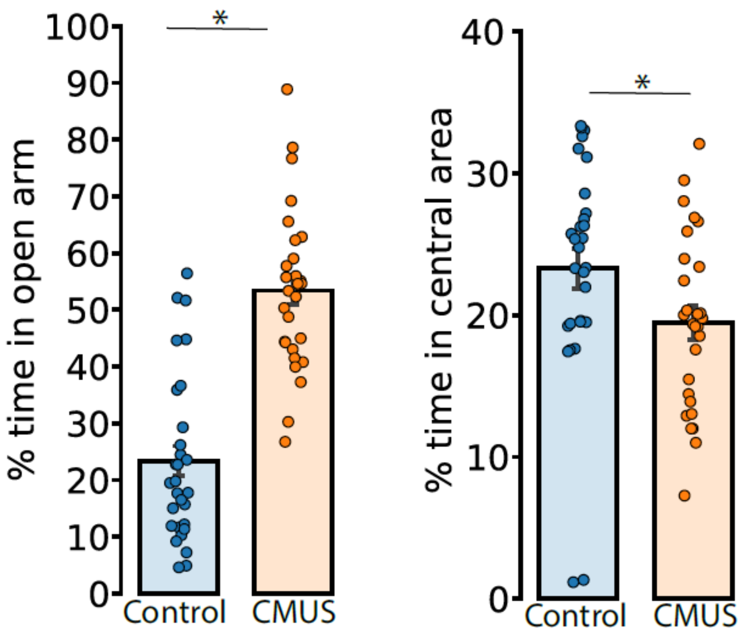
Behavioral effects

Electrophysiological effects

Causal role of PLC using Chemogenetics

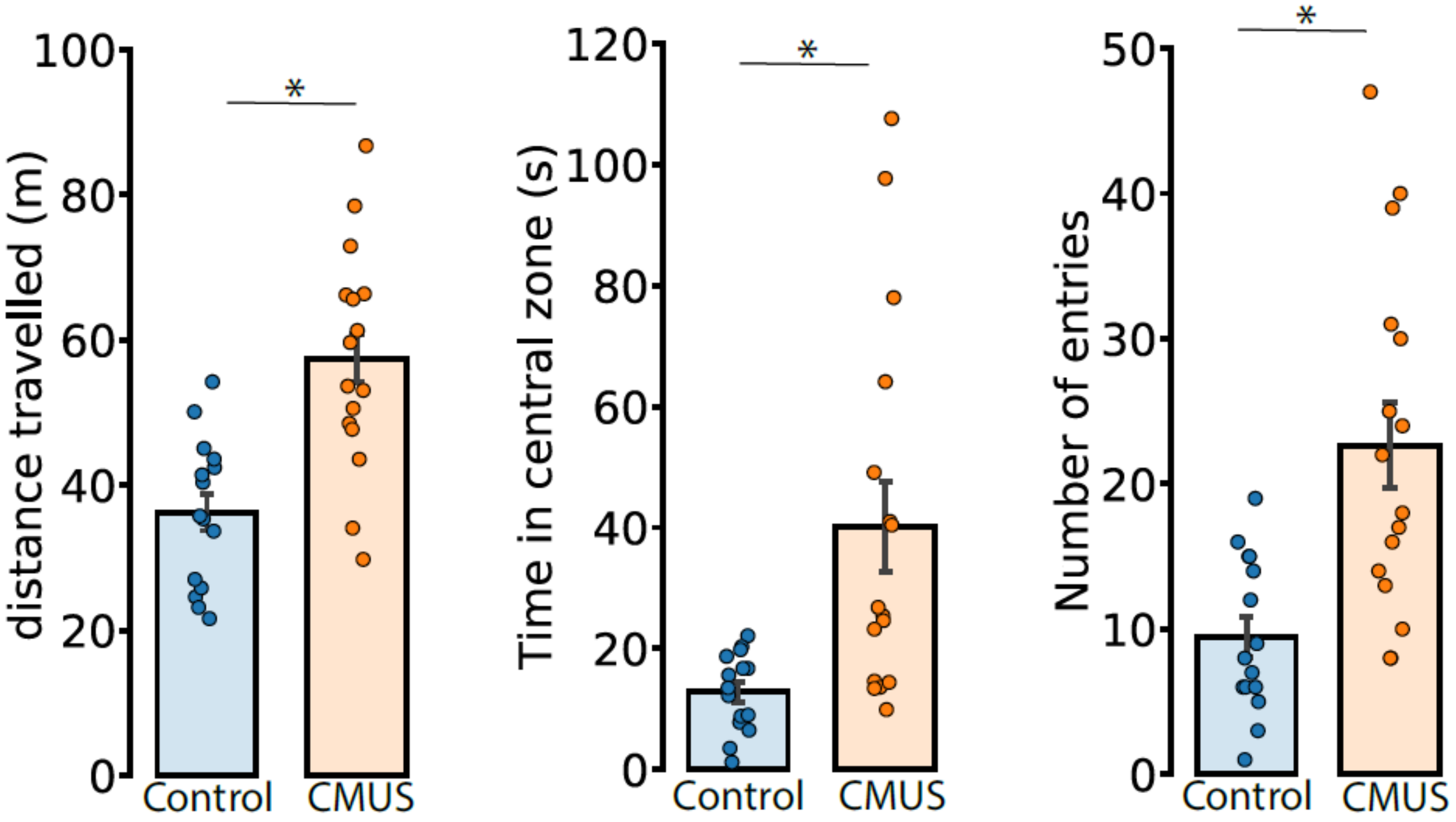
Potential role of neuroinflammation

Disinhibited behaviour on Elevated Plus maze



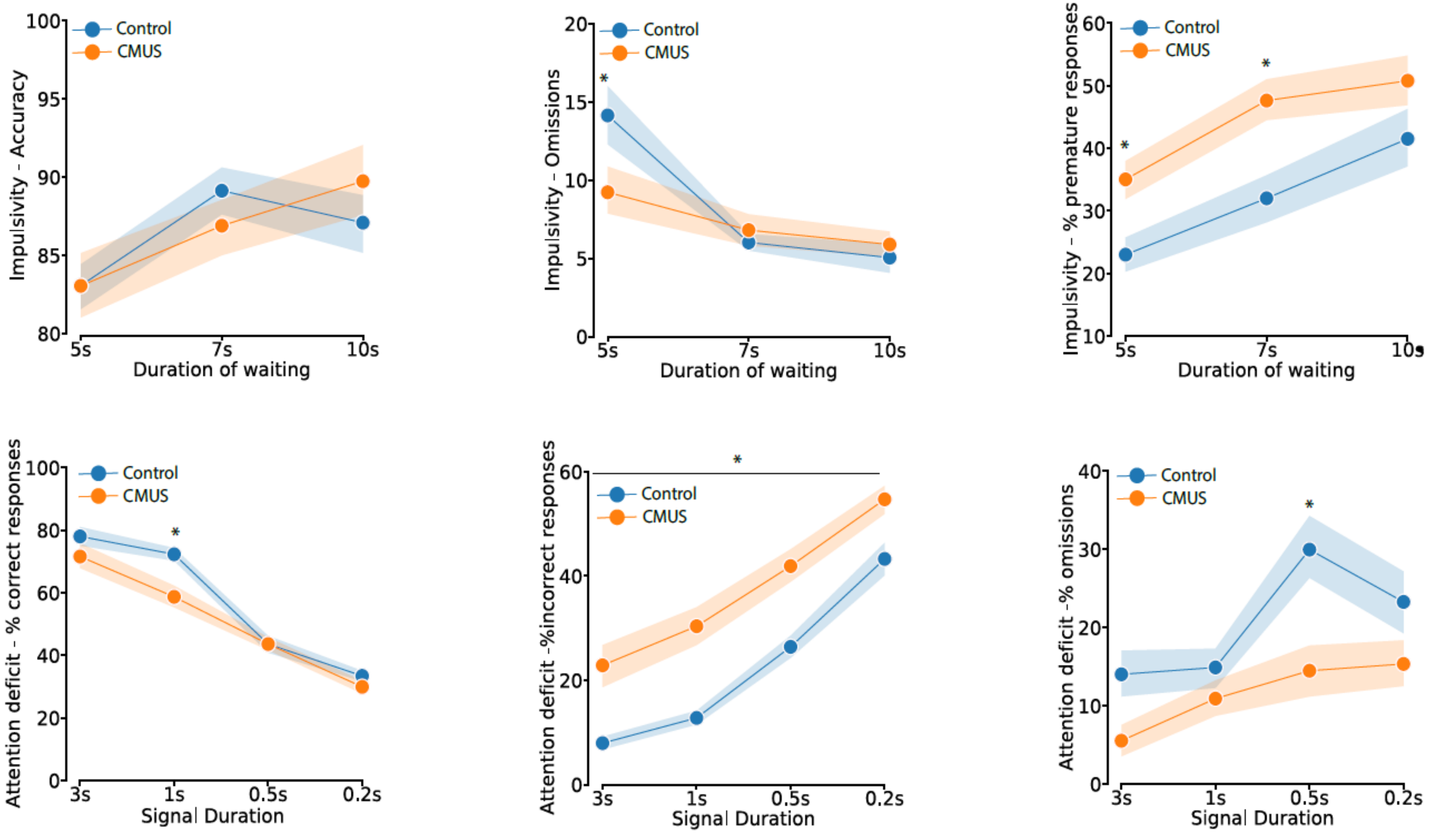
unpaired T test, ***Control n=29, CMUS n=28***

Hyperactivity on the Open Field Test



Unpaired T test, ***Control n=15, CMUS n=16***

Enhanced impulsive actions measured on the 5-CSRTT



Two way repeated measures ANOVA with post hoc Sidak's test, ***Control n=15, CMUS n=18***

Further behavioral characterization

Increased attention deficit

Impulsive choice on Delay Discounting task

Higher motivation for saccharine

Decreased goal directed behavior

Higher habit behavior

Higher inflexible behavior

Higher saccharine seeking despite punishment

Attenuated corticosterone response to acute stress

Chronic Mild Unpredictable Stress (CMUS) in adolescence

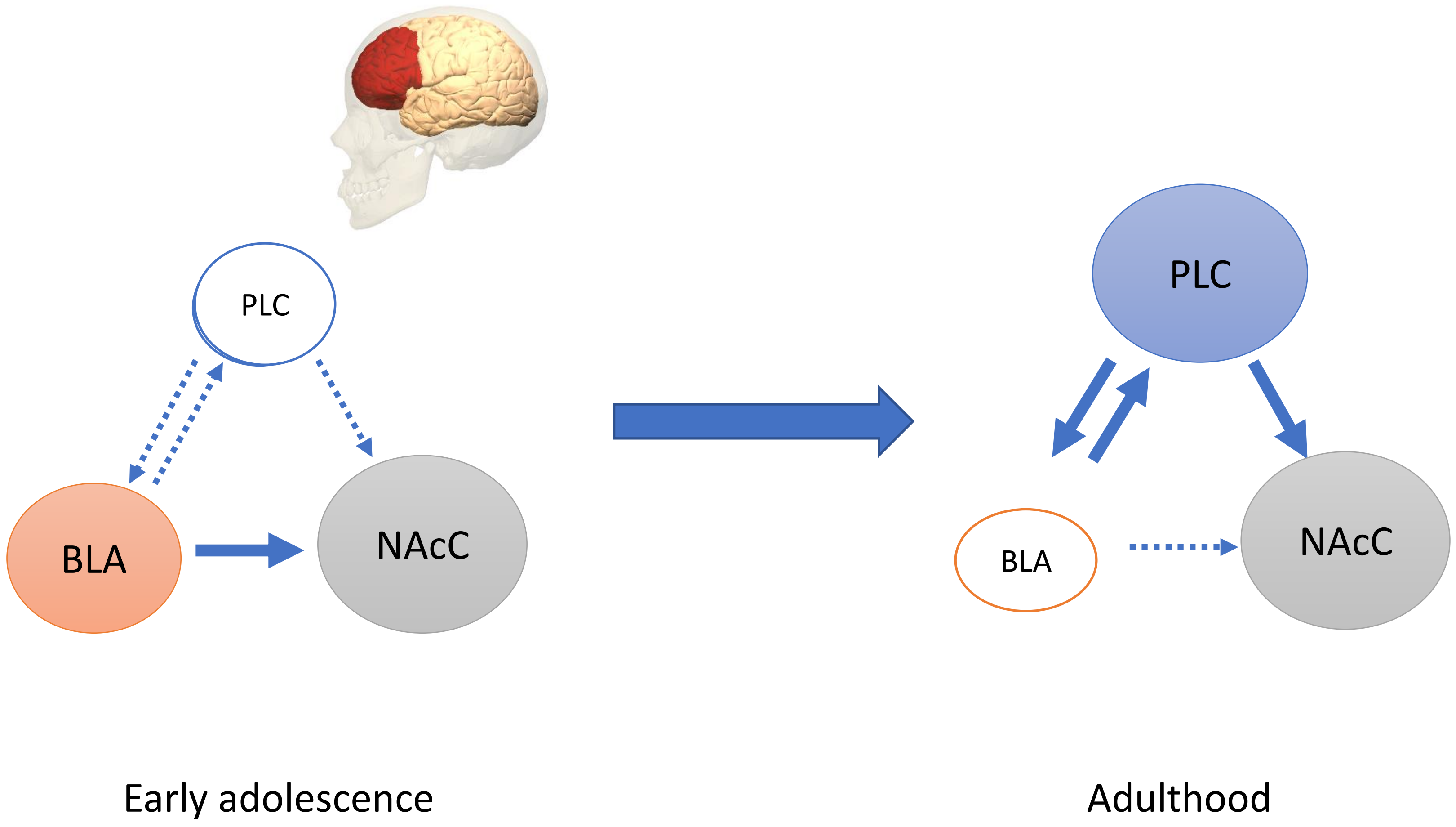
Behavioral effects

Electrophysiological effects

Causal role of PLC using Chemogenetics

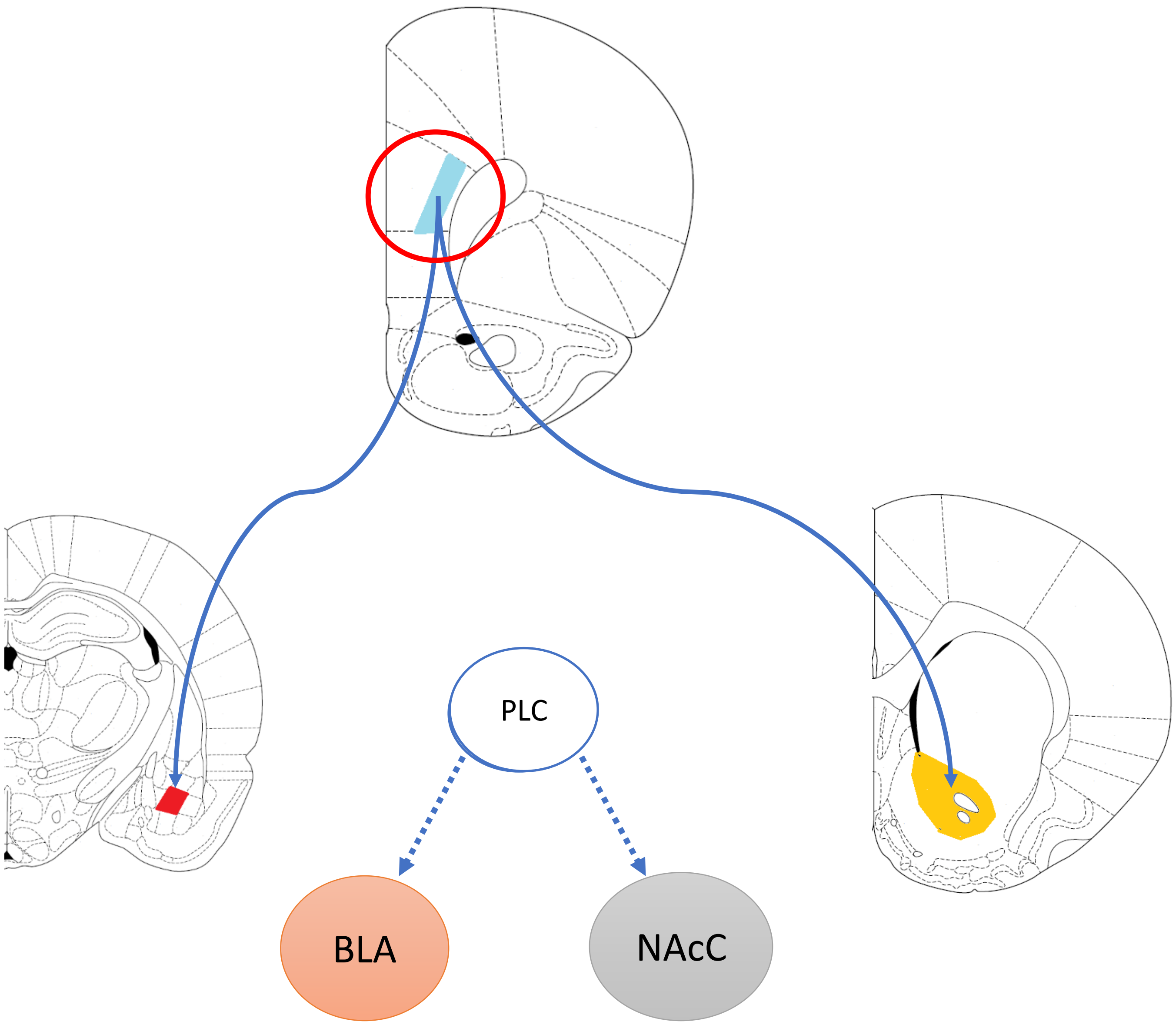
Potential role of neuroinflammation

The imbalance model of the adolescent brain development



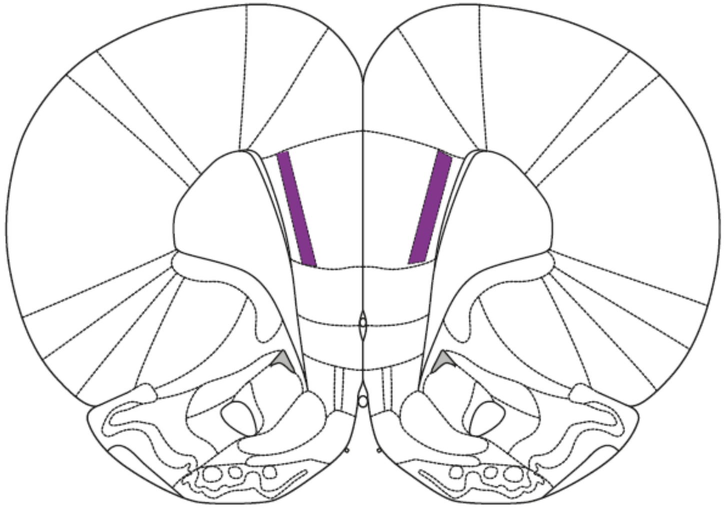
Adopted from Casey *et al.,* A. The adolescent brain. *Developmental Review* (2008)
Jadhav and Boutrel, *European Journal of Neuroscience* (2019)

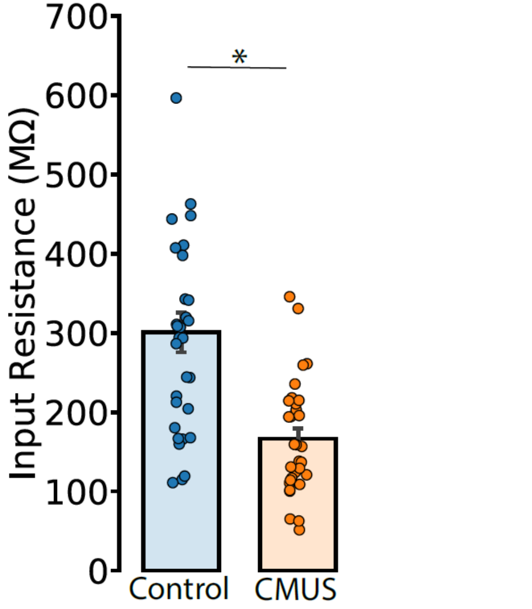
PLC
(layer 5 pyramidal neurons)
Post-synaptic properties



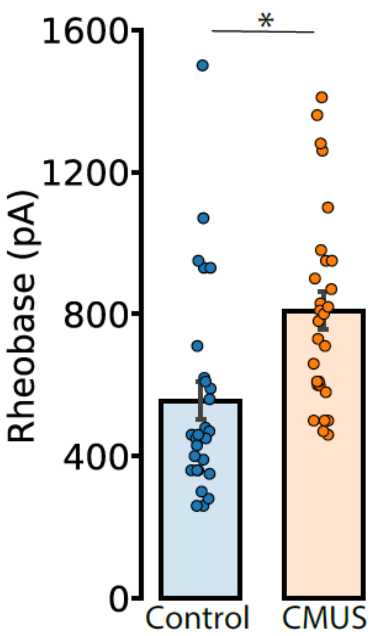
PLC
(layer 5 pyramidal neurons)
hypoexcitable

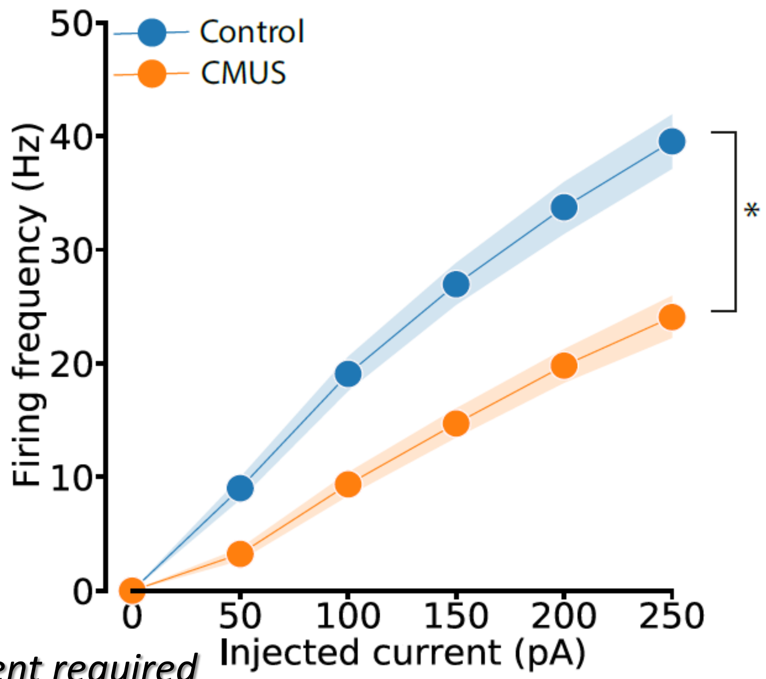
P50

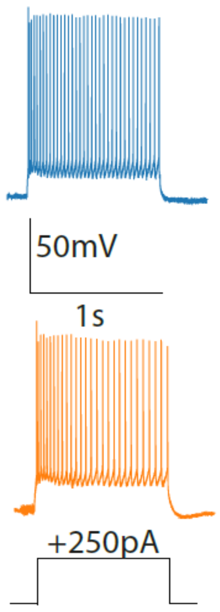




Reflects excitability of the neuron







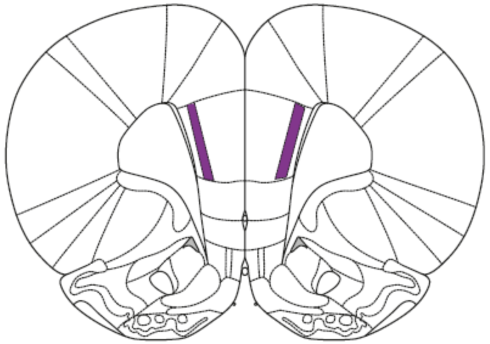
Reflects the amount of current required to inject to induce an action potential

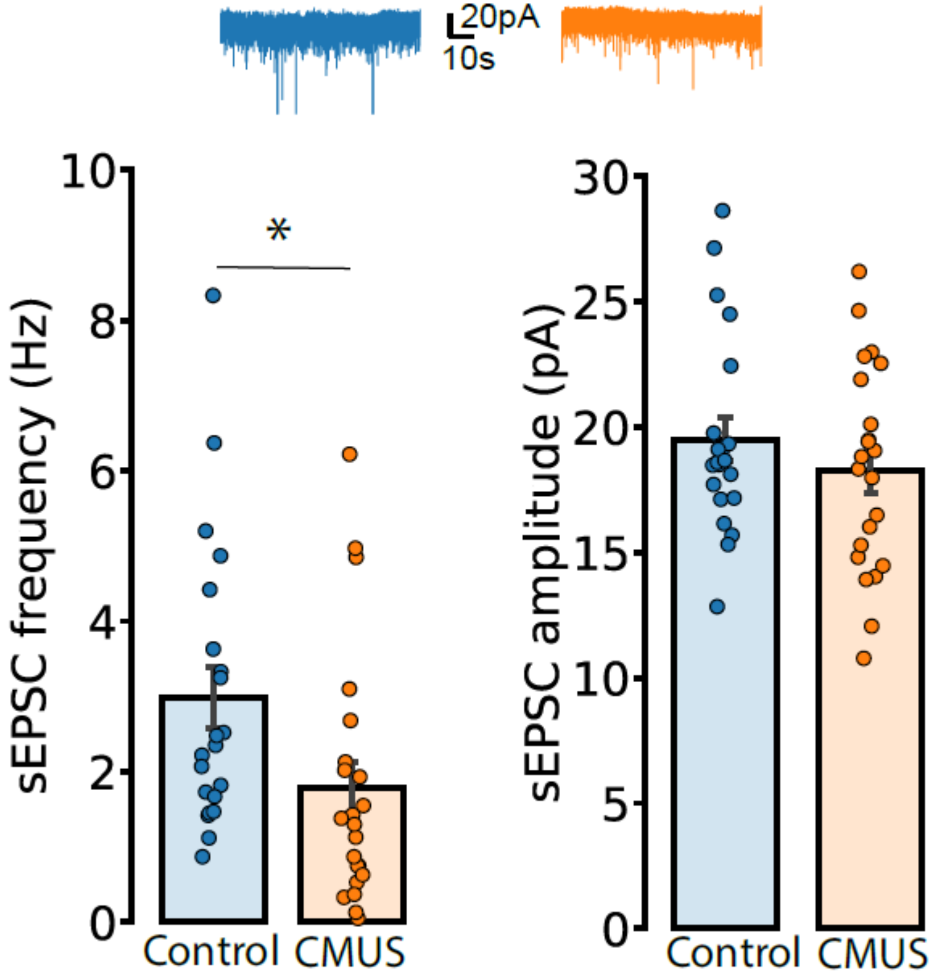
Unpaired t test, ***Control n=31(5) , CMUS n=31(5),***
Two way repeated measures ANOVA with post hoc Sidak's test,
Control n=27(5), CMUS n= 28(5)

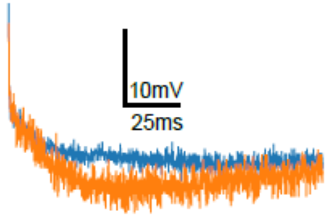
Jadhav *et al., in prep*

PLC
(layer 5 pyramidal neurons)
decreased EPSCs

P50

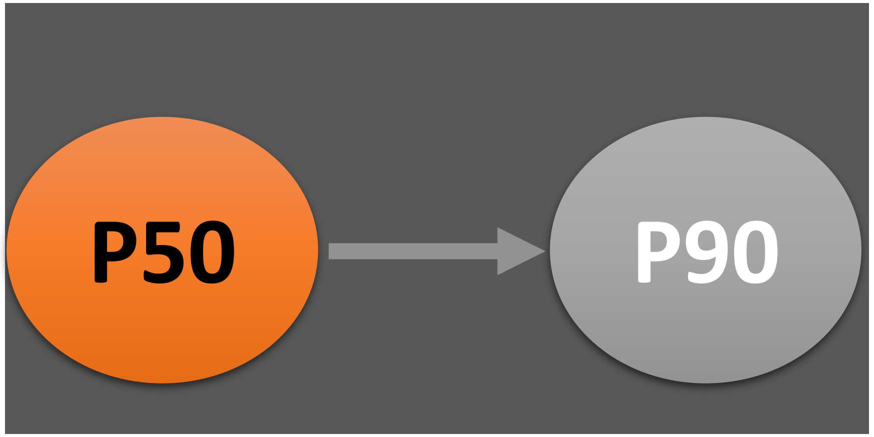






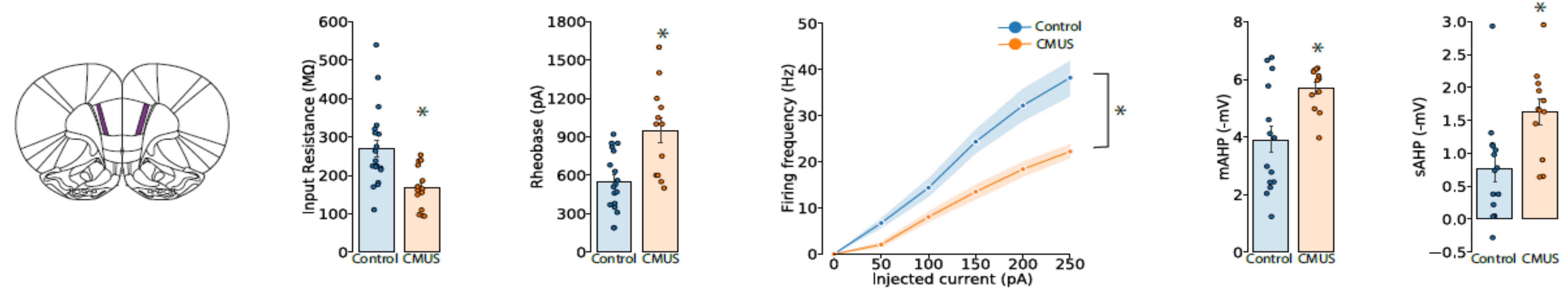
Unpaired T test, ***Control n=21(5), CMUS n=22(5)***

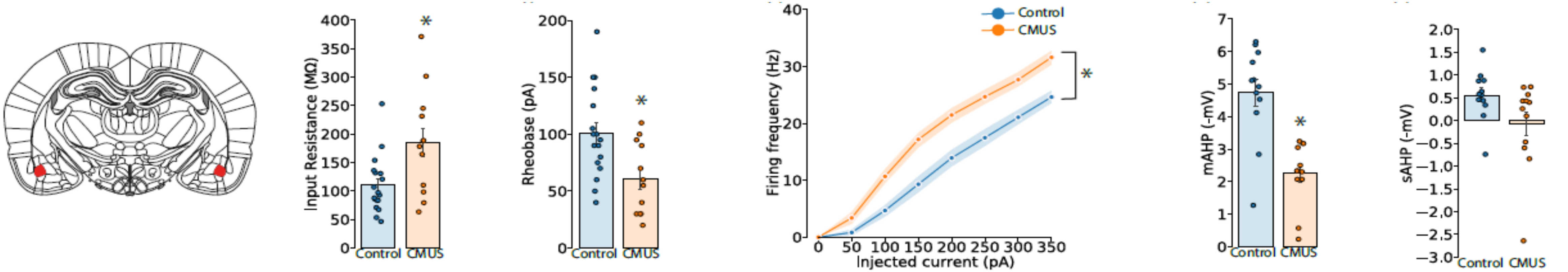
Jadhav *et al., in prep*



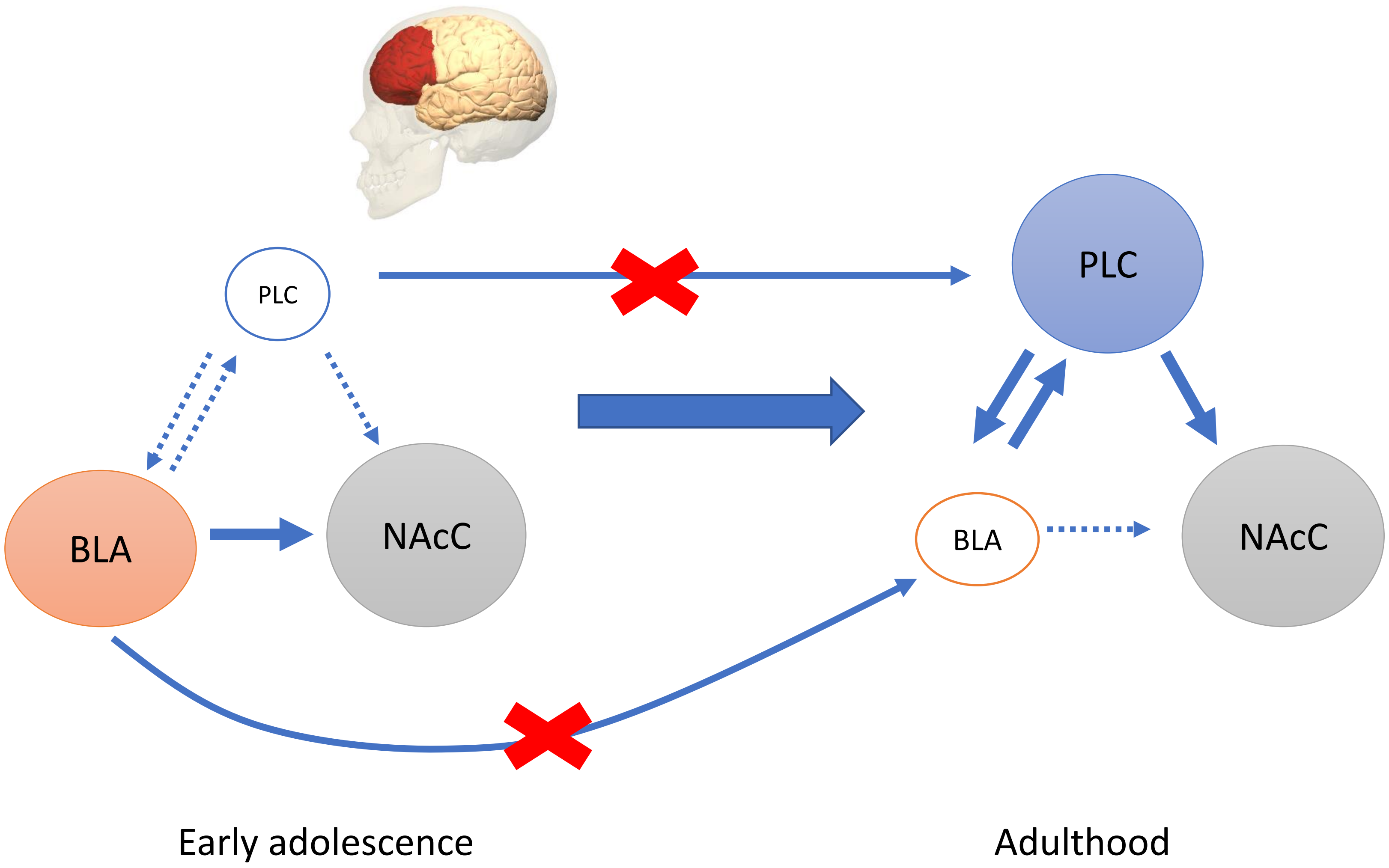
What we see at P50, is also seen at P90.

And we observe an opposite pattern within the BLA.





What is the impact of early stress on the functional development of the PFC?



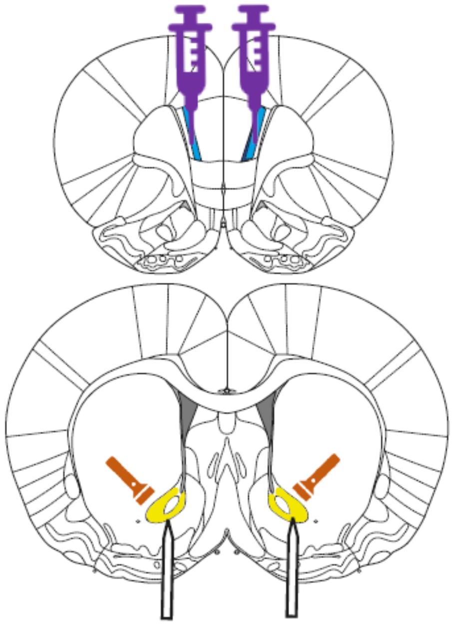
Jadhav *et al., in prep*

Selleck RA *et al*. Limited prefrontal cortical regulation over the basolateral amygdala in adolescent rats. *Sci Rep.* (2018)

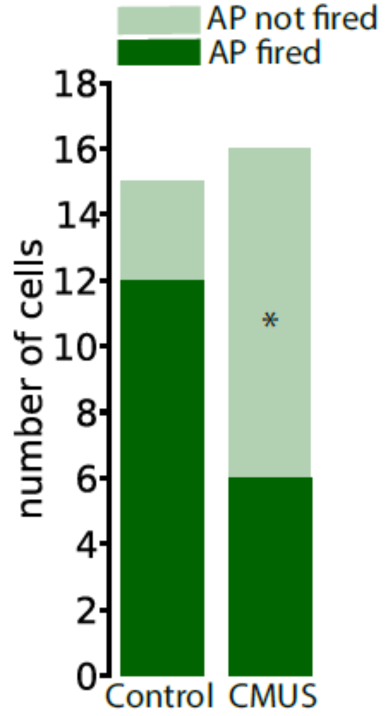
Adapted from Casey BJ, *et al*. The adolescent brain. *Developmental Review* (2008)

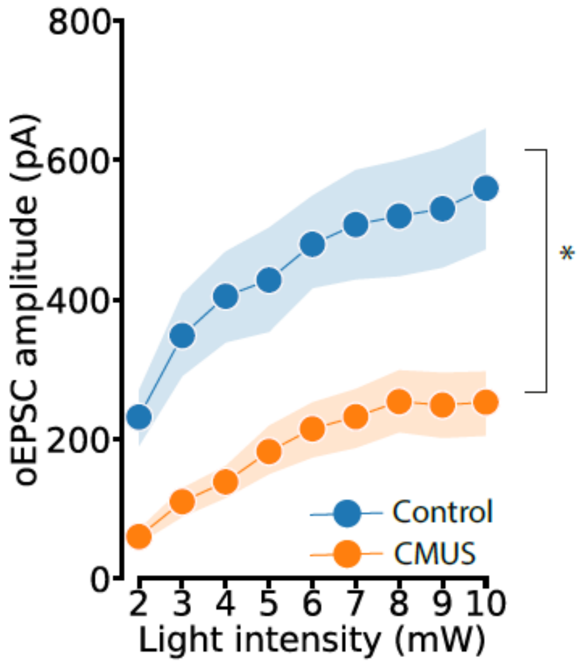
PLC to NAcc glutamatergic projection – a weakening

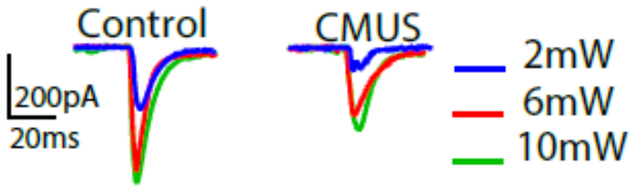
P90



This is achieved by expressing light-sensitive ion channels specifically in the target cells



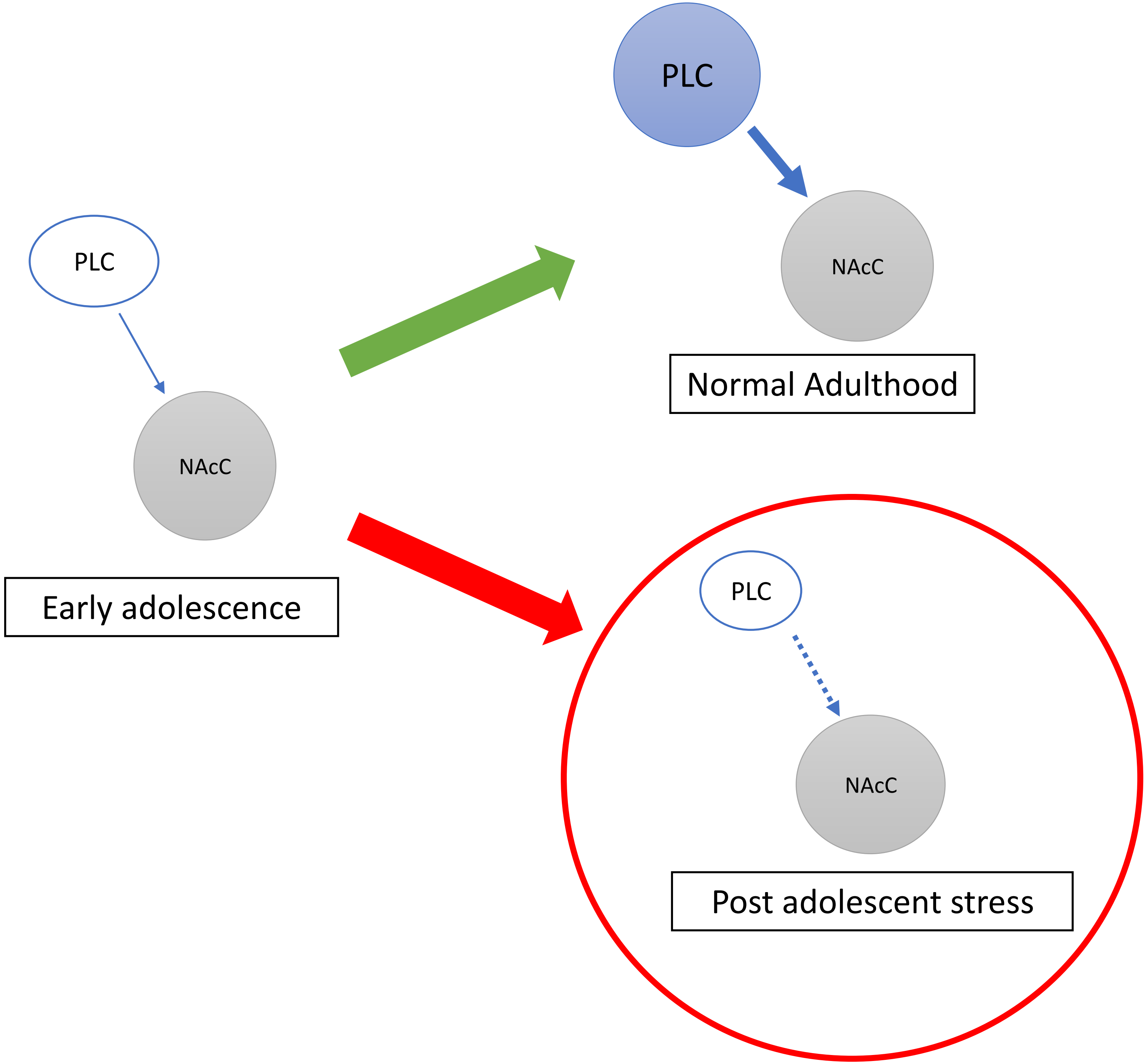




Unpaired t test, ***Control n=15(5) , CMUS n=16(6),***
Two way repeated measures ANOVA with post hoc Sidak’s test,
Control n=15(5), CMUS n= 23(6)

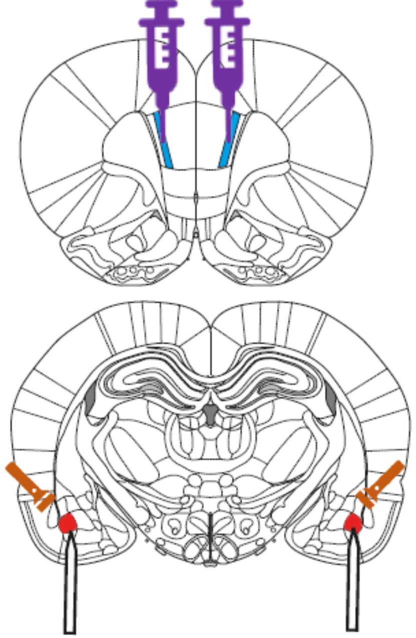
Jadhav *et al., in prep*

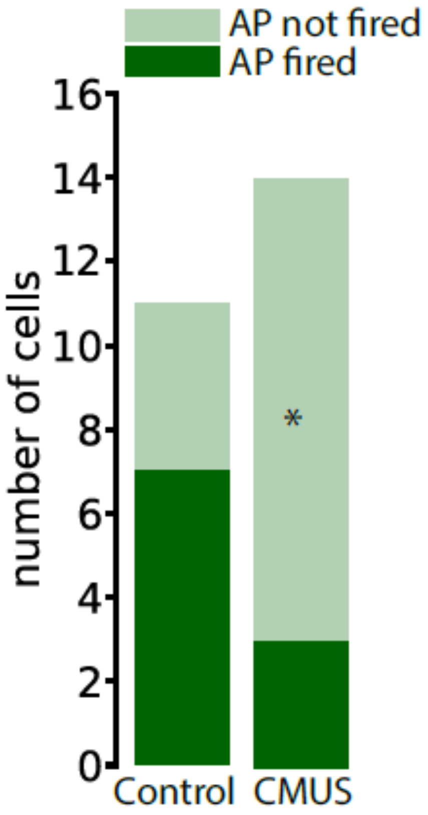
PLC to NAcc glutamatergic projection – a weakening

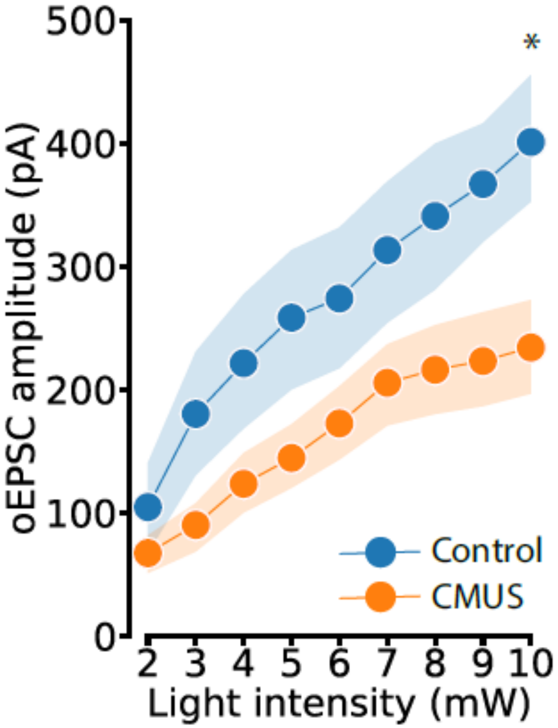


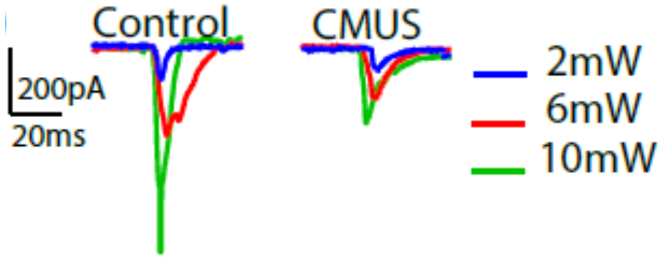
PLC to BLA glutamatergic projection – a weakening

P90





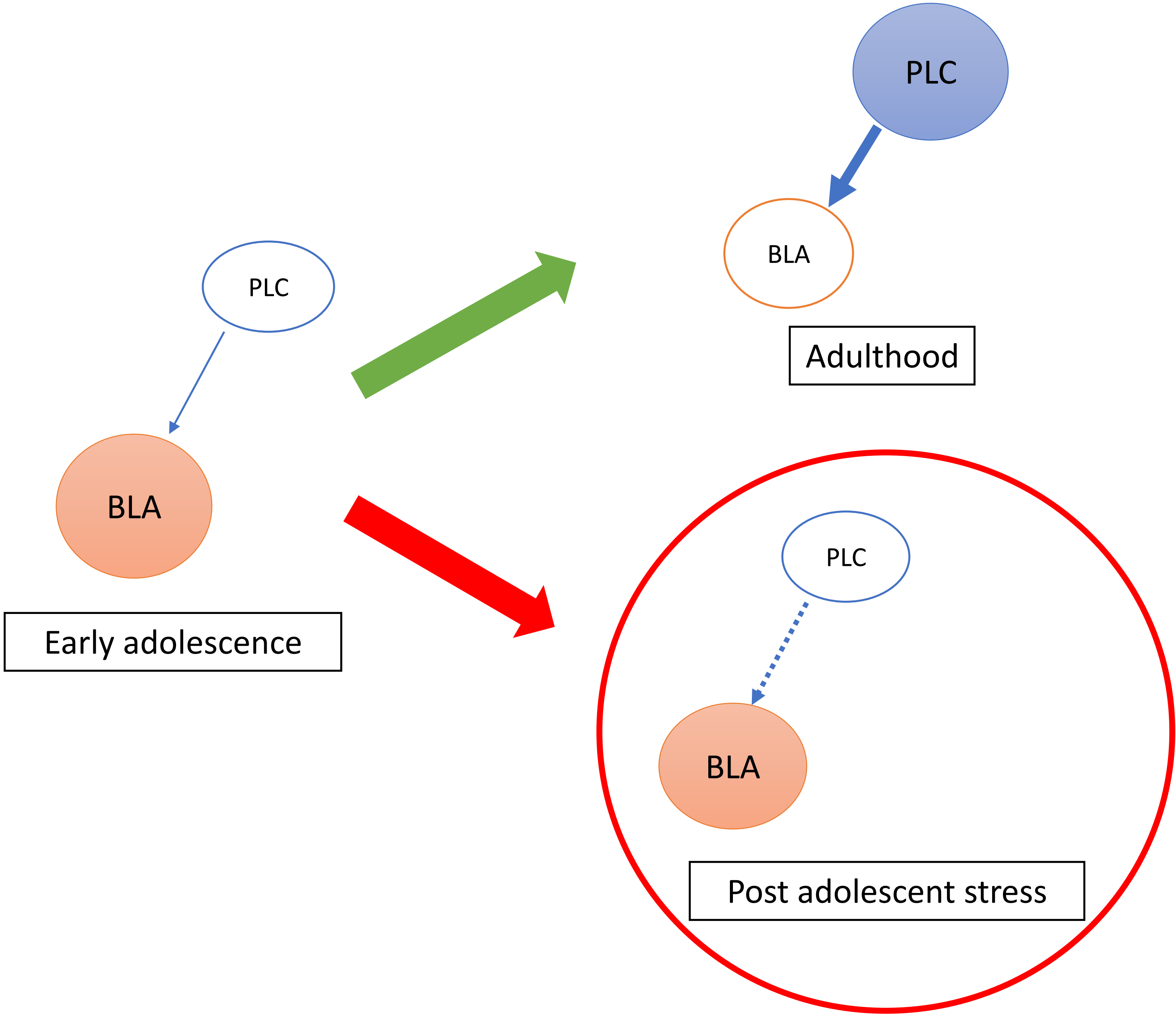




Unpaired t test, ***Control n=11(4) , CMUS n=14(5),***
Two way repeated measures ANOVA with post hoc Sidak's test,
Control n=11(4), CMUS n= 11(5)

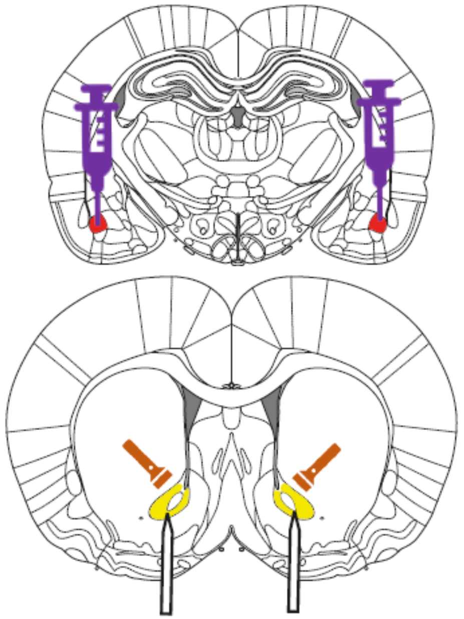
Jadhav *et al., in prep*

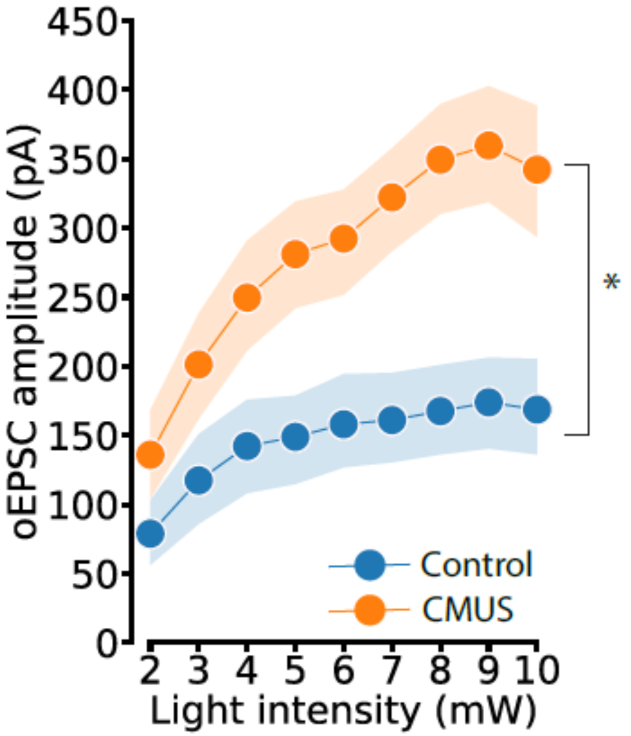
PLC to BLA glutamatergic projection – a weakening

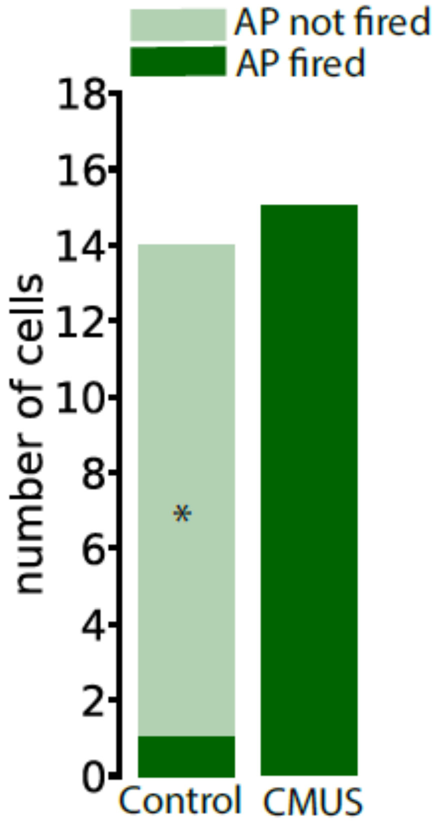


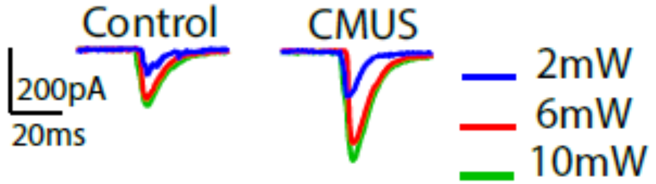
BLA to NAcc glutamatergic projection – a strengthening

P90





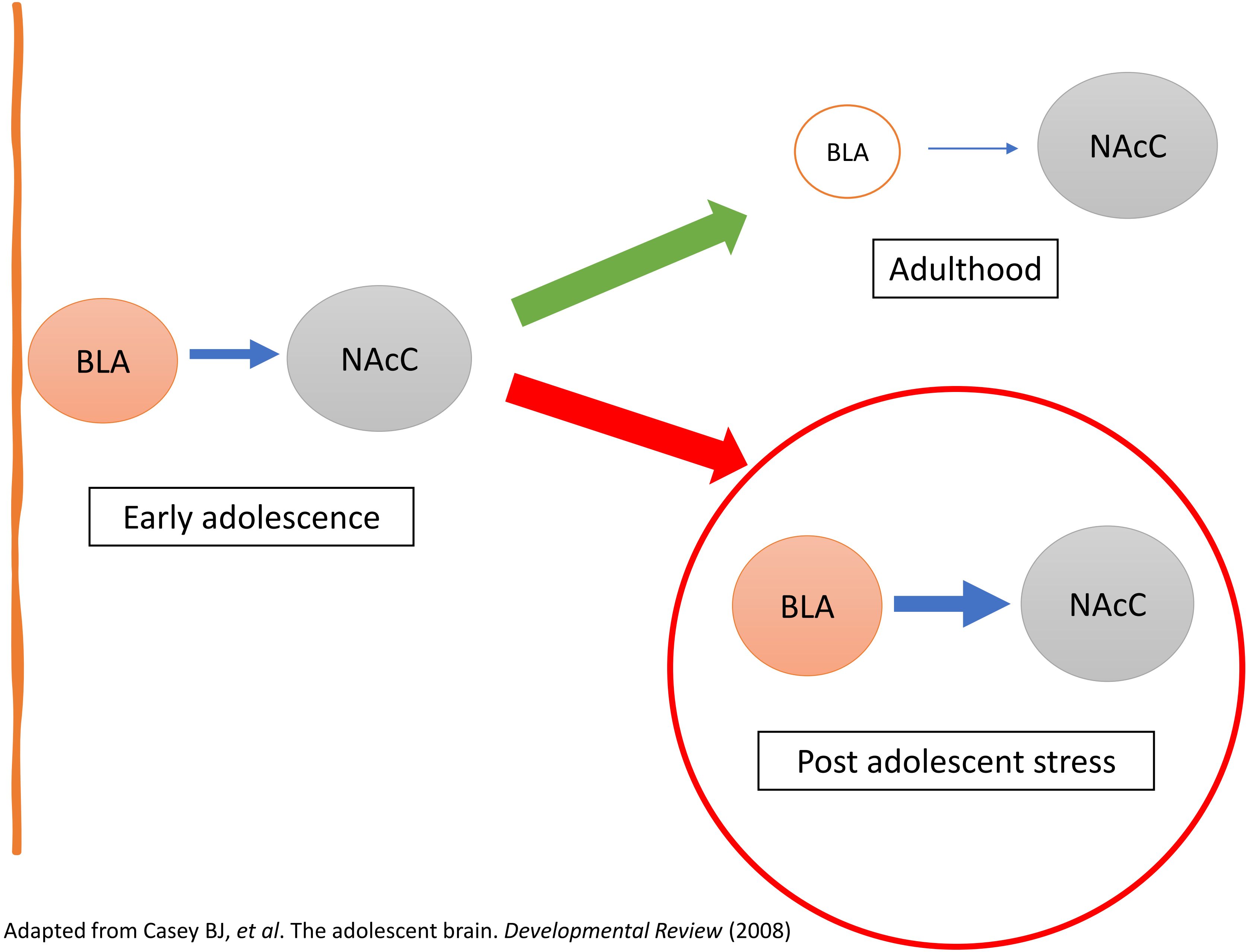




Unpaired t test, ***Control n=14(5) , CMUS n=15(5),***
Two way repeated measures ANOVA with post hoc Sidak's test,
Control n=15(5), CMUS n= 23(5)

Jadhav *et al., in prep*

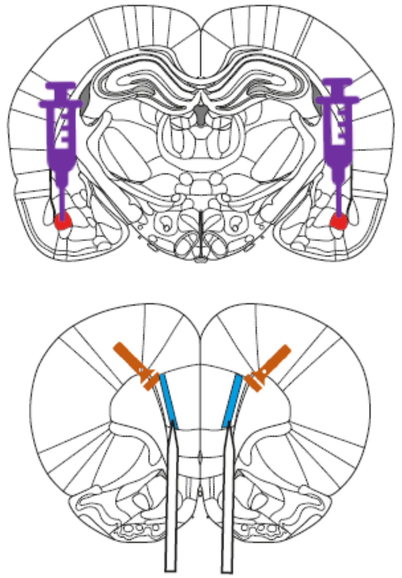
BLA to NAcc glutamatergic projection – a strengthening

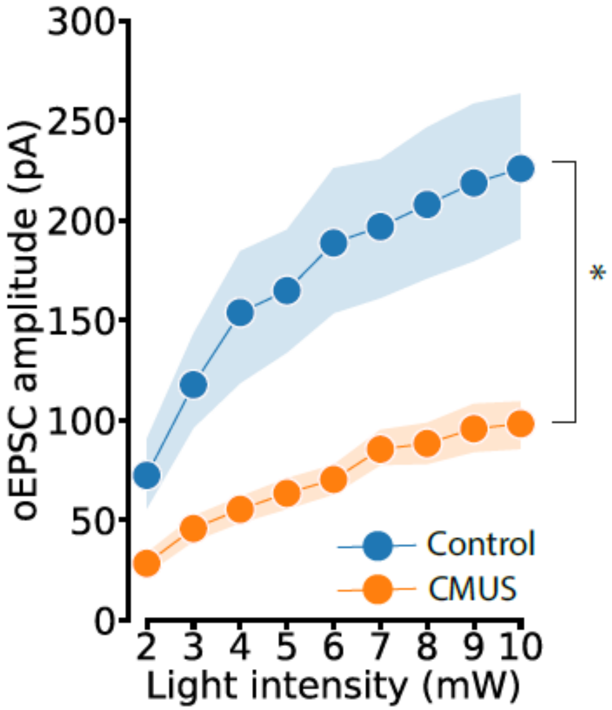


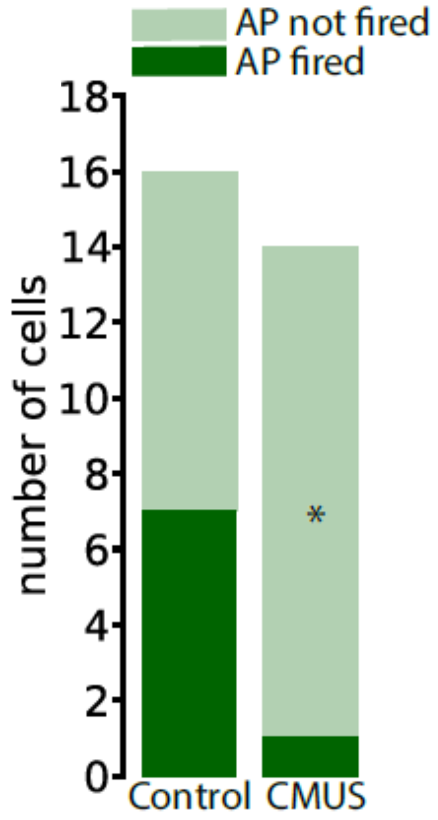
Adapted from Casey BJ, *et al*. The adolescent brain. *Developmental Review* (2008)

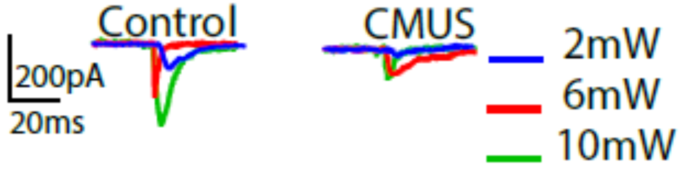
BLA to PLC glutamatergic projection – a weakening

P90









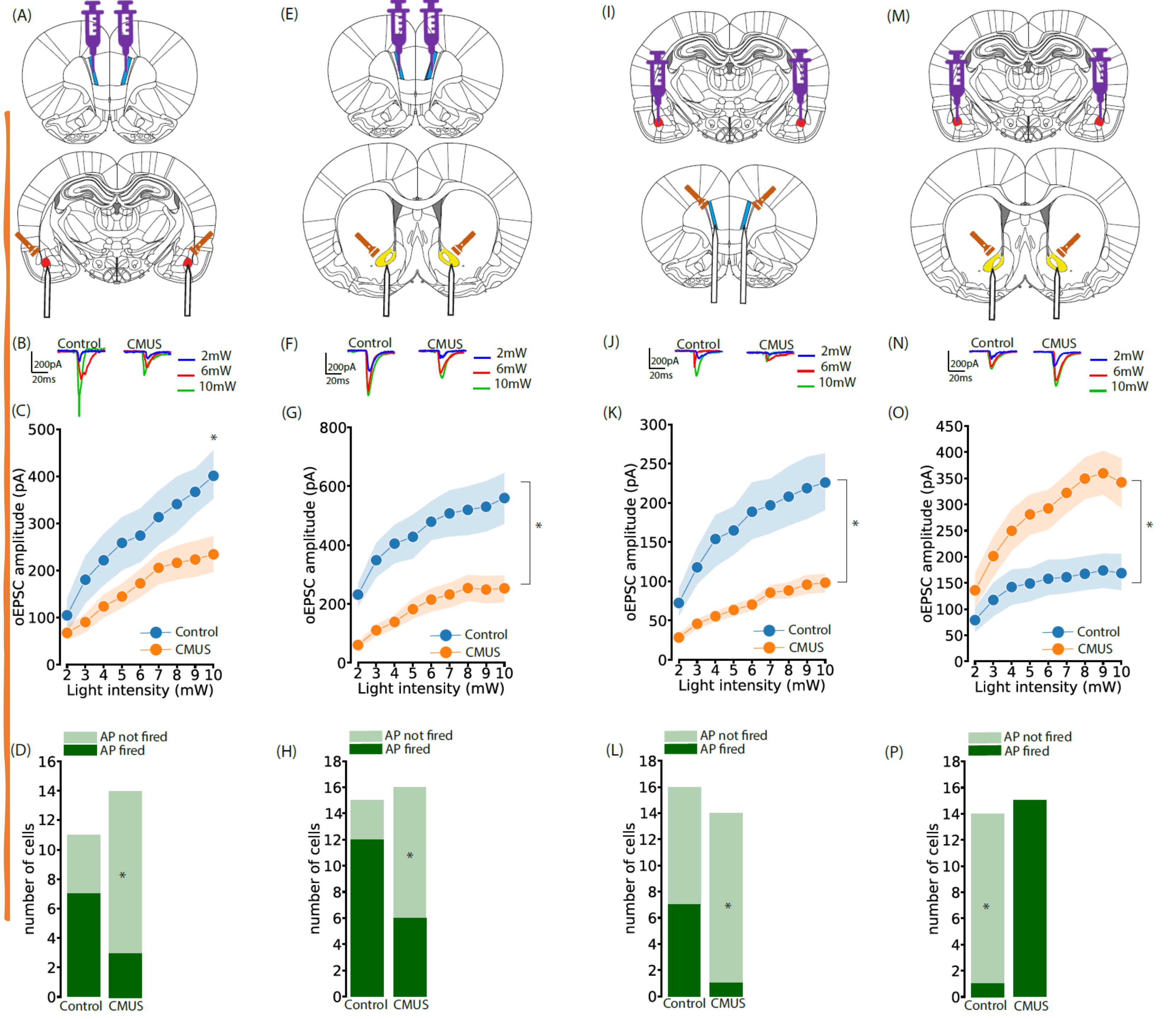
*Unpaired t test, **Control n=16(5) , CMUS n=14(6),***
Two way repeated measures ANOVA with post hoc Sidak’s test,
Control n=14(4), CMUS n= 17(6)

The Stress Deceleration Theory

1. Weaker top down control from PLC to BLA and NAcC

2. Stronger projection from BLA to Nacc

3. Weaker projection from BLA to PLC



Chronic Mild Unpredictable Stress (CMUS) in adolescence

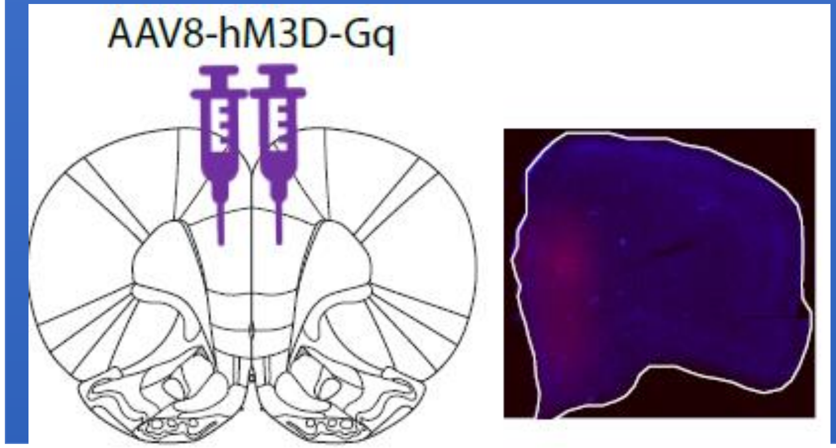
Behavioral effects

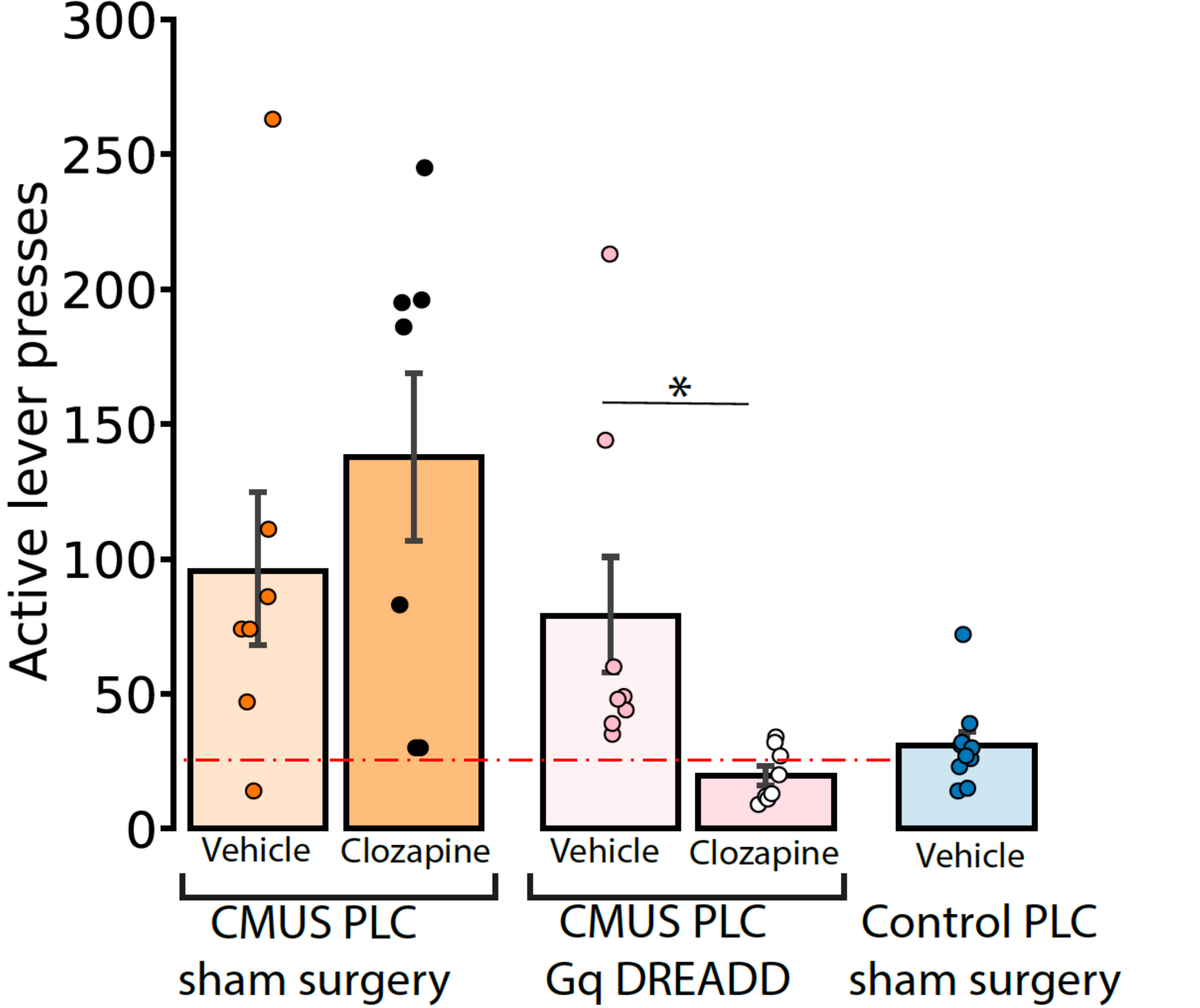
Electrophysiological effects

Causal role using Chemogenetics

Potential role of neuroinflammation

Chemogenetic activation of PLC Pyramidal Neurons rescues the effects of early stress exposure on compulsive behaviors

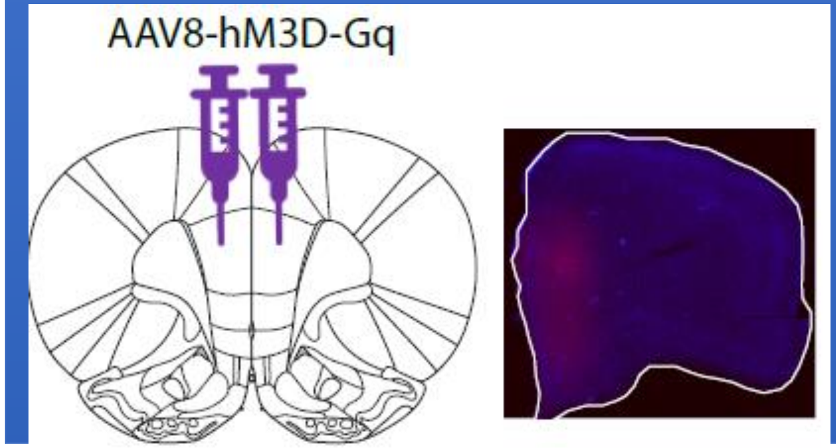


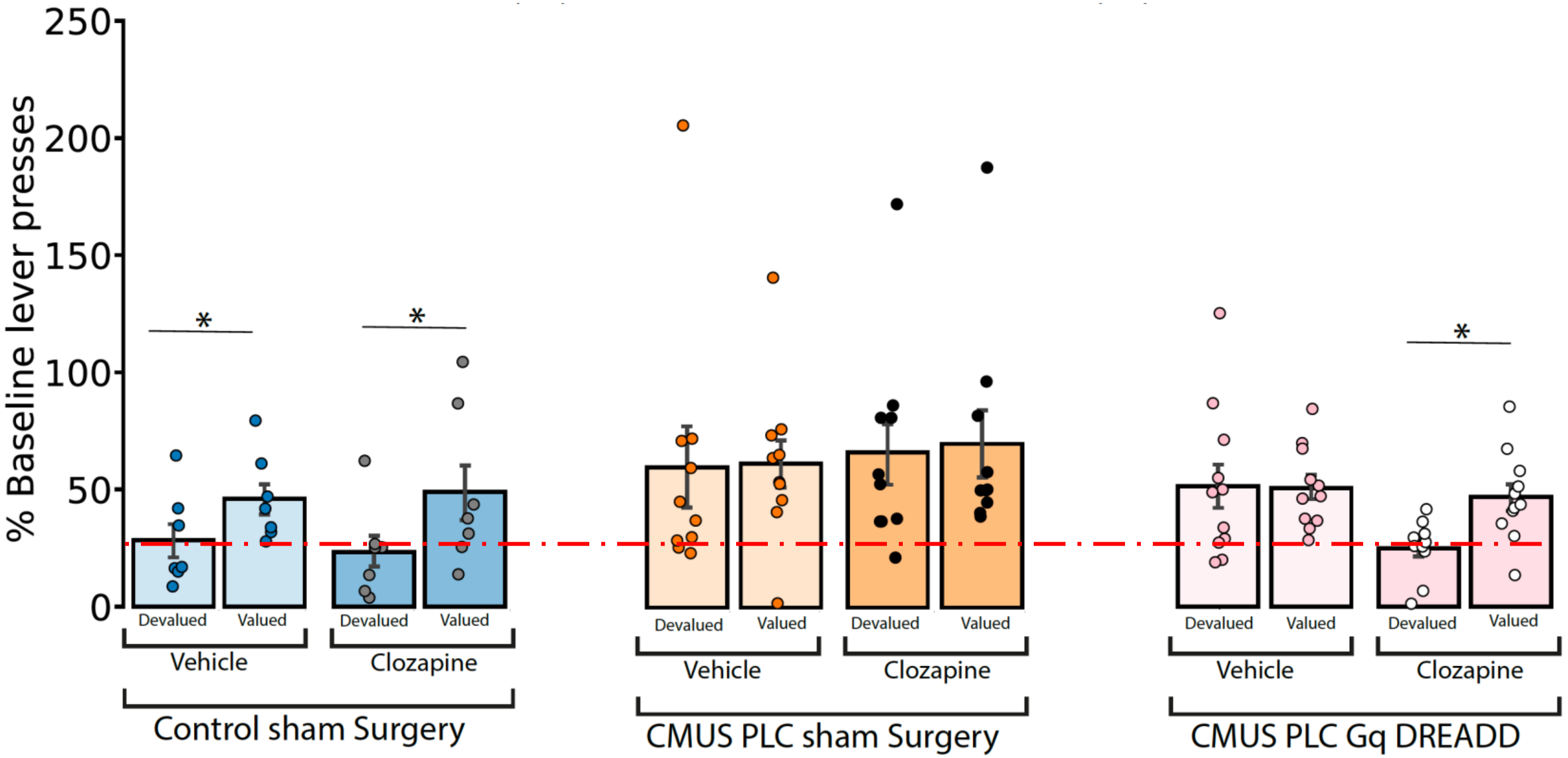


Two way repeated measures ANOVA with post hoc Sidak's test,

CMUS PLC sham – Vehicle (n=7), CMUS PLC sham – clozapine (n=7), CMUS PLC Gq DREADD –vehicle (n=8), CMUS PLC Gq DREADD-clozapine (n=8),

Chemogenetic activation of PLC Pyramidal Neurons rescues the effects of early stress exposure on goal directed behaviors





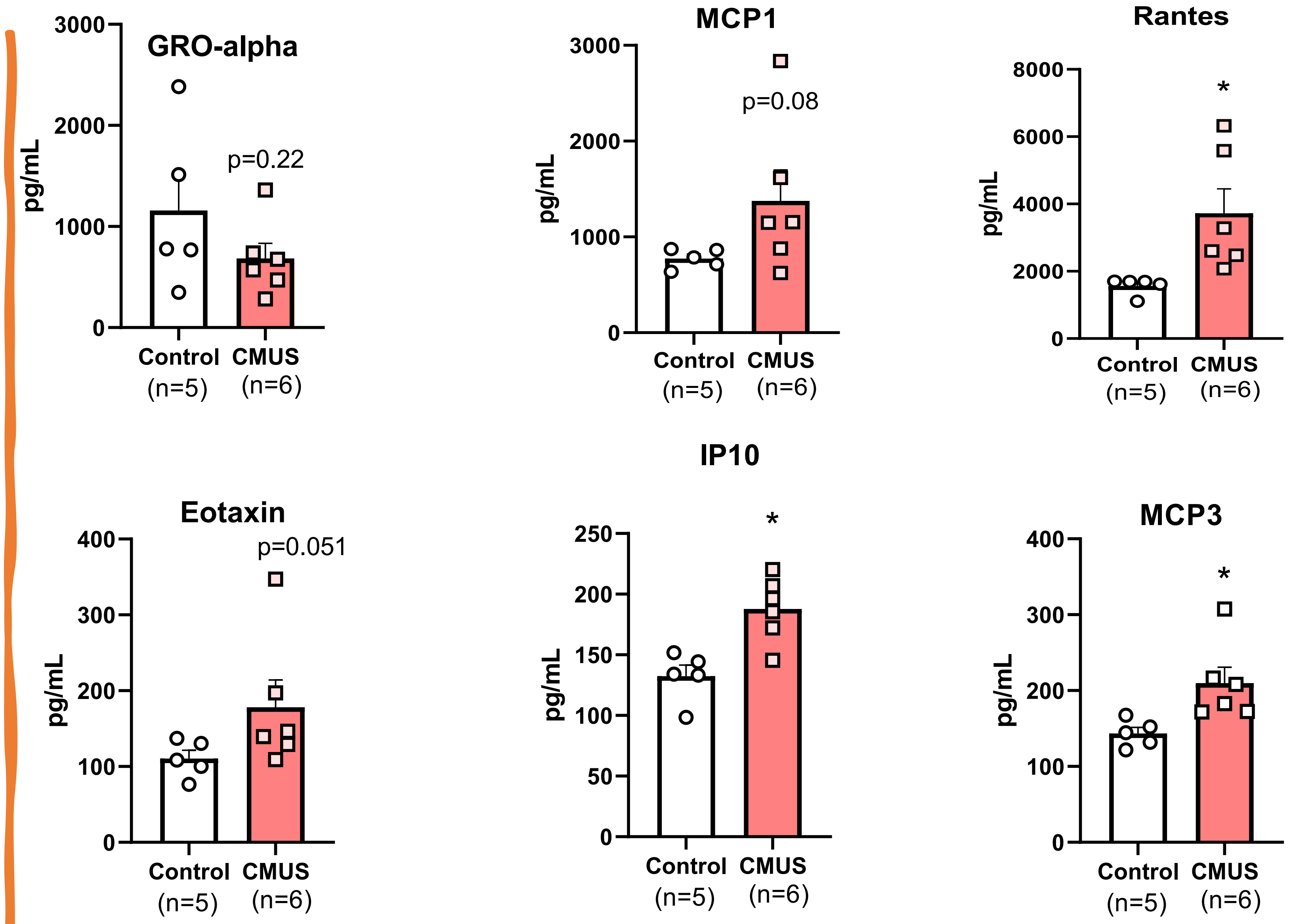
Two way repeated measures ANOVA with post hoc Sidak's test,

CMUS PLC sham – Vehicle (n=7), CMUS PLC sham – clozapine (n=7), CMUS PLC Gq DREADD –vehicle (n=8), CMUS PLC Gq DREADD-clozapine (n=8),


STRESS can affect its development
Just as experiences mold and nurture our brain

A nod towards inflammation

P50

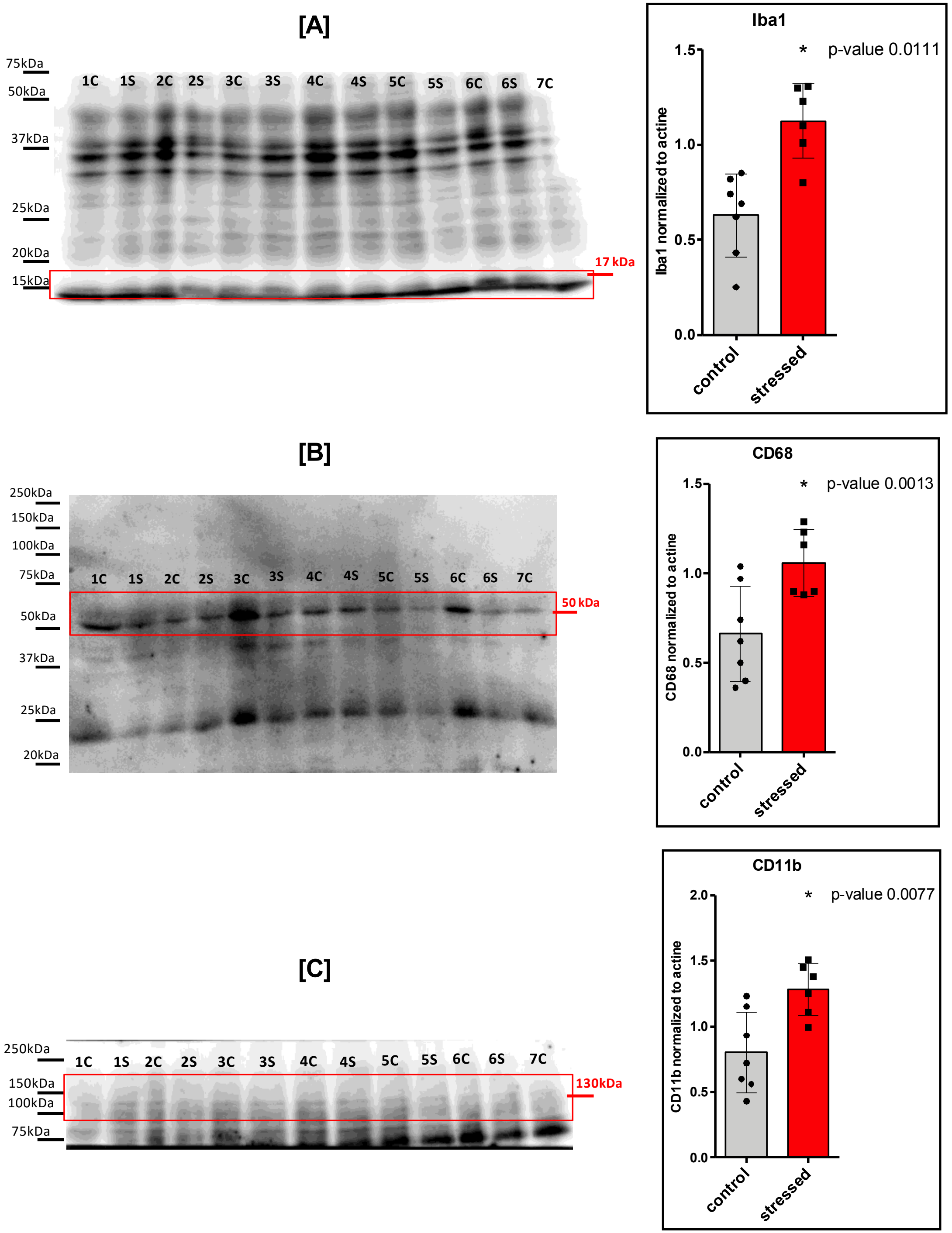


Unpaired t test

A nod towards inflammation

Persistent increased expression of microglial activation markers at P90 in the PLC

P90



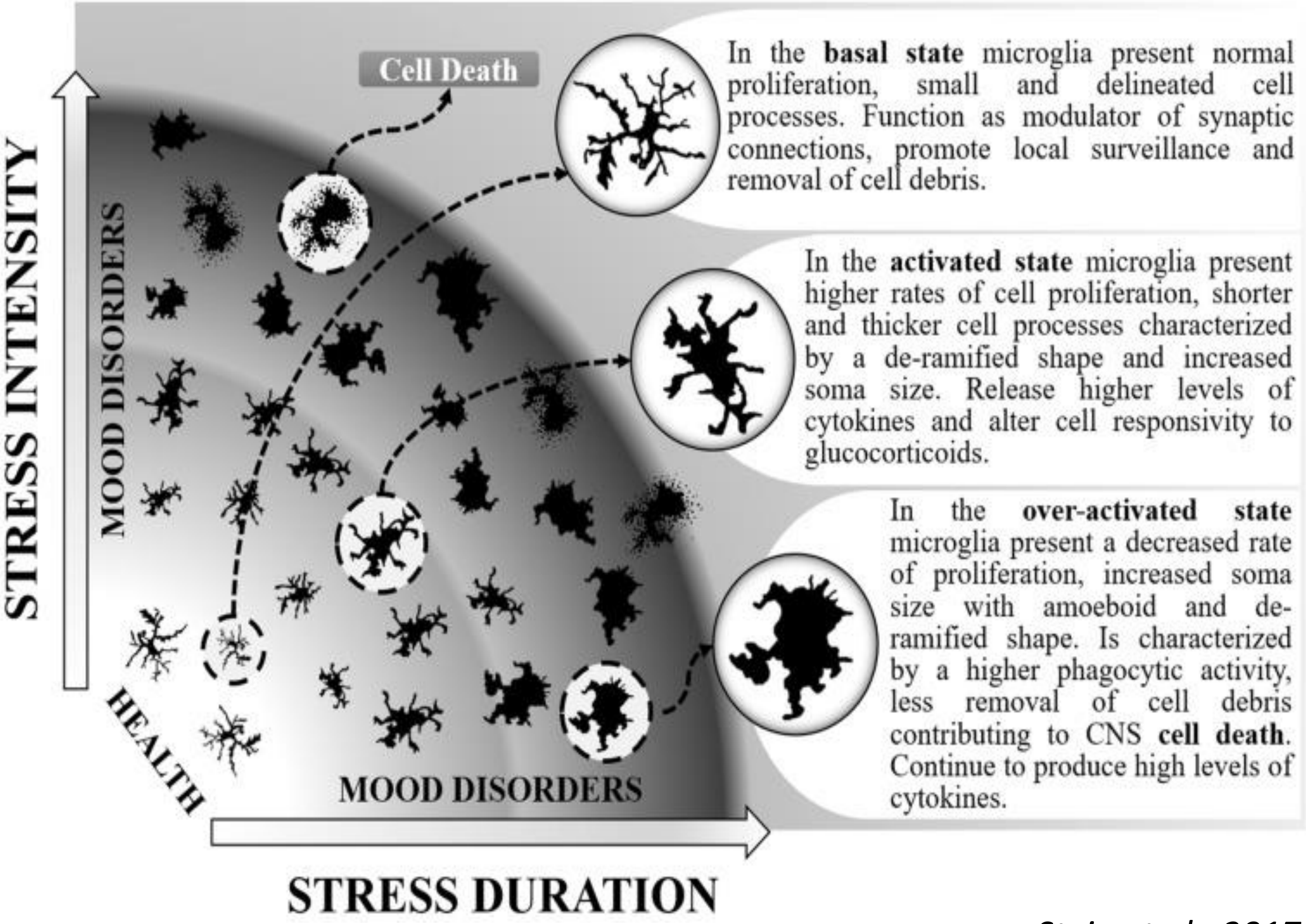
Microglia: multitasking cells within the CNS

- **Innate immune cells of the brain**: first line of defense against any threat to the brain homeostasis

- **Phagocytic activity:** role as the resident macrophages of the CNS

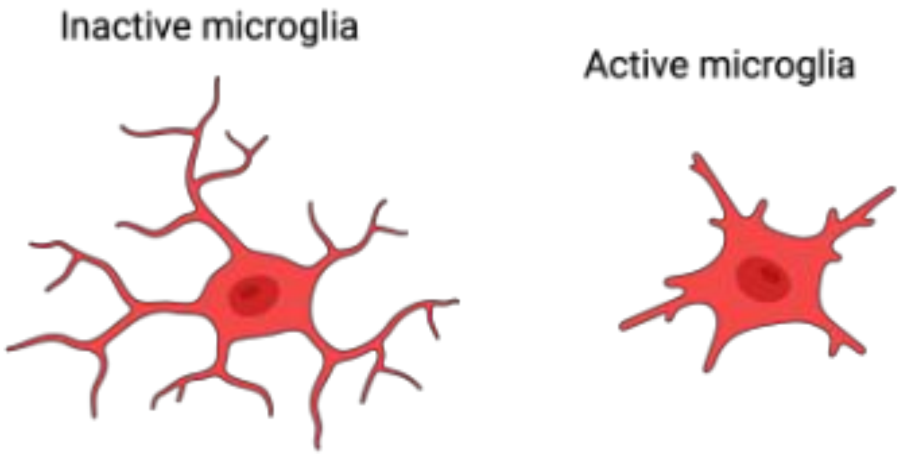
- **Highly active and motile:** constant surveillance of the brain

- **Cellular mediatory of inflammation:** release and respond to cytokines such as IL-6 and TNF-α



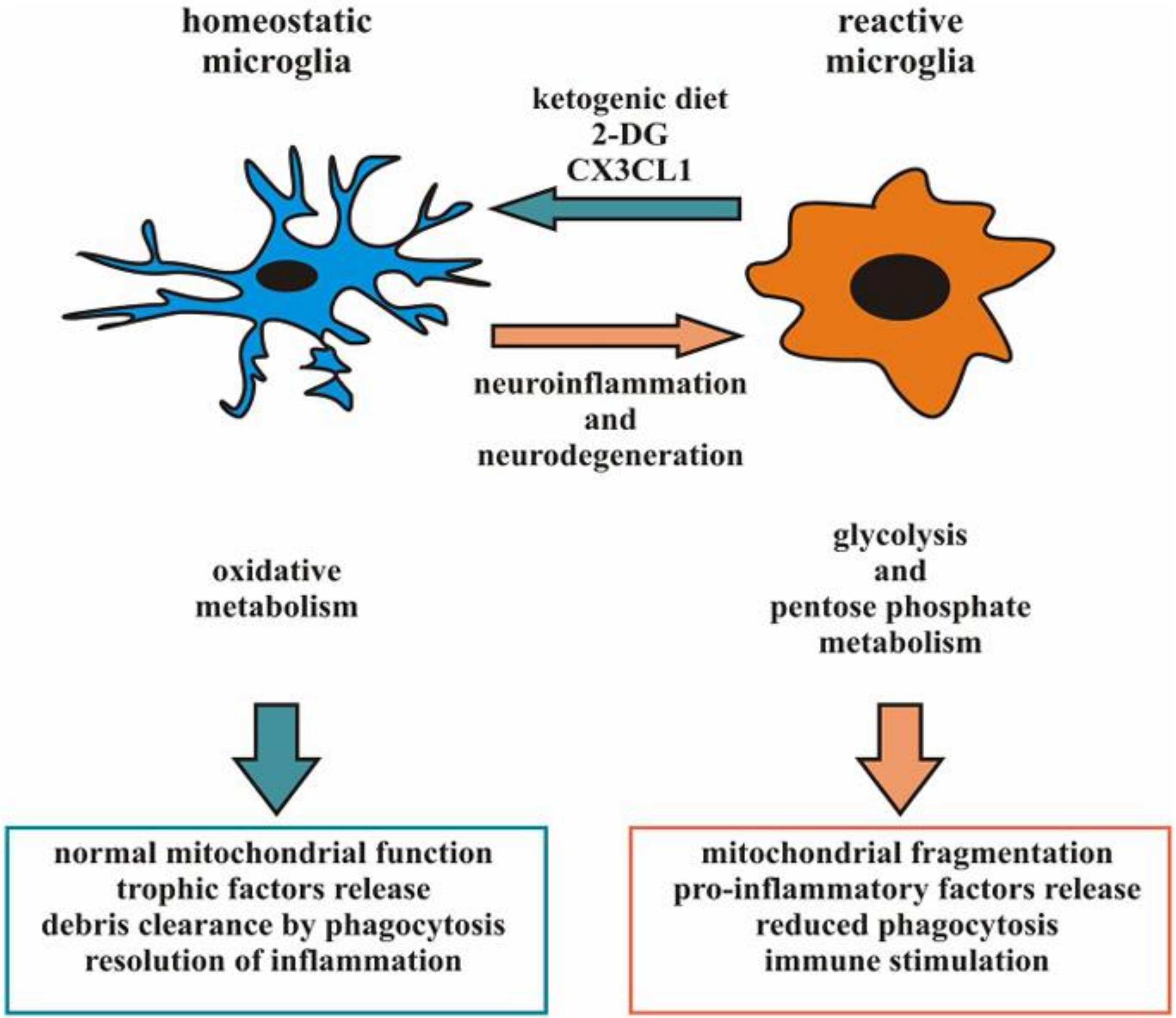
Stein et al., 2017

Does stress induce central inflammation



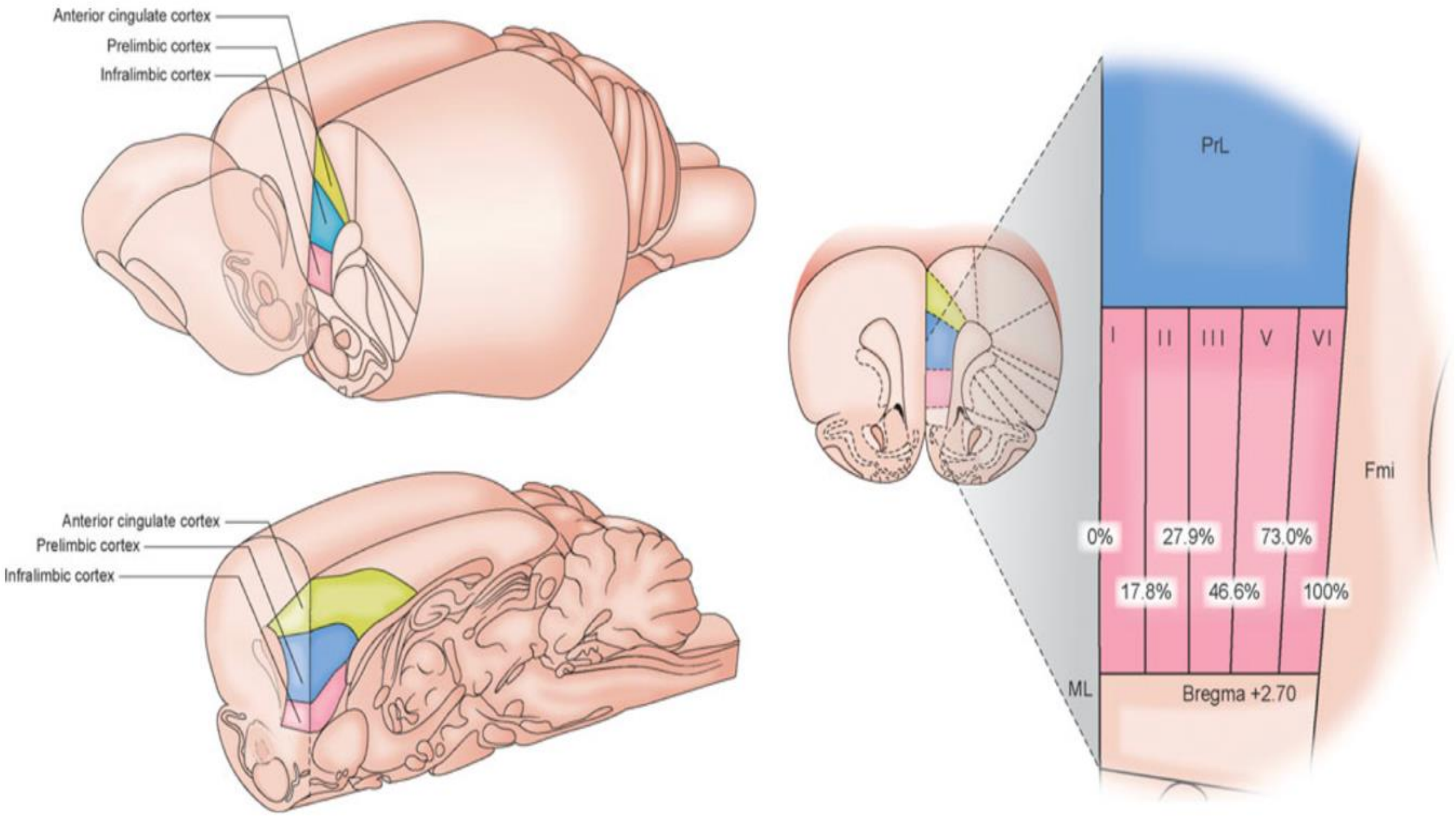
Narimane Bouzourène
PhD Student

Metabolic Reprograming of Microglia in the Regulation of the Innate Inflammatory Response

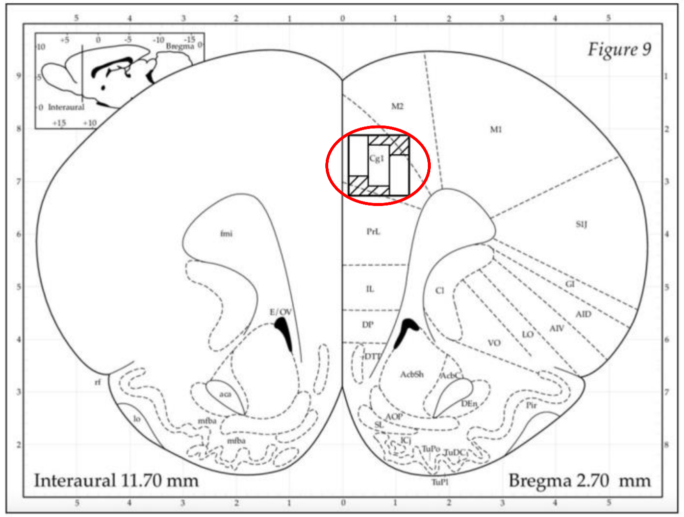


Lauro and Limatela (2020) Frontiers in Immunology

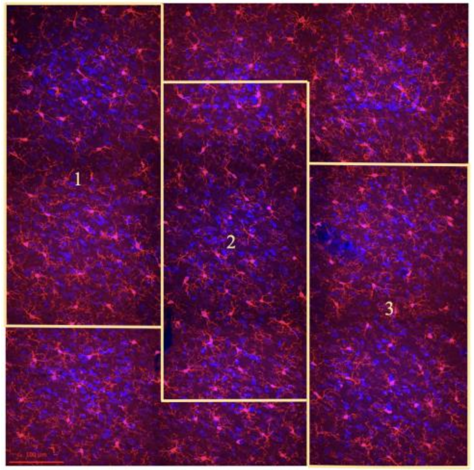
Central Inflammation Analyses



Tynan et al., 2013

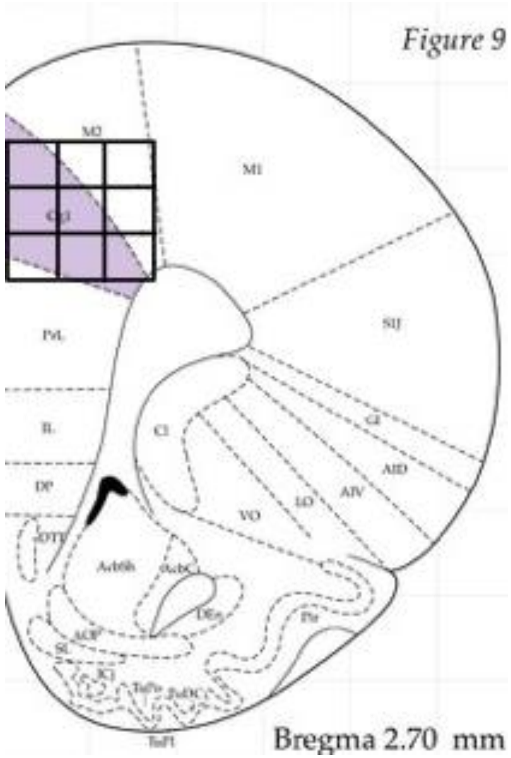


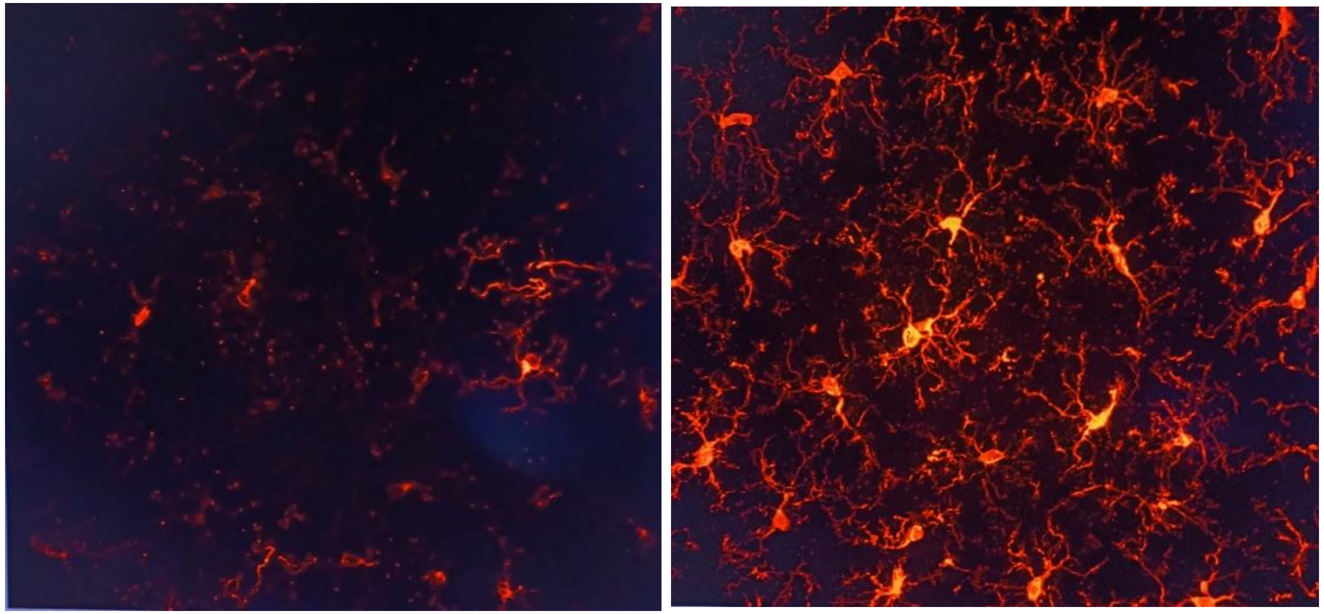
Adapted from Paxinos & Watson, 1982



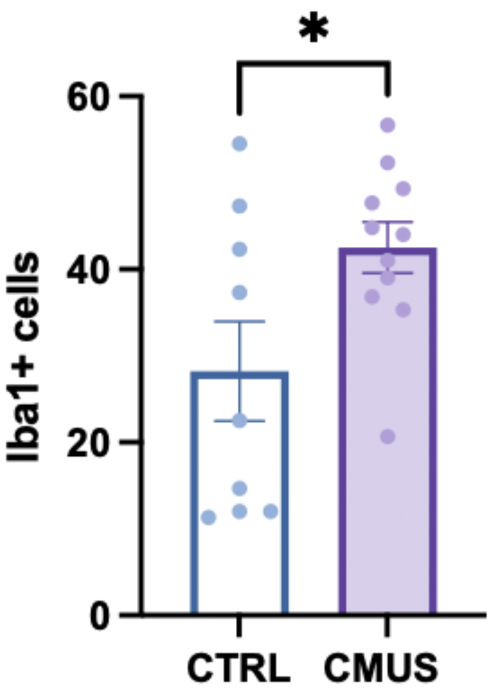
60X,
Iba1,
DAPI,
ROIs

Early stress triggers neuroimmune response within the Anterior Cingulate Cortex





Controls *LSM 780, 40x oil, ACC (Iba1, A594)* CMUS



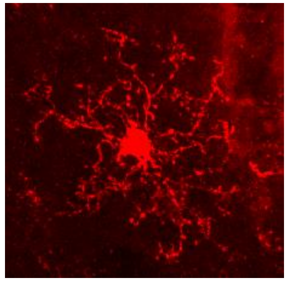
Student unpaired t-test

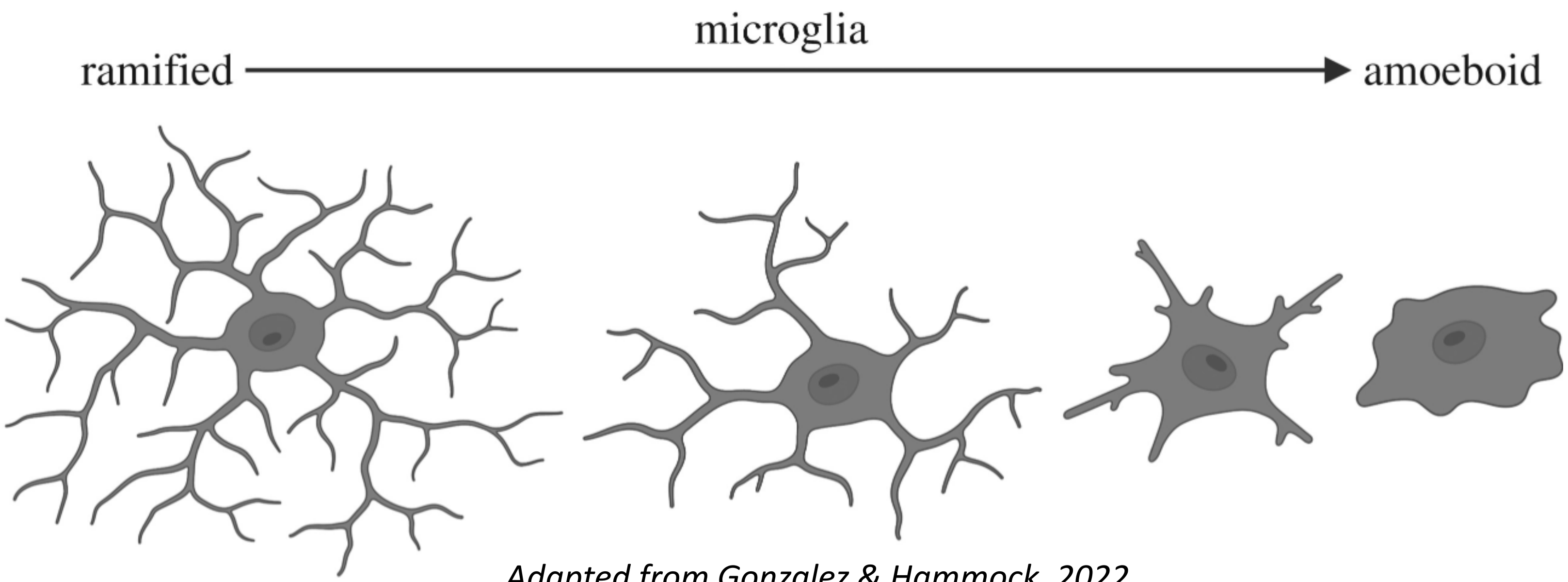
- CMUS from **PND21** to **PND42**
- Sacrificed *(perfusion)* at PND150

- IHC with **Iba1** antibody

Early stress triggers neuroimmune response within the Anterior Cingulate Cortex

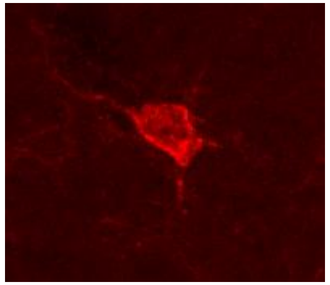
Anti-inflammatory state





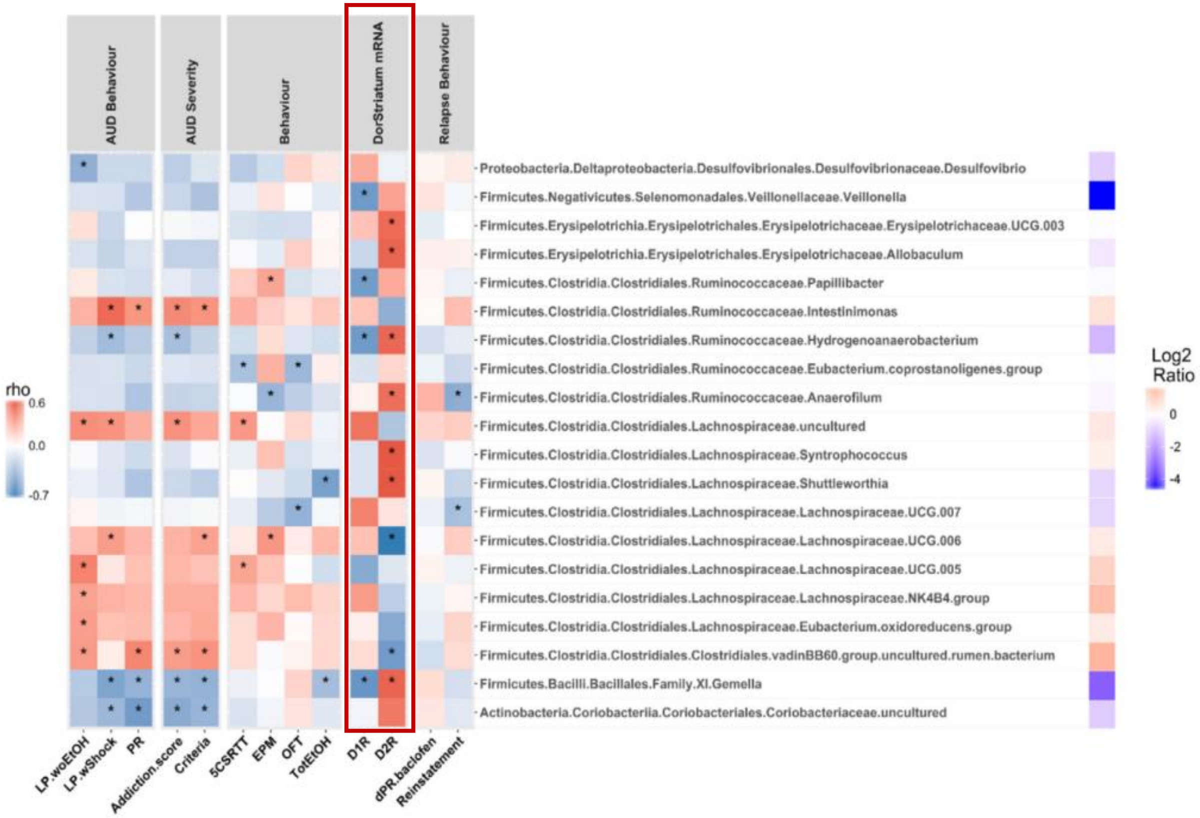
Adapted from Gonzalez & Hammock, 2022

Pro-inflammatory state

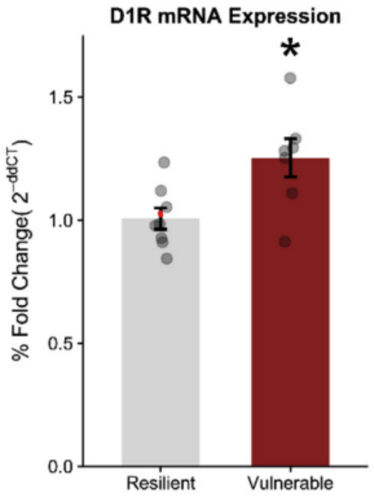


- More microglial cells in stressed rats than in controls
- Microglia of stressed rats have a smaller area, a smaller density, less branches, less junctions and less endpoints than controls
- Evidence for less ramified and more amoeboid-like state

Behavioral predisposition to lose control over alcohol consumption correlates with specific bacterial taxa abundance



Prof John F. Cryan

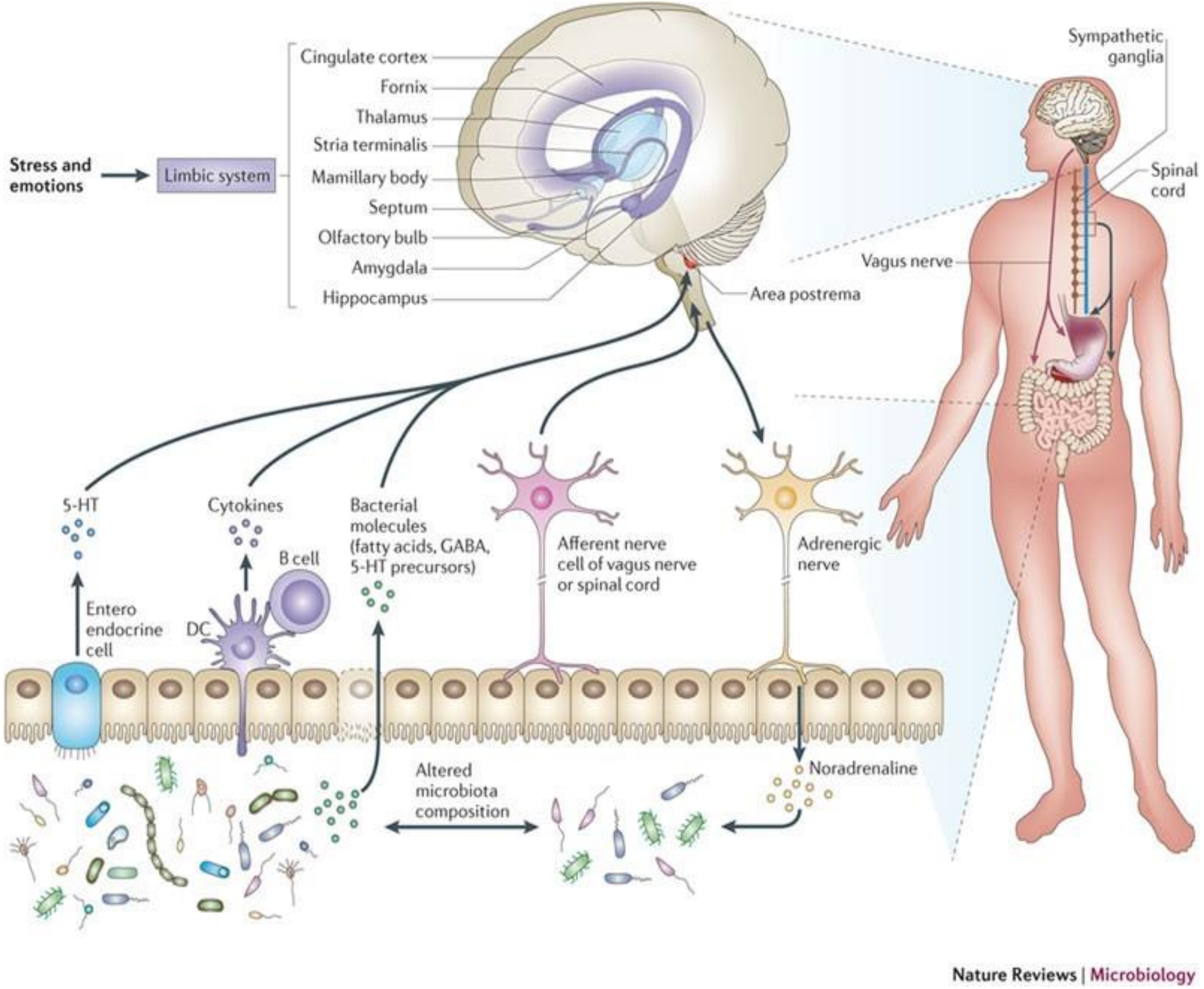


Vulnerable rats have **reduced striatal dopamine 2 receptor (DR2)** expression & **increased DR1** expression

Gut microbiome: Cause or Consequence ?

Jadhav et al., 2018

The bidirectional microbiota gut brain axis

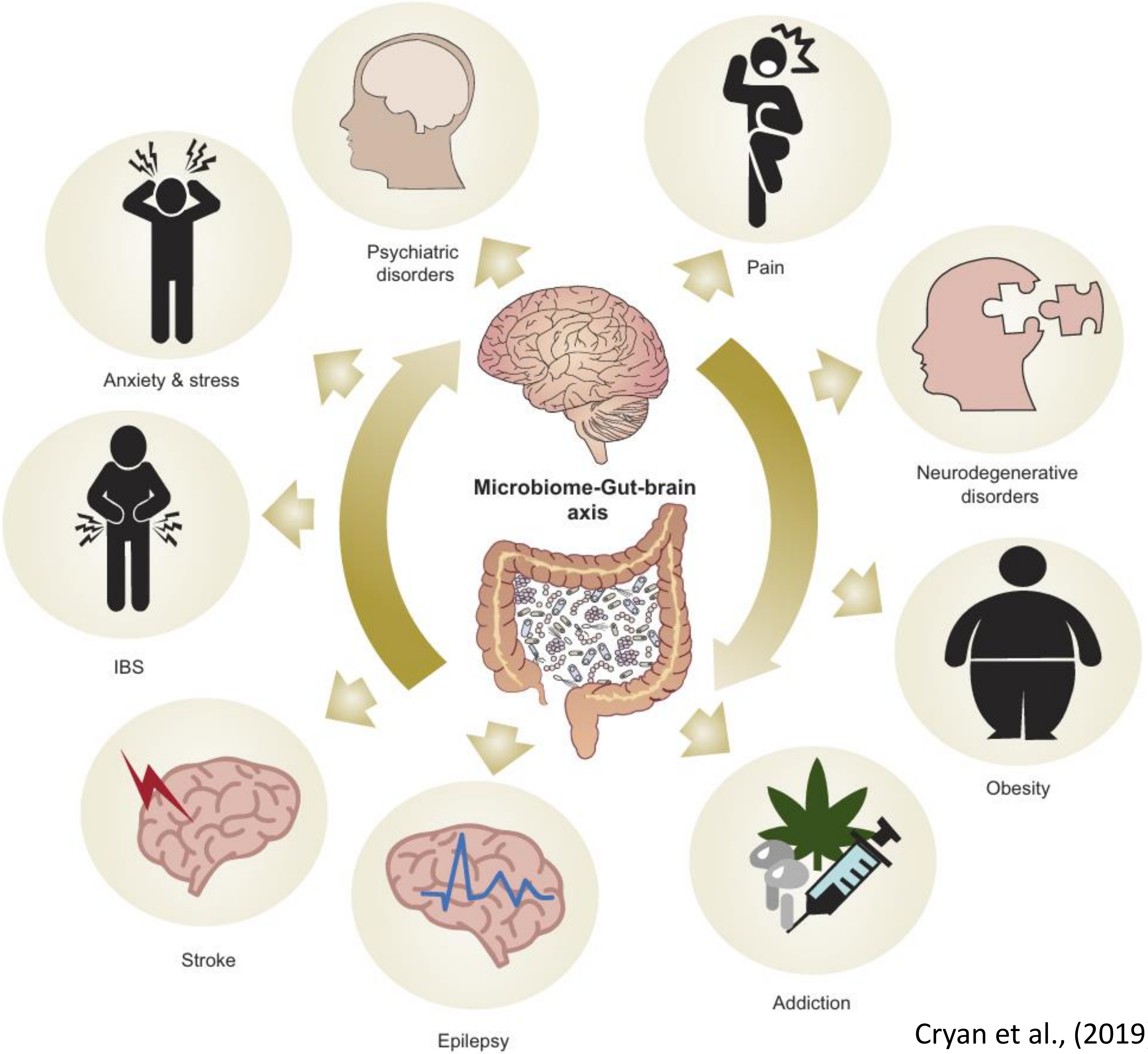


Collins et al., 2012

This communication offers a potential pathway for the gut microbiota and its metabolites to interact with the brain, and this takes place via **neural, immunological, endocrine and metabolic pathways**.

Different ways for bacteria to reach the brain and impact behavior:

- bacterial products that enter the brain through the bloodstream and the area postrema
- cytokine release from mucosal immune cells
- gut hormones release like 5-HT from enteroendocrine cells
- afferent neural pathways as the vagus nerve



Cryan et al., (2019) Physiol Rev 99:1877–2013

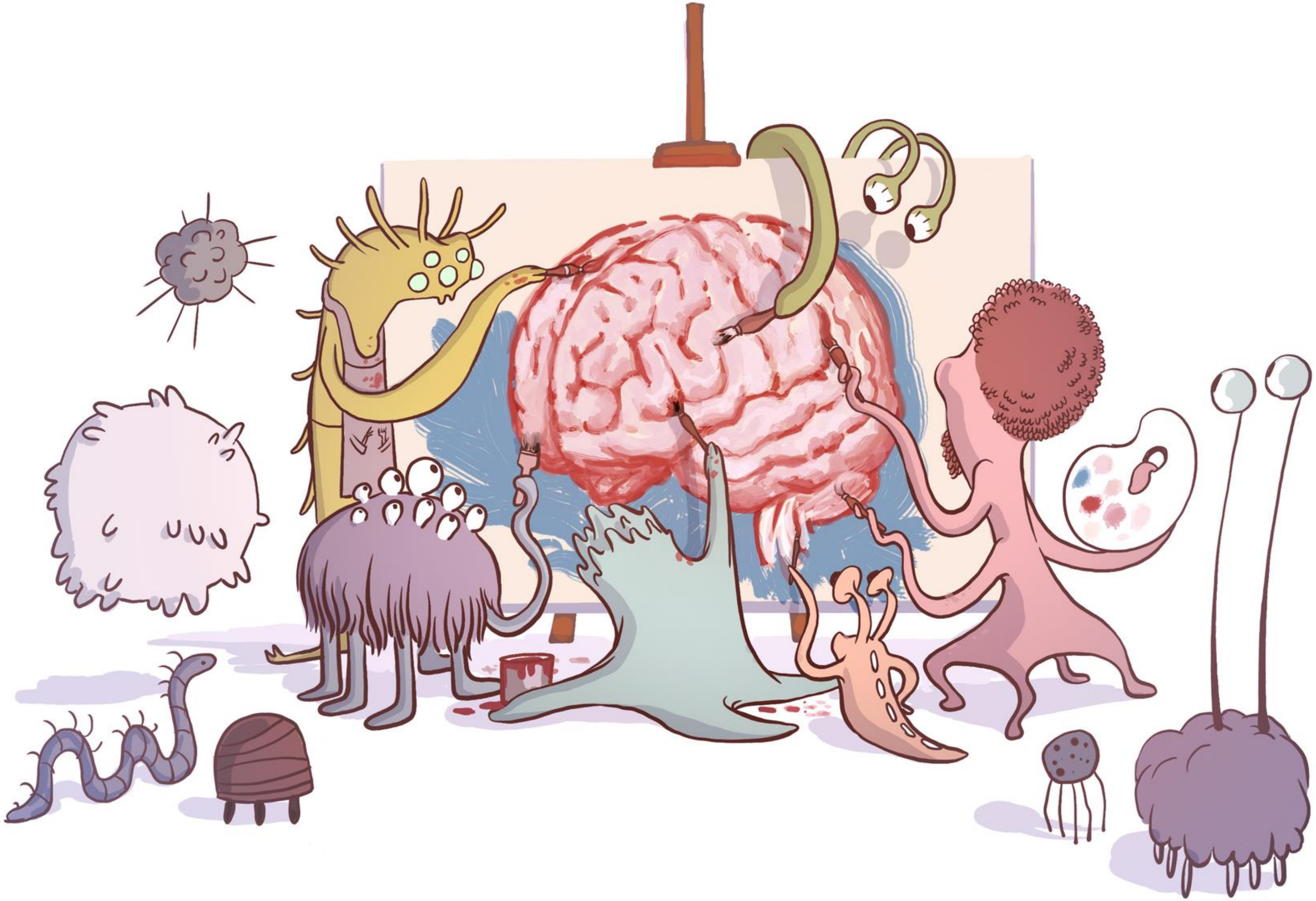


Illustration: Benjamin Arthur for NPR

While the host genome and environment concur to shape the microbiome, the opposite is true as well

- The gut is one of the largest immune organs and a major site of microbial-host interface.
- The host immune system is considered essential for maintaining homeostasis with the microbial commensals, ensuring the beneficial and mutualistic nature of the host-microbial.
- If microbial commensals influence the host social behaviors, and notably mating, then the microbiome might play a significant role in driving the evolution of their hosts, possibly contributing critically to the evolution of metazoan species.

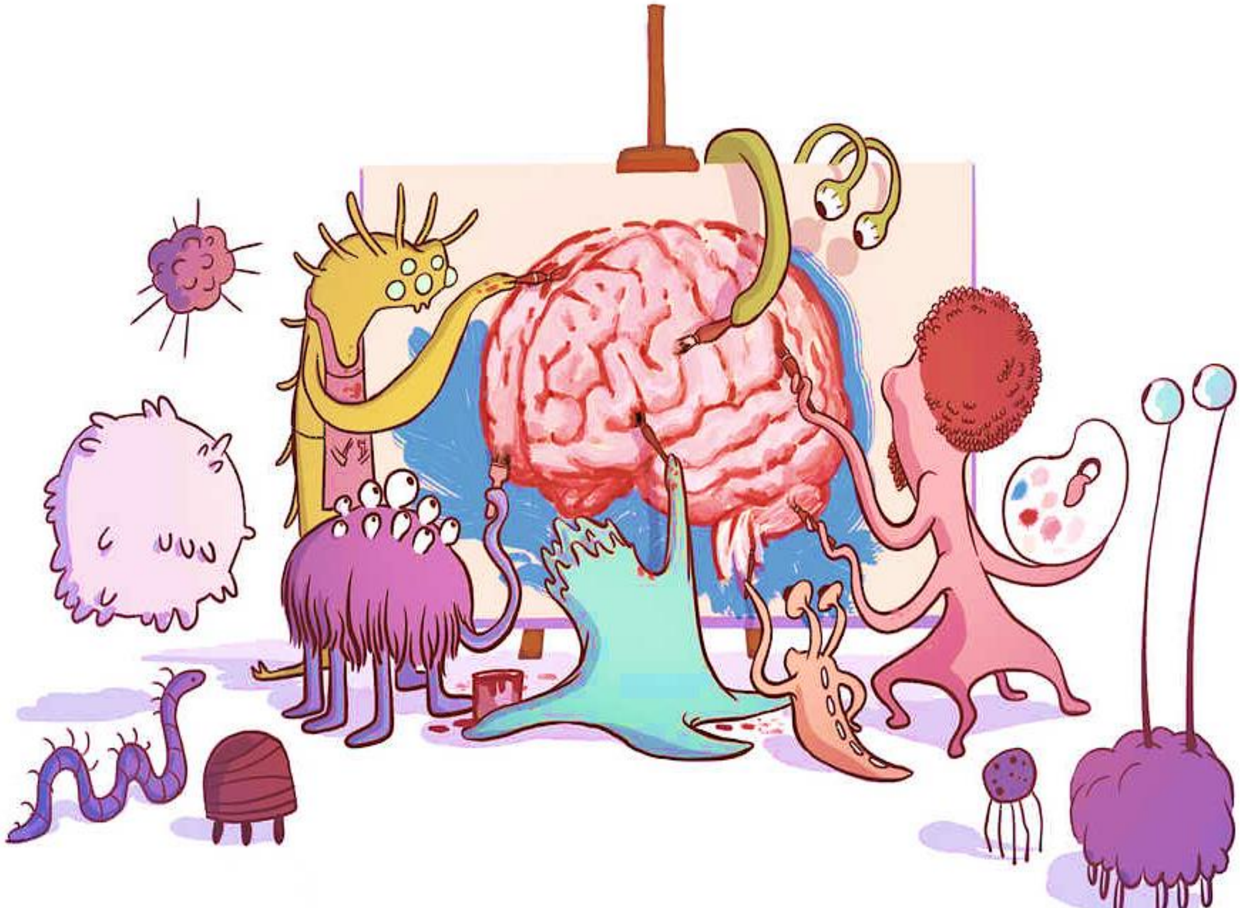


Illustration: Benjamin Arthur for NPR

- The microbiome composition is predominantly shaped by non-genetic factors, suggesting it contributes to adapt the innate host code to the environment pressure, across the lifespan. In particular, the microbiome may play an important role in epigenetic control of gene expression associated with cognition and anxiety.
- Food preferences, social behavior, stress responses, immune functions and cognitive abilities of the host would respond optimally to microbiome variation, to the mutual benefit of the host and microbes.

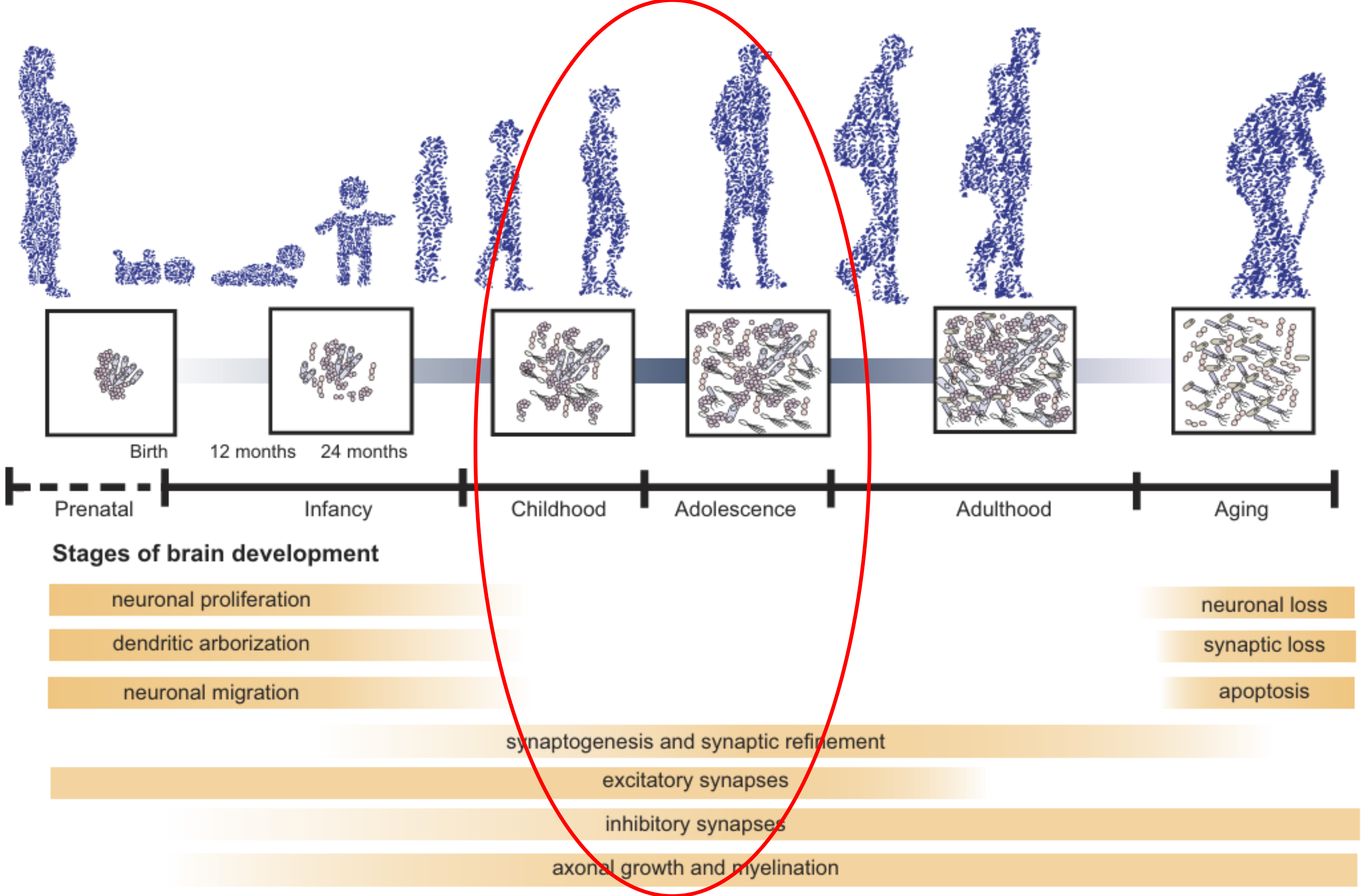
Cryan and Dinan (2012) Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. ***Nat Rev Neuroscience***

Stilling, R.M., et al., (2014) Friends with social benefits: host-microbe interactions as a driver of brain evolution and development? ***Front Cell Infect Microbiol***

Hooper et al. (2012) Interactions between the microbiota and the immune system. ***Science***

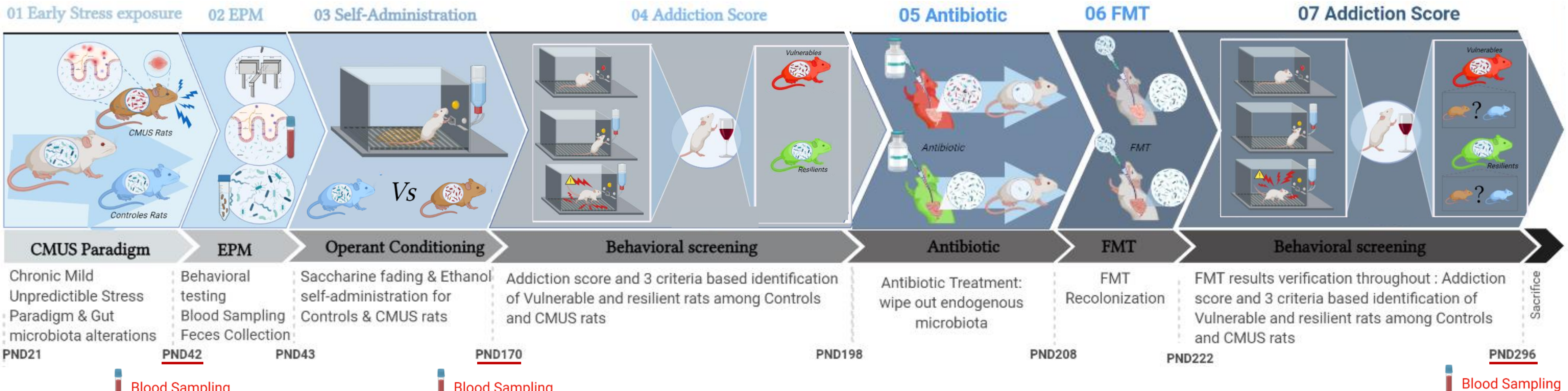
Sampson, T.R. and S.K. Mazmanian, (2015) Control of brain development, function, and behavior by the microbiome. ***Cell Host Microbe***

Morai et al. (2020) The gut microbiota-brain axis in behaviour and brain disorders. ***Nat Rev Microbiol***



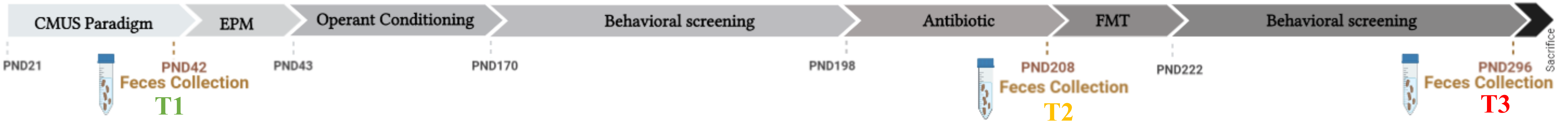
Cryan et al., (2019) Physiol Rev 99:1877–2013

Specific aim: Investigating the causal link between the Gut Microbiota composition, the inflammation response & the vulnerability to lose control over ethanol seeking



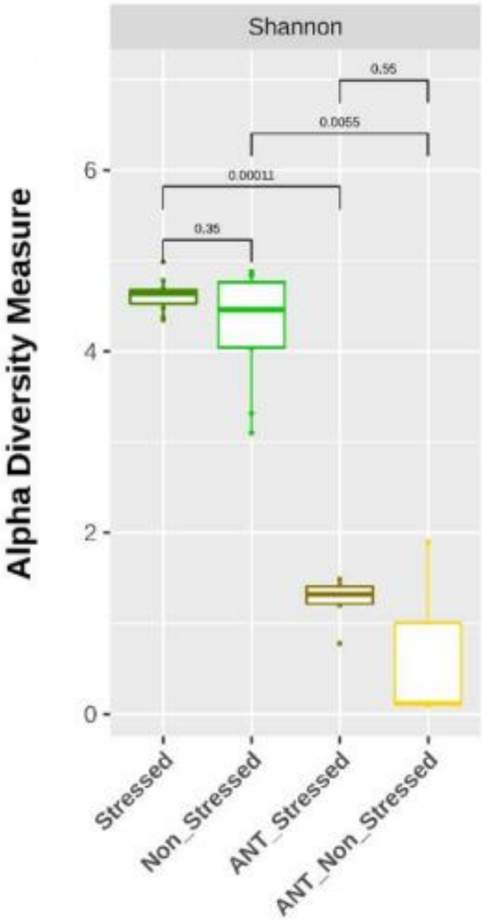
Léa Aeschlimann, PhD student

Results: *Gut Microbiota Analysis*



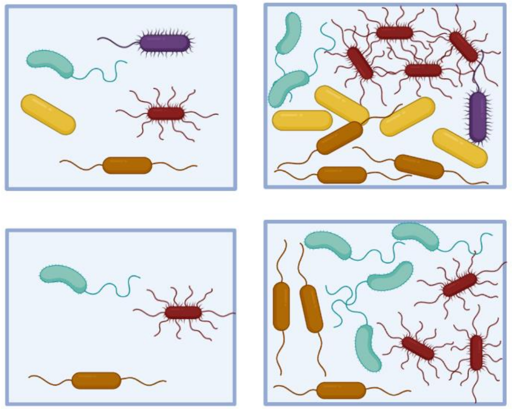
Antibiotic effect on **α-diversity**

FMT effect on **α-diversity**



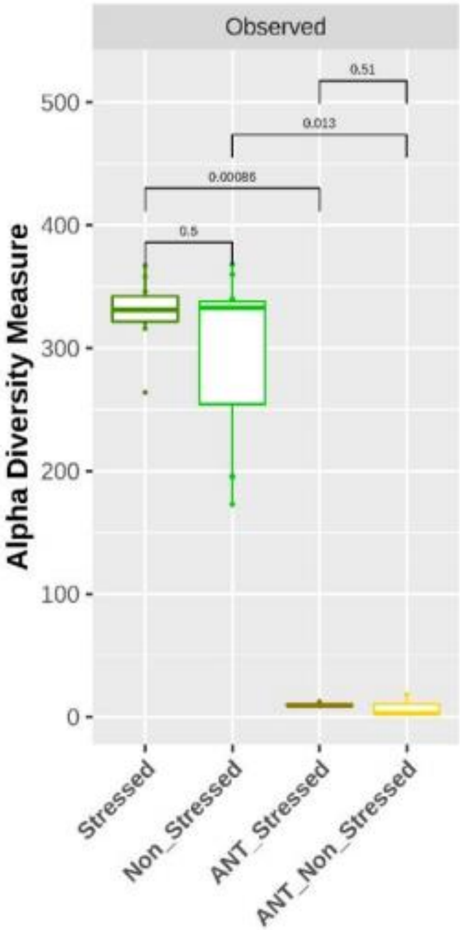
α -diversity : measure of microbiota diversity applicable to a single sample

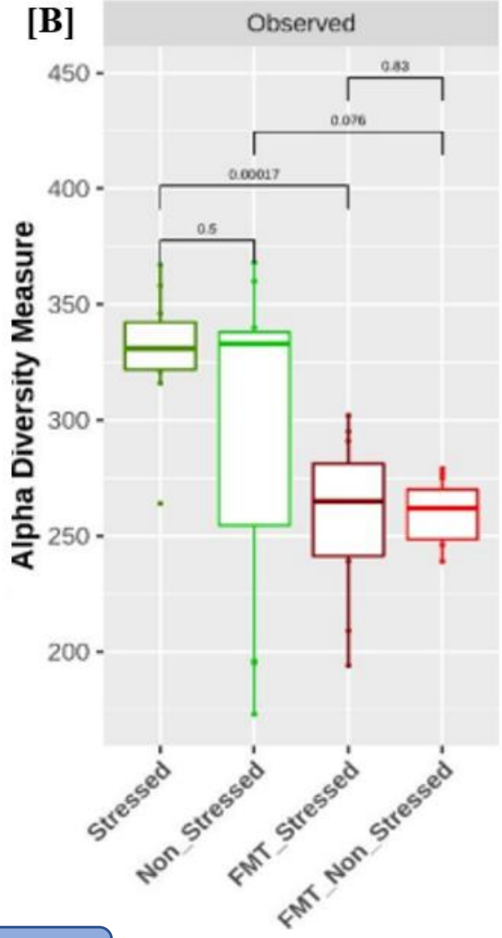
Richness *Eveness*



Number of taxonomic groups

Distribution of abundances of the groups

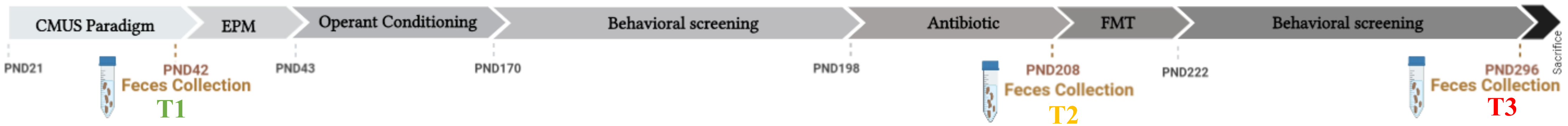




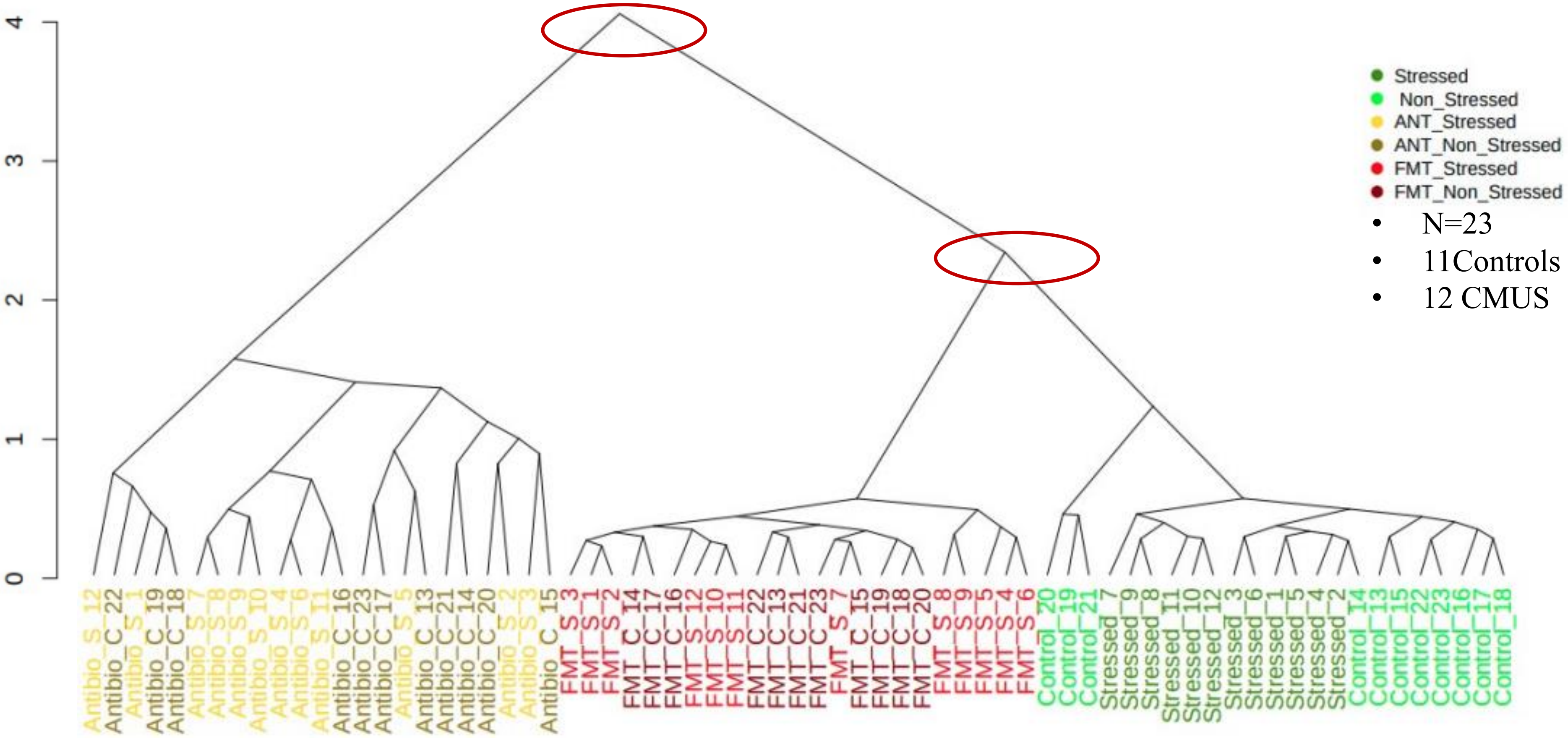
- N=23
- N= 11 Controls
- N=12 CMUS

Antibiotic treatment and FMT modified the gut microbiota of rats

Results: *Gut Microbiota Analysis*



Hierarchical Clustering based on Jaccard Distance

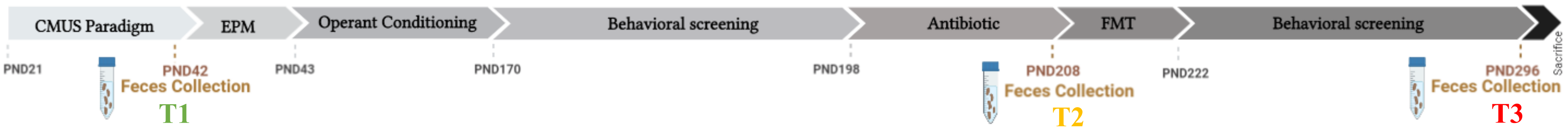


- N=23
- 11Controls
- 12 CMUS

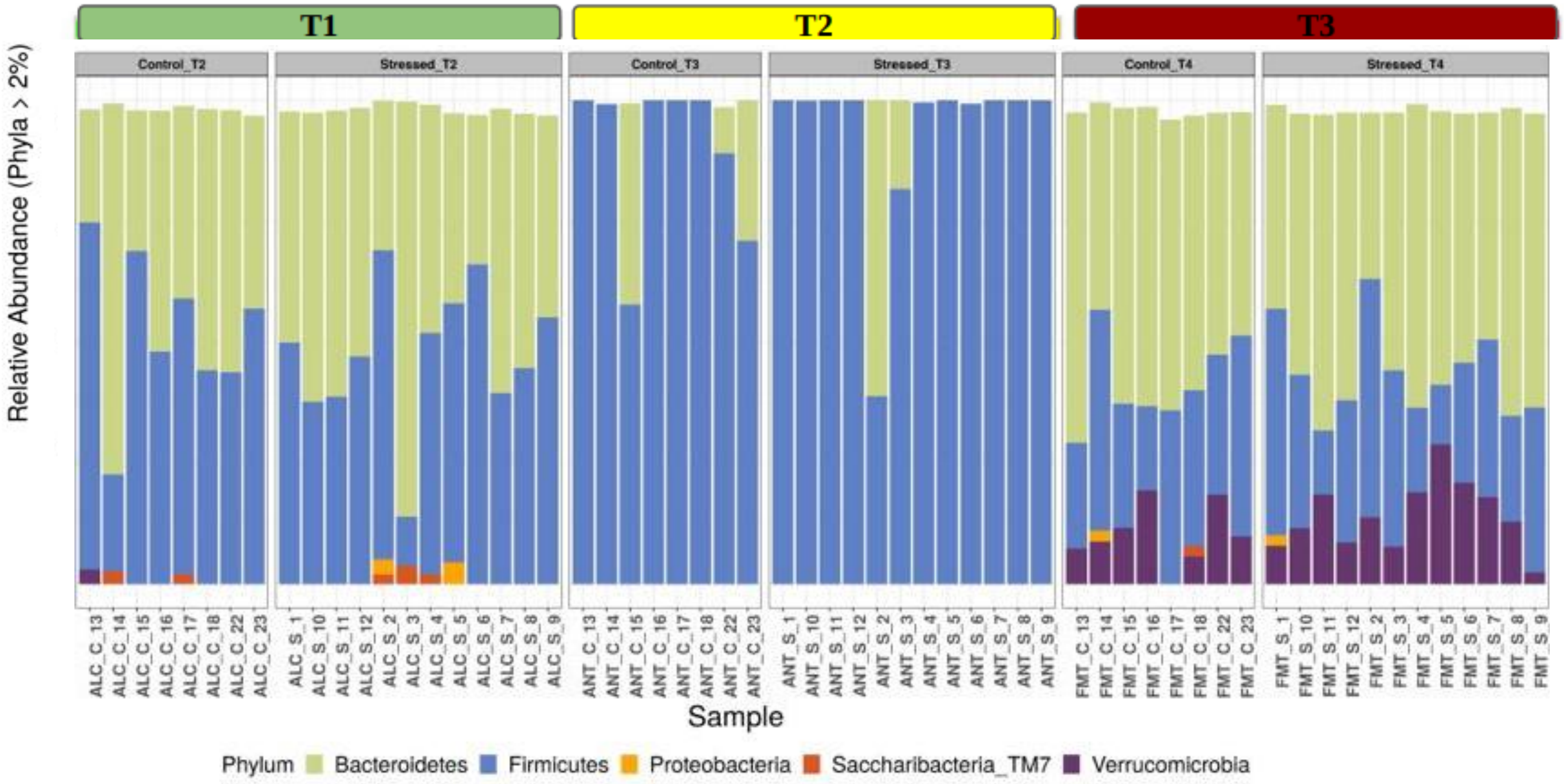
- N=23
- N= 11 Controls
- N=12 CMUS

Hierarchical clustering demonstrates that the FMT clearly modified the gut microbiota of recipient rats

Results: *Gut Microbiota Analysis*



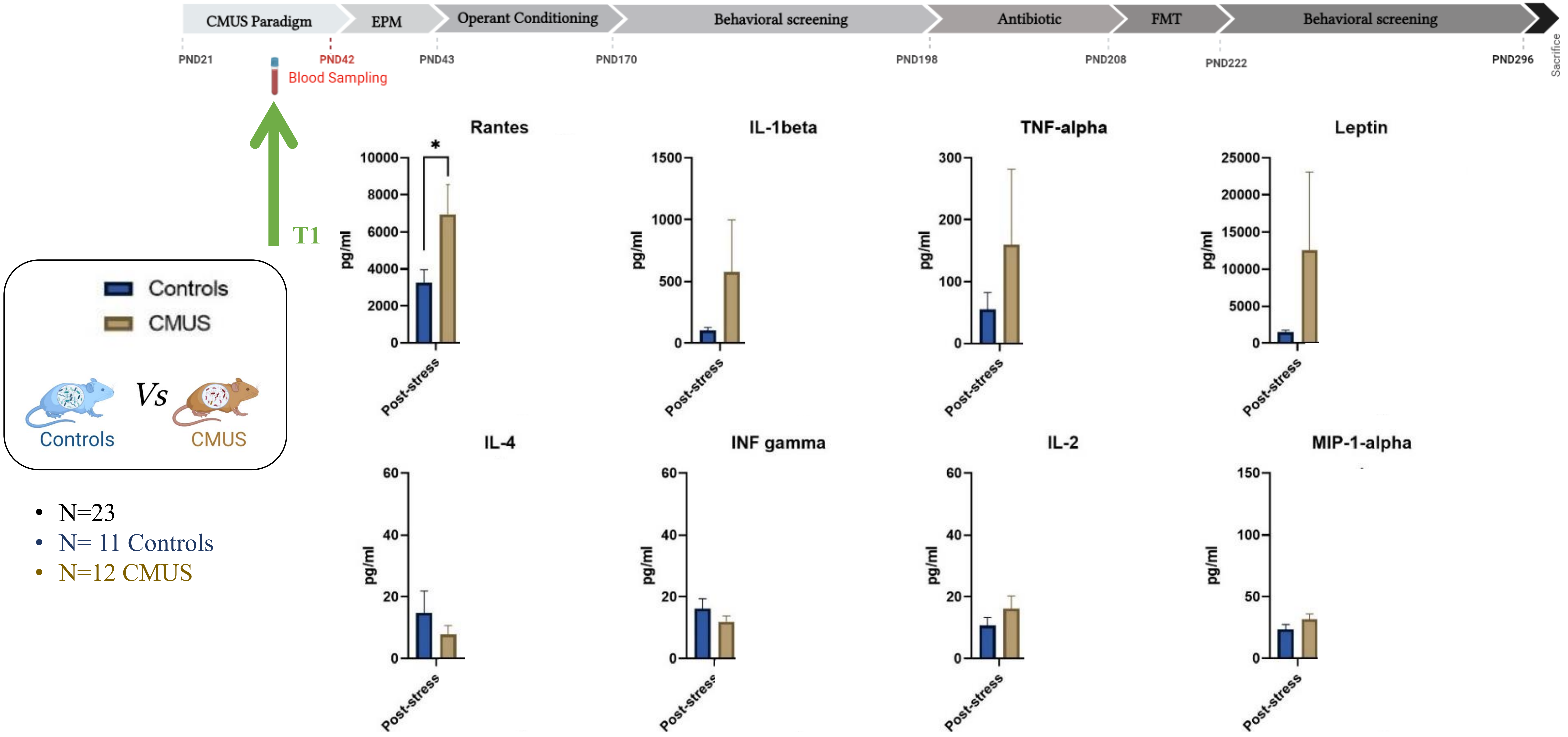
Microbiota Profiling (Phylum)



- N=23
- N= 11 Controls
- N=12 CMUS

- The stacked bar chart represents the abundance of organisms in each sample

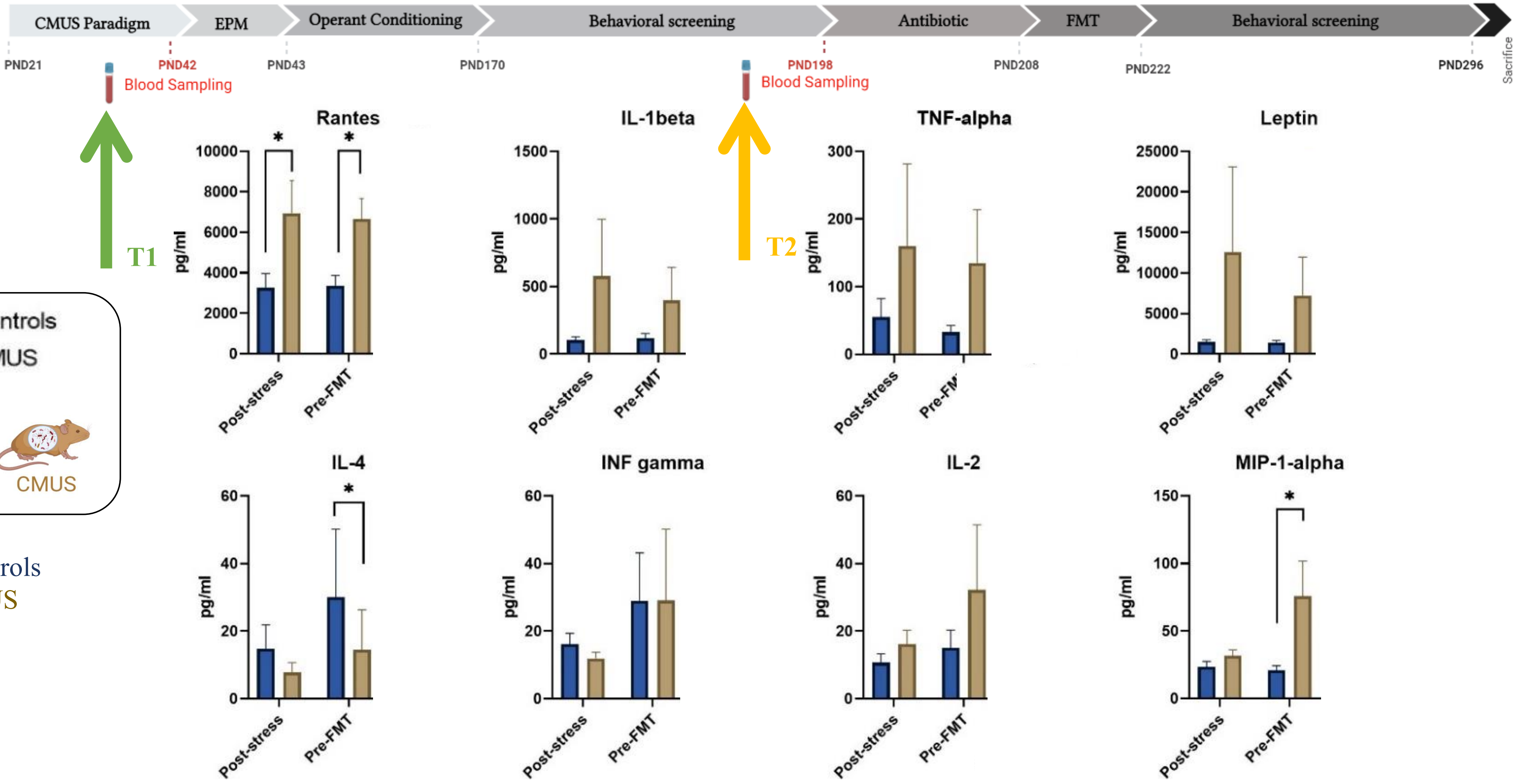
Results: *Peripheral Inflammation Analysis*

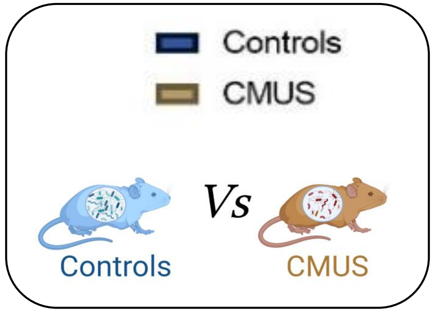


- N=23
- N= 11 Controls
- N=12 CMUS

Stress increases the blood levels of inflammation modulators

Results: *Peripheral Inflammation Analysis*

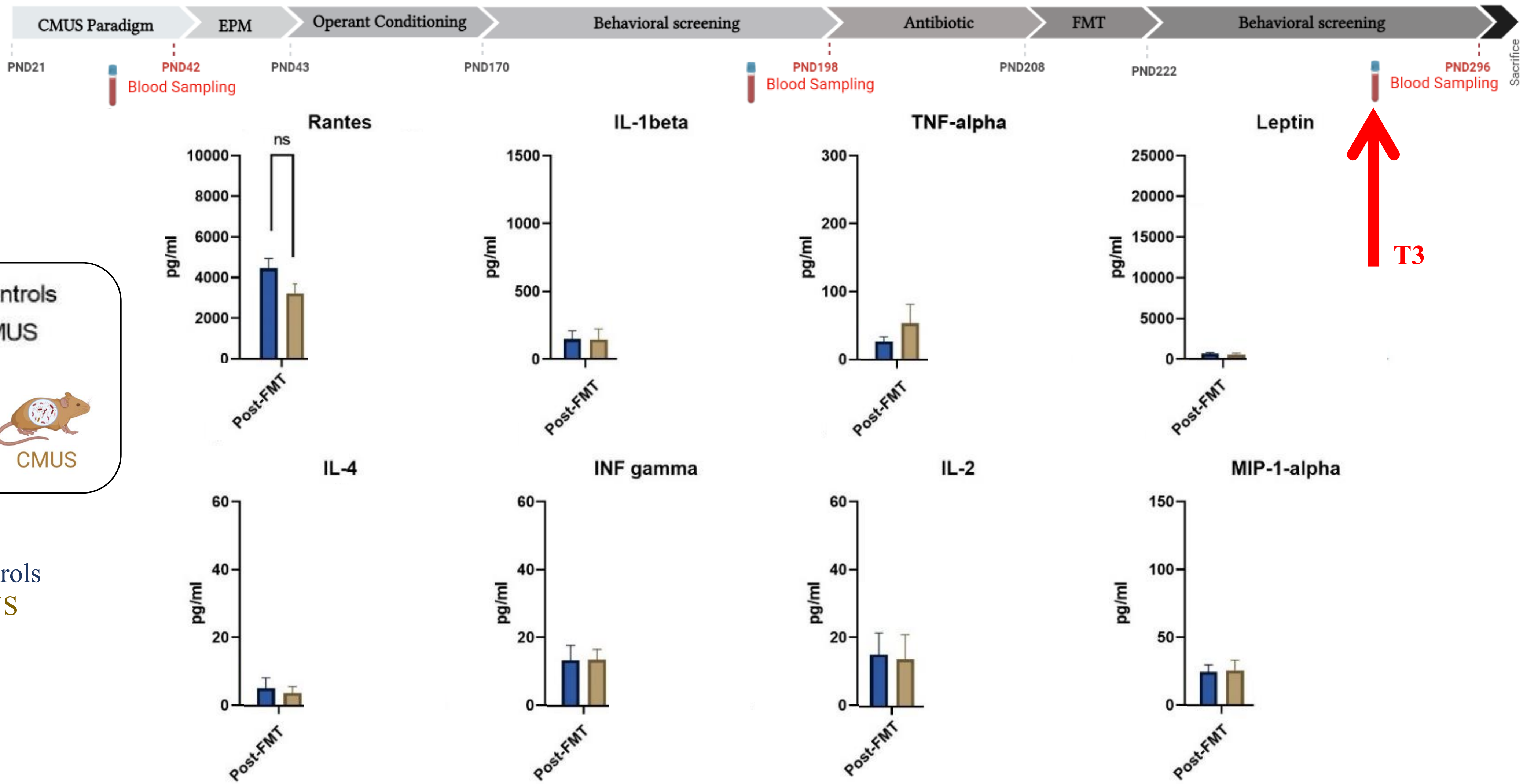


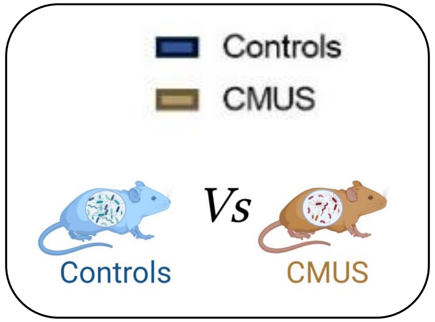


- N=23
- N= 11 Controls
- N=12 CMUS

Stress and alcohol consumption increase the levels of inflammation modulators

Results: *Peripheral Inflammation Analysis*





- N=23
- N= 11 Controls
- N=12 CMUS

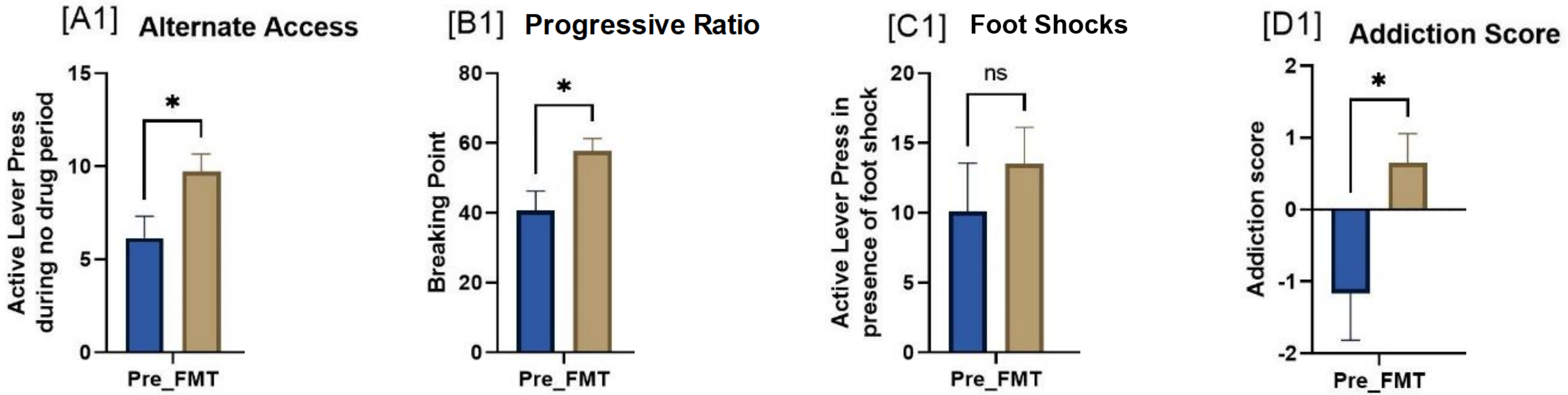
FMT lowered the levels of inflammation modulators in stressed rats

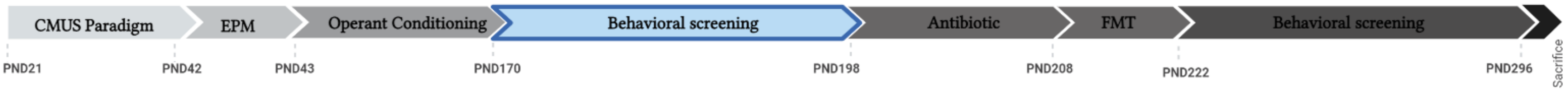
Stress increases the vulnerability to lose control in CMUS rats

Pre-FMT:

Addiction-like behavior screening in **Control** and **CMUS** rats

- N=39
- N= 14 Controls
- N=25 CMUS
- PND 170





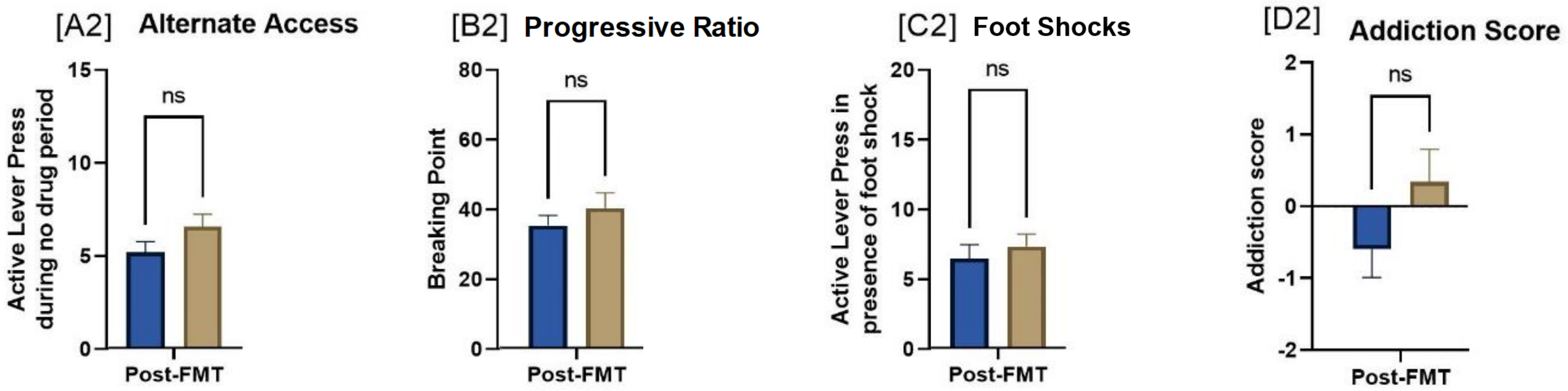
Results: *Behavioural Screening*

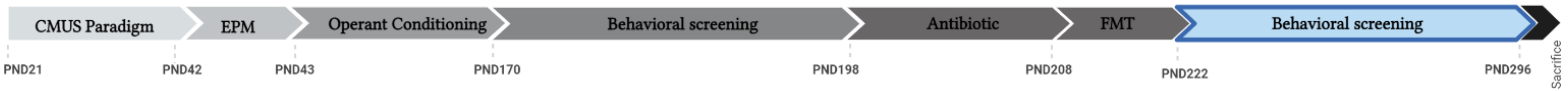
FMT reduces Addiction-like Behaviours

Post-FMT:

Addiction-like behavior screening in **Control** and **CMUS** rats

- N=39
- N= 14 Controls
- N=25 CMUS
- PND 170
- **DONORS: naïve rats similar to controls**





Conclusion

- Stress is ubiquitous in life and short-term neurocircuit adaptations are essential for adjustment to temporary stressors. Whereas these adaptations can be beneficial in dealing with short-term stressors, they can be detrimental to developing brain circuits and behavior when the stress is sustained over a longer period of time.

- Chronic Mild Unpredictable Stress prevents the fine tuning of brain networks during adolescence ultimately triggering a wide array of maladaptive behaviors

- Rats continue to express adolescent-like impulsive, hyperactive, and compulsive behaviors into late adulthood.

- Hypoexcitability of prelimbic cortex (PLC) pyramidal neurons (PN) and reduced PLC-mediated synaptic glutamatergic control of BLA and nucleus accumbens core (NAcC) neurons that lasts late into adulthood.
- Chemogenetic reversal of this PLC hypoexcitability decreased compulsivity and improved the expression of goal-directed behavior in rats exposed to stress during adolescence

We identified a long-lasting peripheral inflammation in stressed rats and not only fecal microbiota transfer lowered stressed rats' preference for alcohol but it restored inflammation modulators levels to those observed in controls.

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