

Chronic exposure to antiseizure drugs impacts the gut microbiome community and function

Camille Dop¹, Stephane Auvin², Patricia Lepage¹, Zehra Esra Ilhan¹

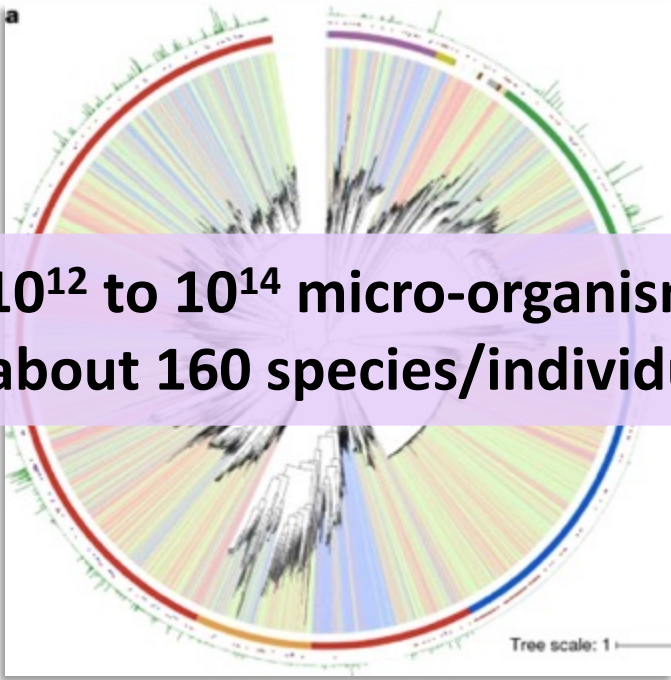
¹ Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Domaine de Vilvert, Jouy-en-Josas 78350, France

² APHP, Robert Debré University Hospital, Pediatric Neurology Department, Paris, France & Université de Paris, INSERM NeuroDiderot, Paris, France

The human microbiome evolves and adapts over time

Composition

- Phylum
- Actinobacteria
 - Bacteroidetes
 - Cyanobacteria
 - Firmicutes
 - Fusobacteria
 - Proteobacteria
 - Saccharibacteria
 - Spirochaetes
 - Synergistetes
 - Tenericutes
 - Verrucomicrobia



Evolution

Core microbiome

Tentative relative proportions of microbial phyla

- Firmicutes
- Bacteroides
- Actinobacteria
- Proteobacteria

Bacteroides; Bifidobacteria

Firmicutes; Bacteroides

Bacteroides; Firmicutes



Infancy



Puberty



Adulthood

Ravinder et al. (2018), Nutrition and Healthy Aging

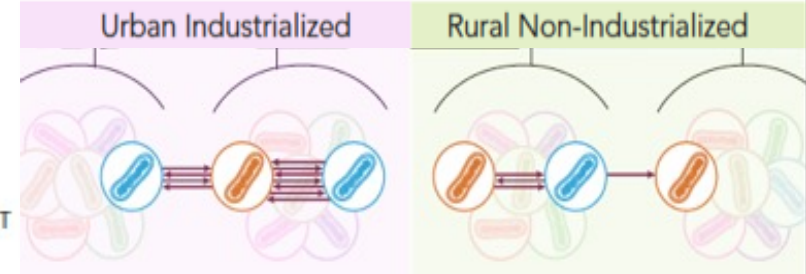
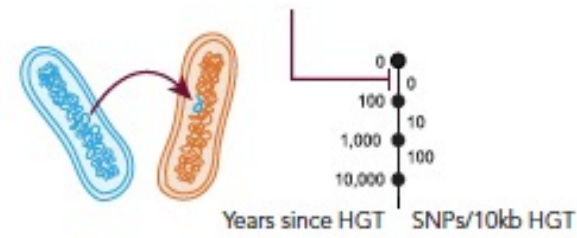
Adaptation

10^{12} to 10^{14} micro-organisms about 160 species/individual

Microbiome



Horizontal gene transfer (HGT)



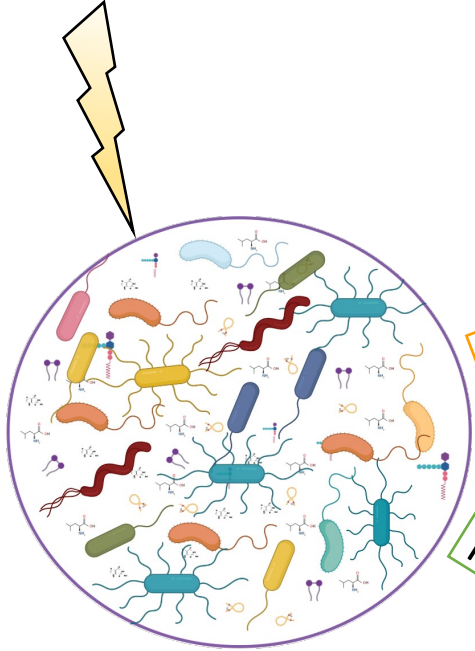
HGT is common in the human microbiome; Increases with industrialisation

Almeida et al.(2019), Nature

Groussin et al. (2021) Cell

Xenobiotics alter complex microbial communities

Xenobiotics

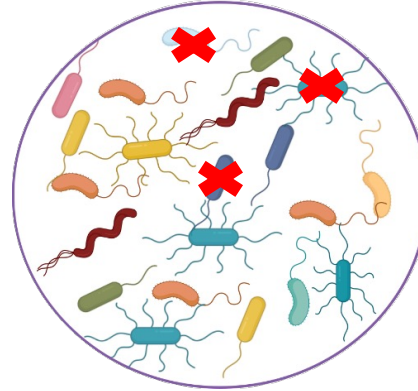


microbial communities

Composition

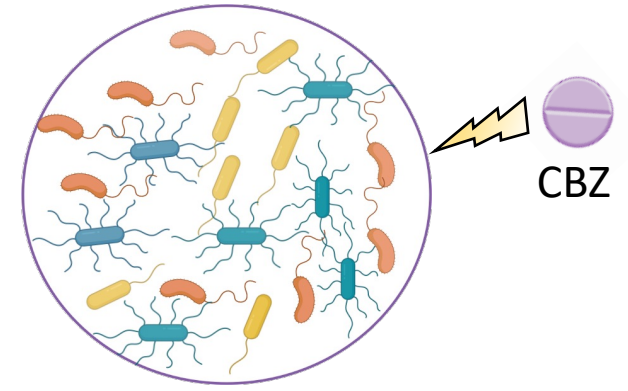
Metabolic function

Anti-microbial properties of antipsychotics drugs



Maier et al.(2018), Nature

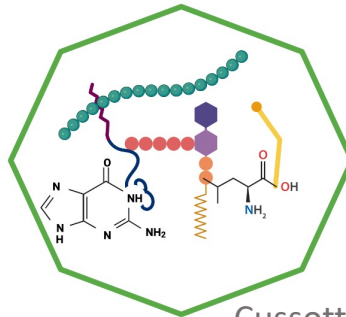
Shift in the microbial composition



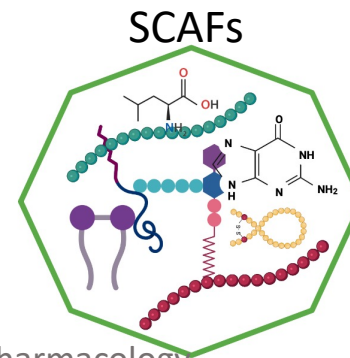
Environmental microbial communities

Zhang et al. (2020), Bioresource Technology

Zhang et al. (2020), Bioresource Technology



Valproate



Propionate and Butyrate

Isovalerate

Cussotto S et al.(2019), Psychopharmacology

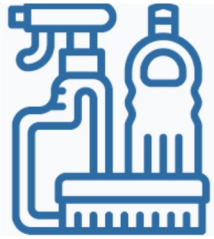
Children's gut microbiome are vulnerable to xenobiotics



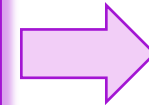
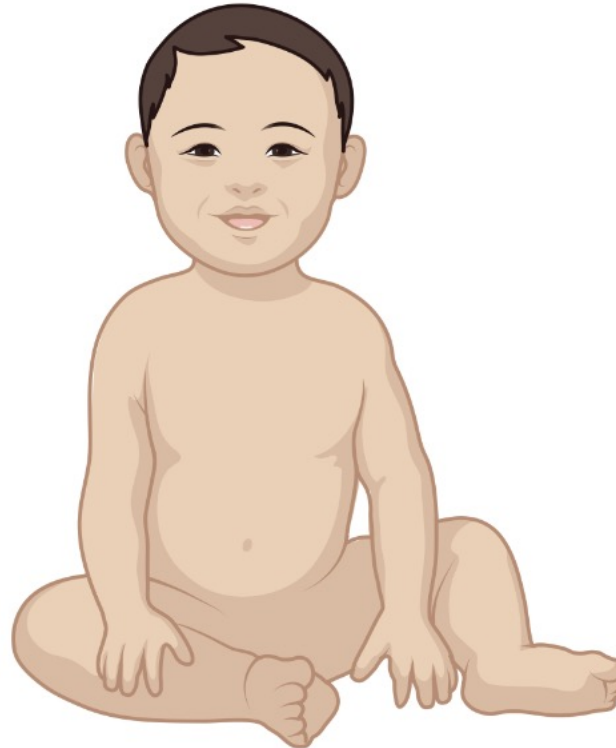
Food



Pesticides



Cleaning supply



Antiseizure drugs

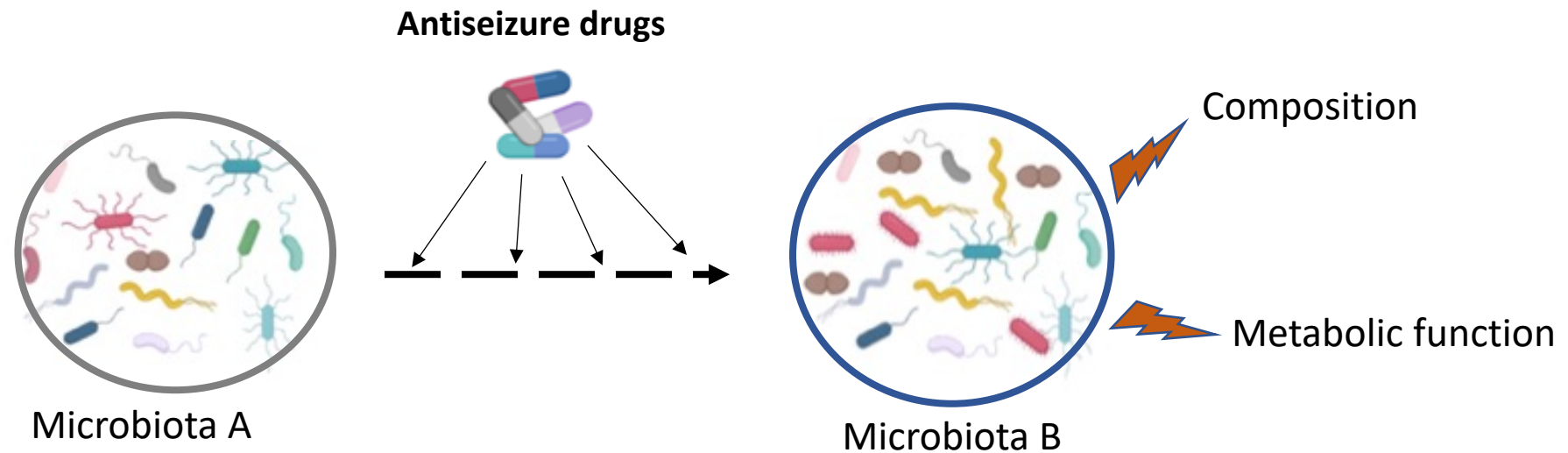


Industrial pollution

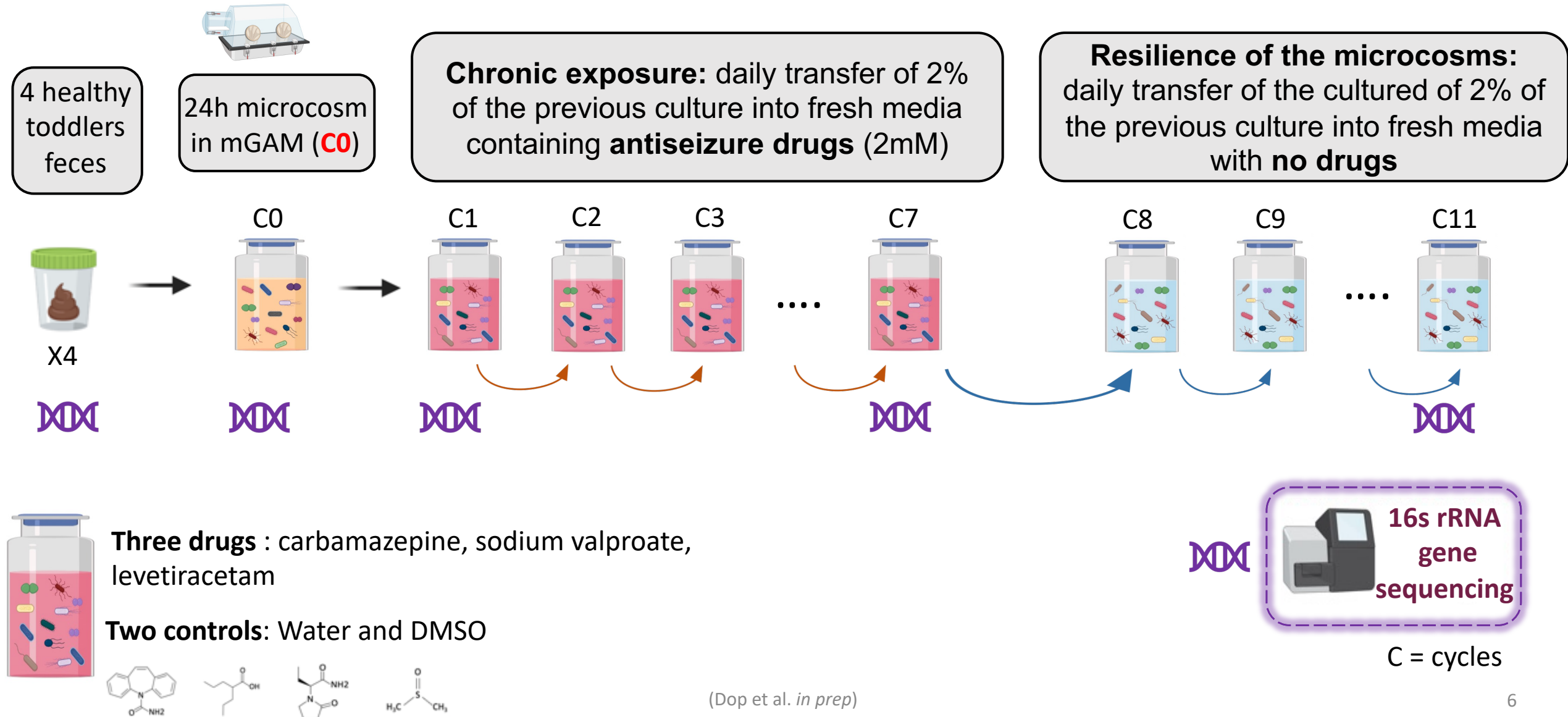


Cream/ shampoo

How does longitudinal exposure to antiseizure drugs (carbamazepine, sodium valproate, and levetiracetam) influence the early life gut microbiome structure and function?

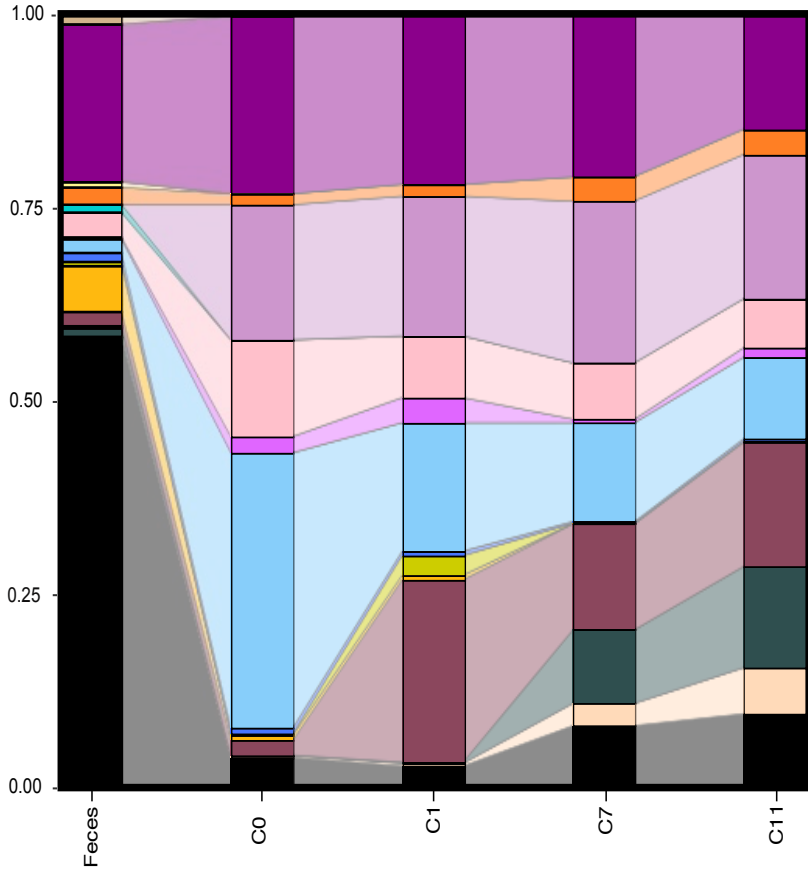


Our experimental approach relied on establishing semi-continuous microcosms

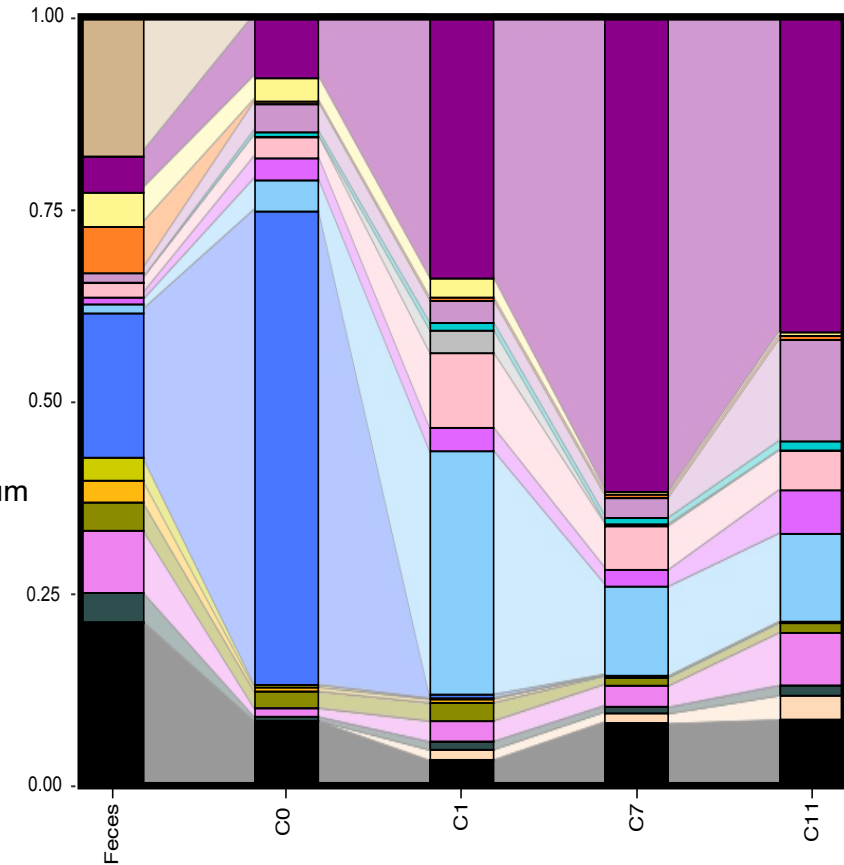


1. Feces composition was the main determinant of the microcosm structure during semi-continuous cultivation

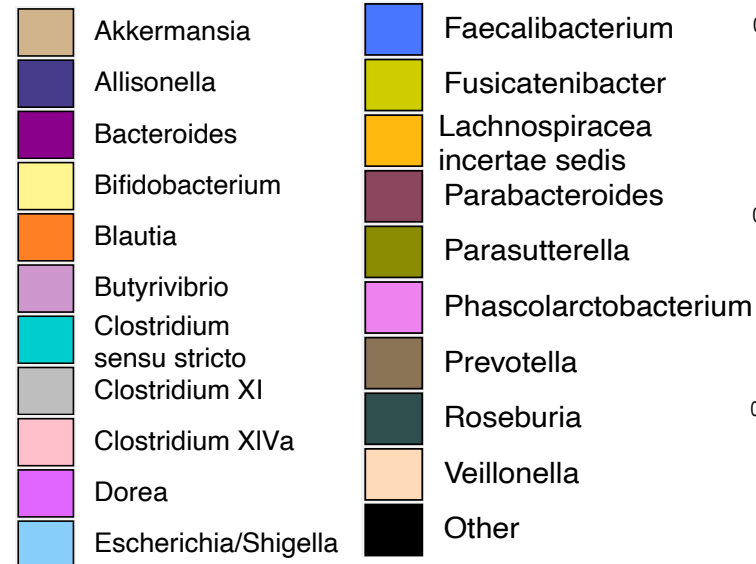
Feces A



Feces D



Genus

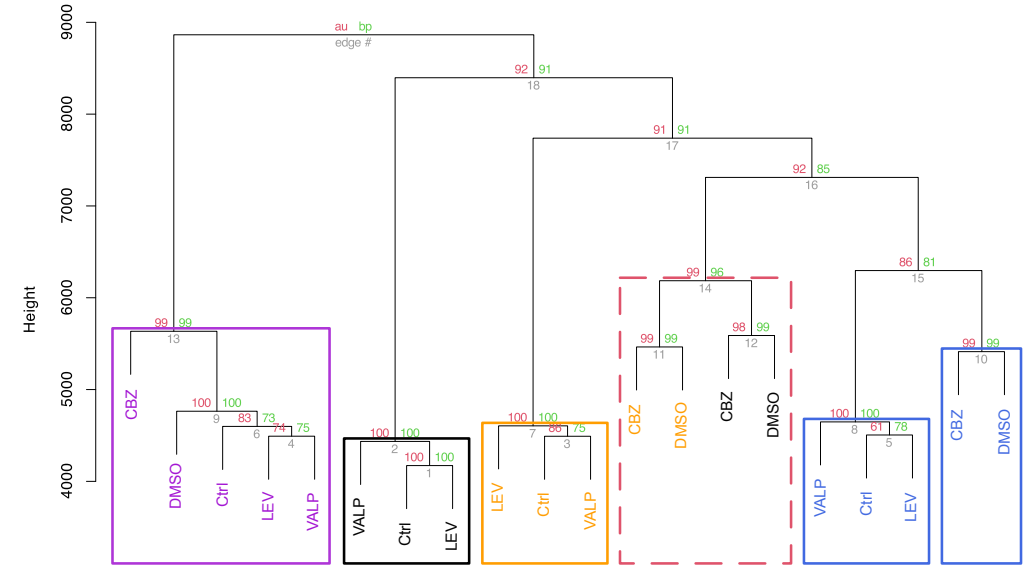
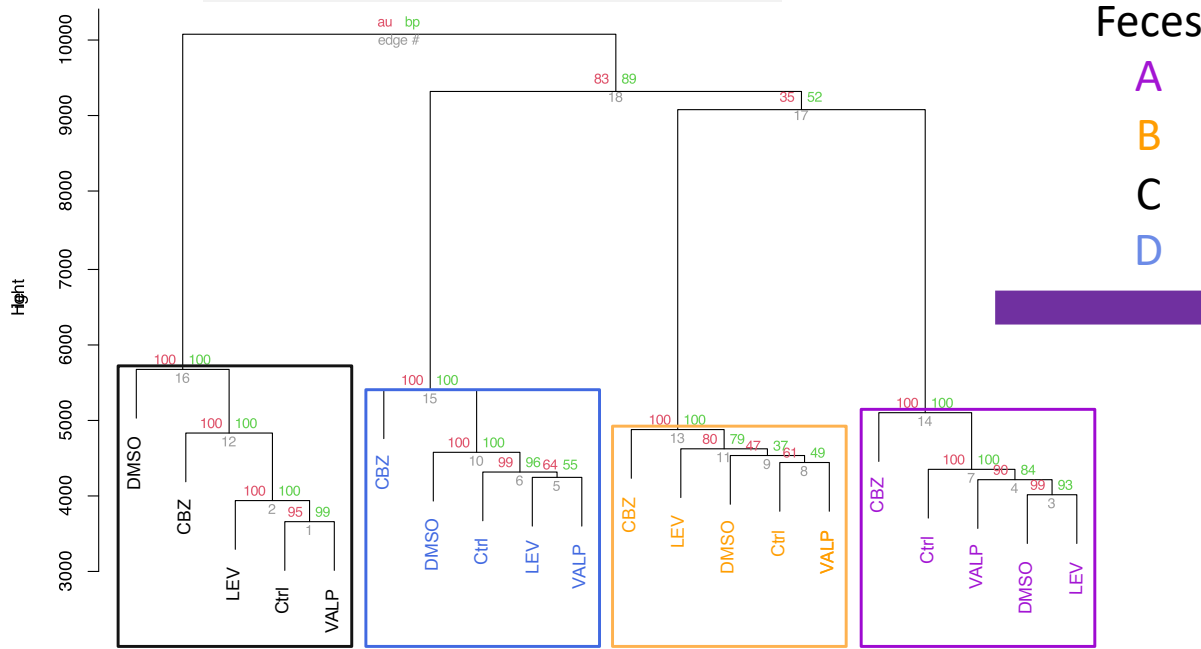


Medium and cultivation strategies generate compositionally different microcosms dependent on the initial feces composition

2. Among the three drugs, carbamazepine had the greatest impact on the microbial communities

Cycle 1 (acute exposure)

Cycle 7 (chronic exposure)



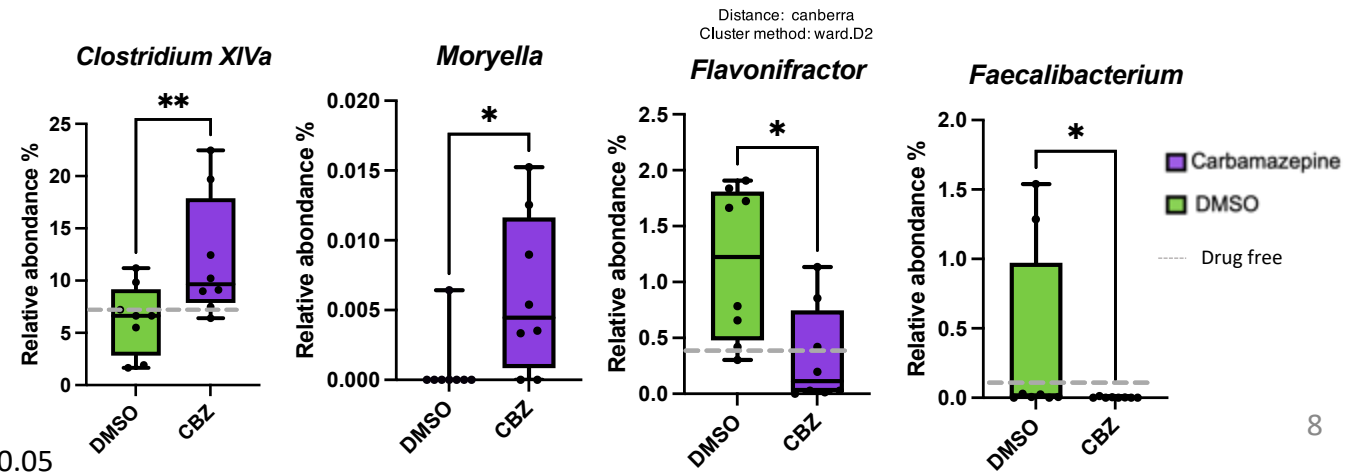
multiscale bootstrap resampling:

and Approximately unbiased (AU) probability values $\geq 95\%$

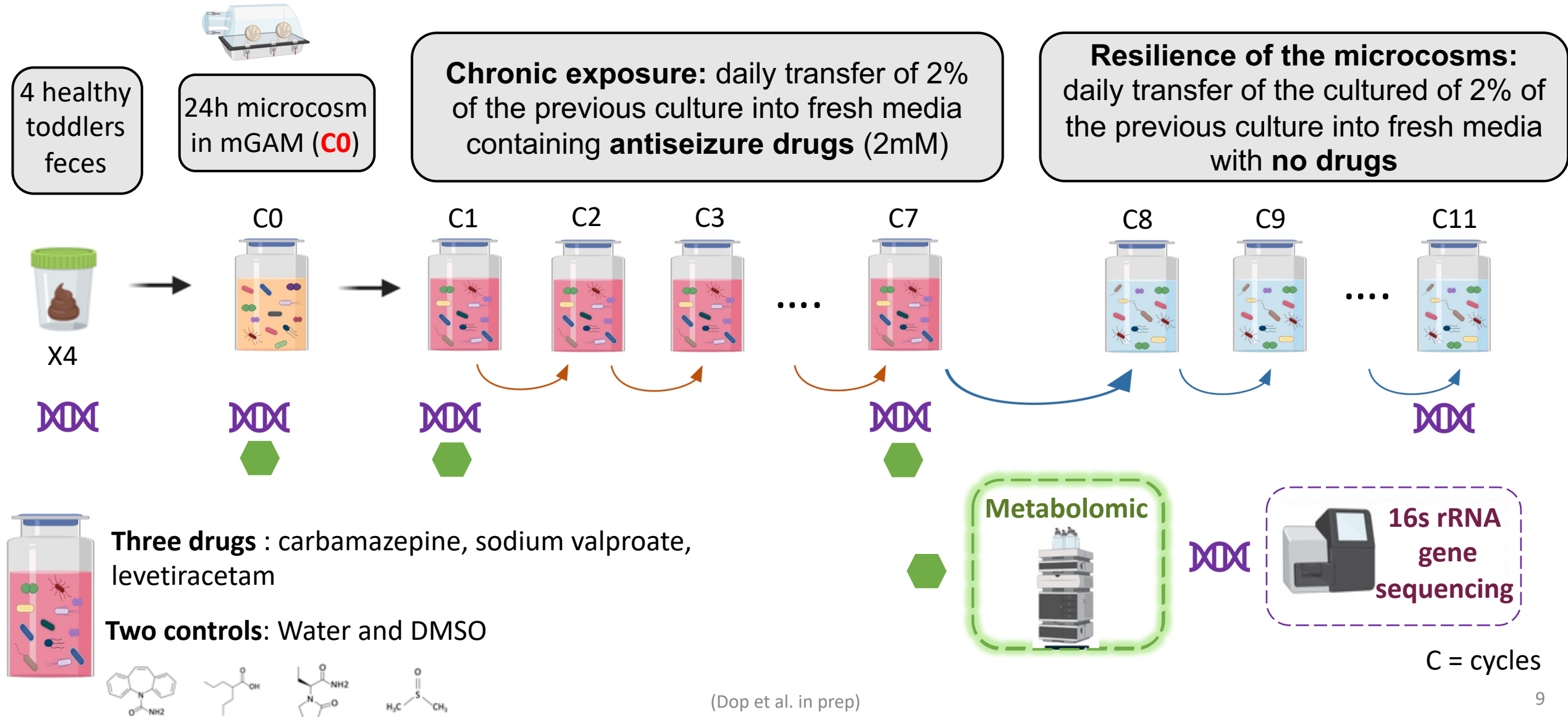
Compare to **acute exposure**, **chronic exposure** to carbamazepine had larger impact

(Dop et al. *in prep*)

Mann-Whitney = * $P < 0.1$ ** $P < 0.05$

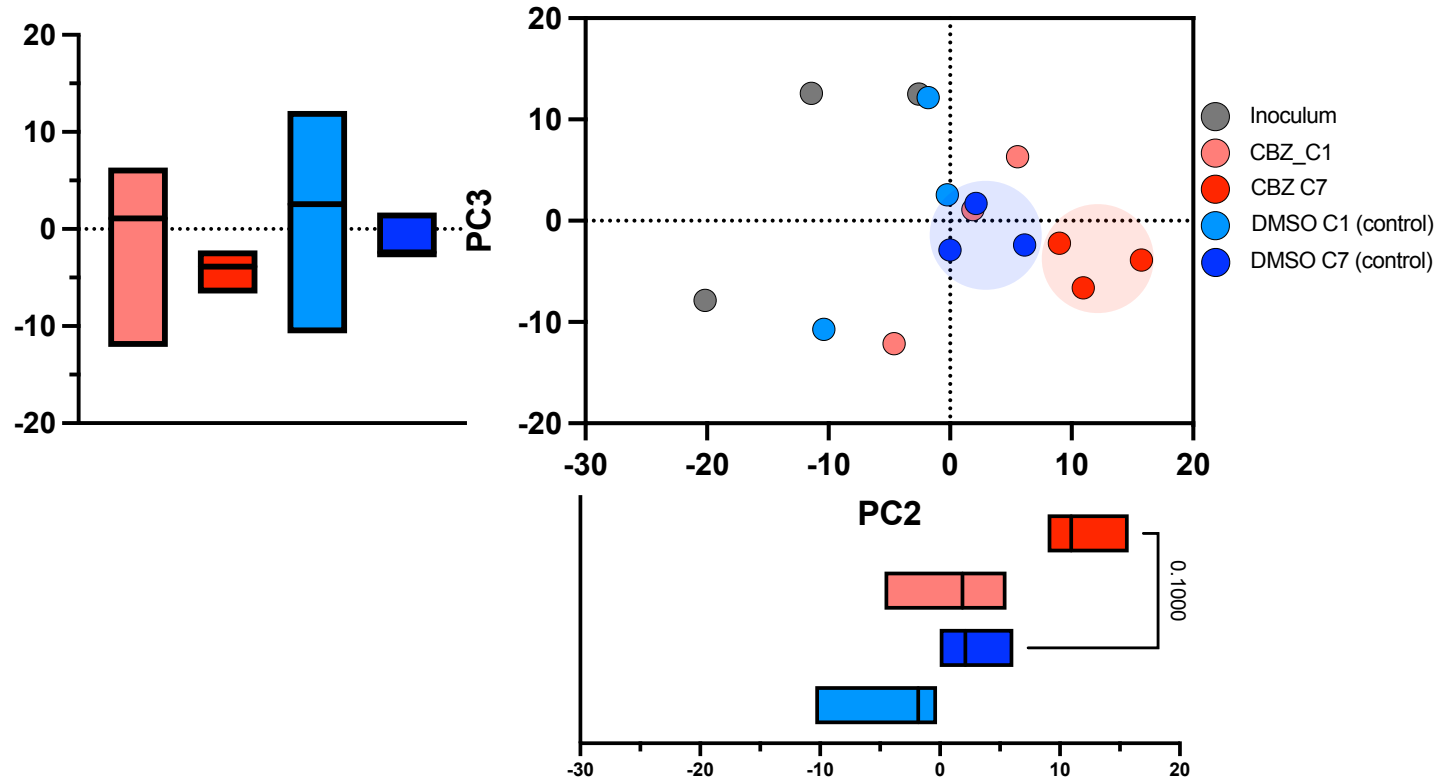


Our experimental approach relied on establishing semi-continuous microcosms



3. Chronic exposure to carbamazepine depleted 52 metabolites.

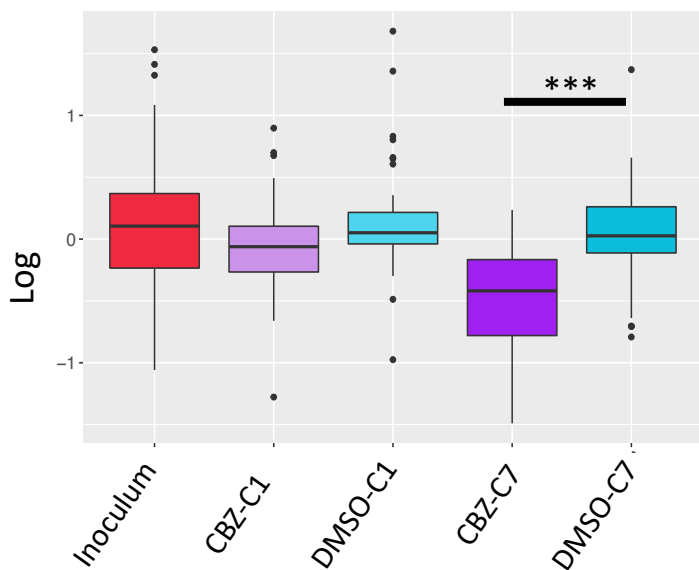
The impact of carbamazepine was greater on metabolomes on C7 than C1



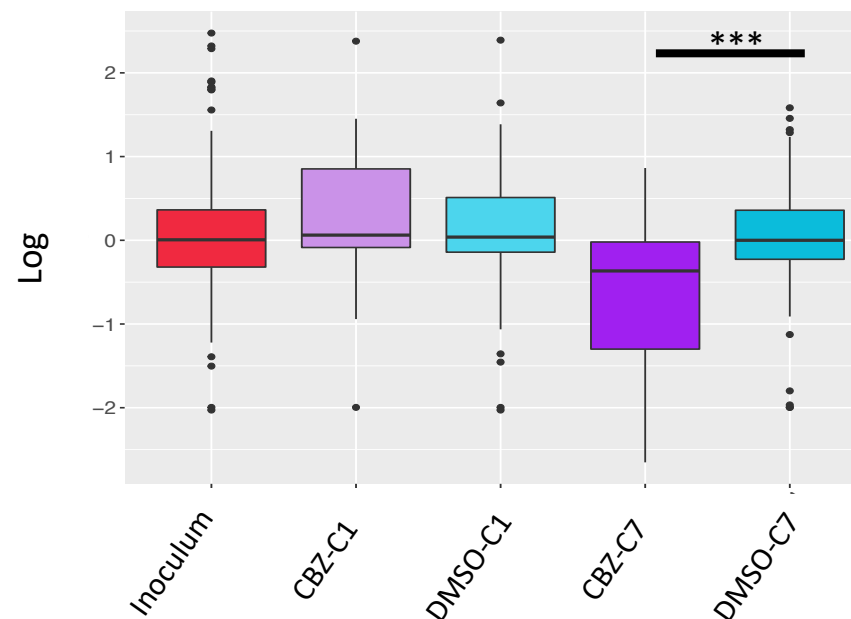
52 metabolites were significantly **lower** in CBZ treatment compared to DMSO control, and **11 metabolites** were significantly **higher**

4. Chronic exposure to carbamazepine leads to a decrease in dicarboxylic acid and dipeptides metabolites in the microcosms

Fatty Acid, Dicarboxylate sub-pathway



Dipeptide, Sub-pathway

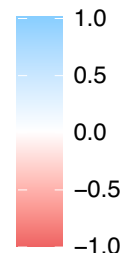


GROUP_NAME

- Inoculum
- Carbamazepine-C1
- DMSO -C1 (Control)
- Carbamazepine-C7
- DMSO -C7 (Control)

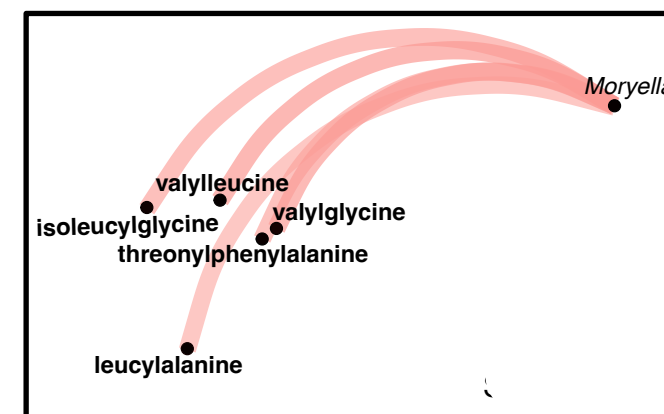
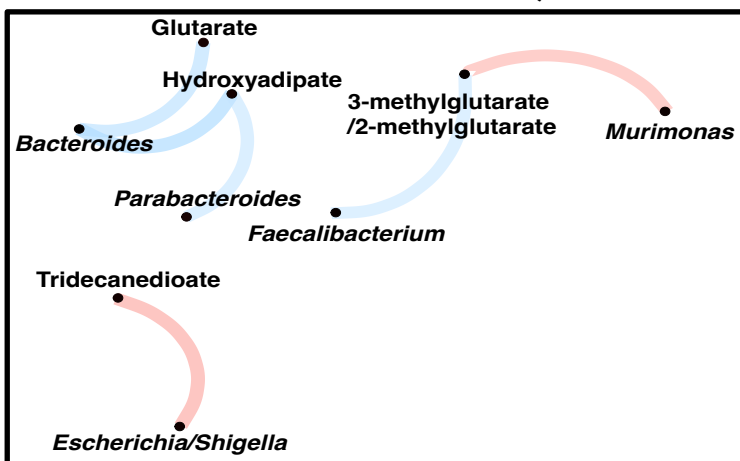
Dunn test = *** P < 0.01

Spearman correlation

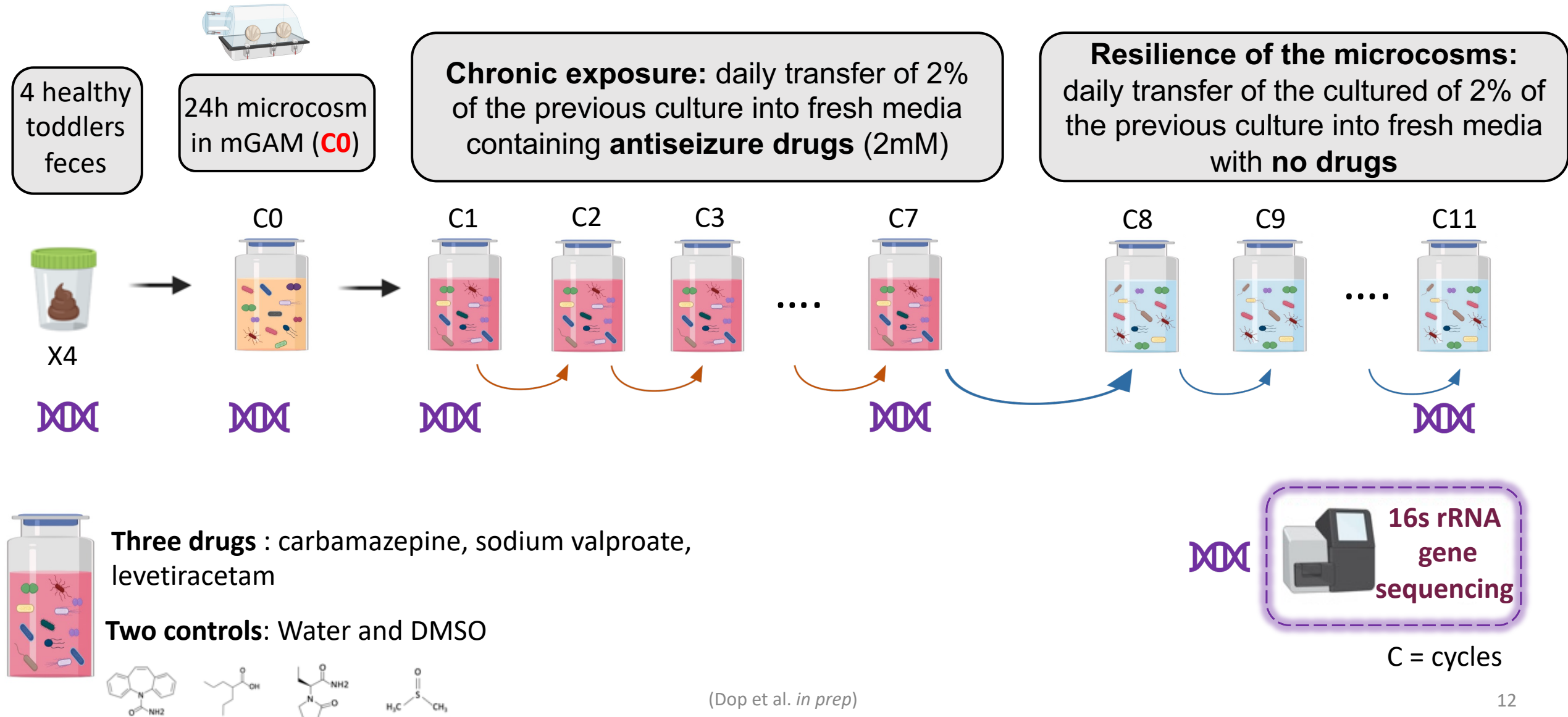


All correlation represented have a p < 0,05

(Dop et al. in prep)

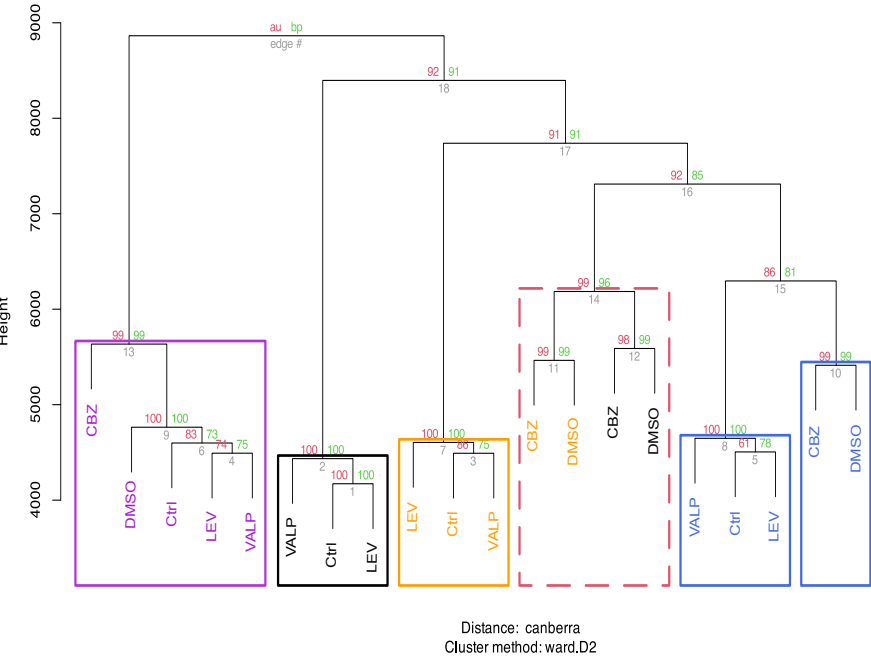


Our experimental approach relied on establishing semi-continuous microcosms



5. Drug-free cycles partially alleviate the impact of carbamazepine

Cycle 7 (chronic exposure)



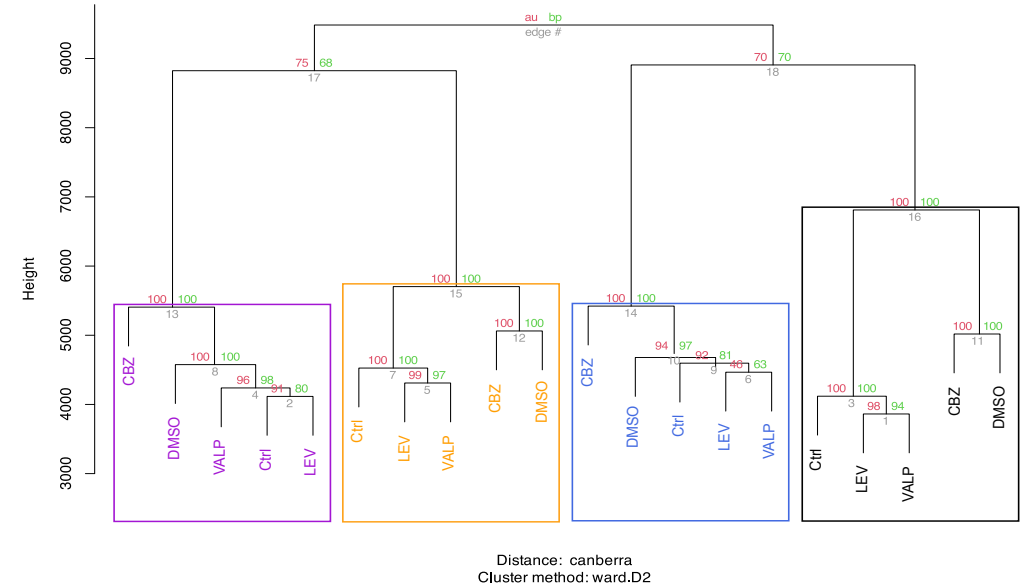
Feces

- A
- B
- C
- D

Drug-free
(4 days)



Cycle 11 (after 4 drug-free cycles)

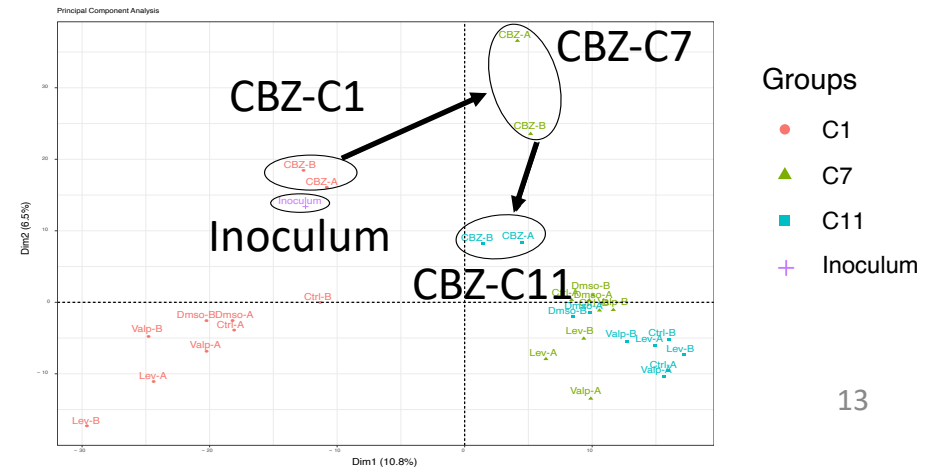


Feces

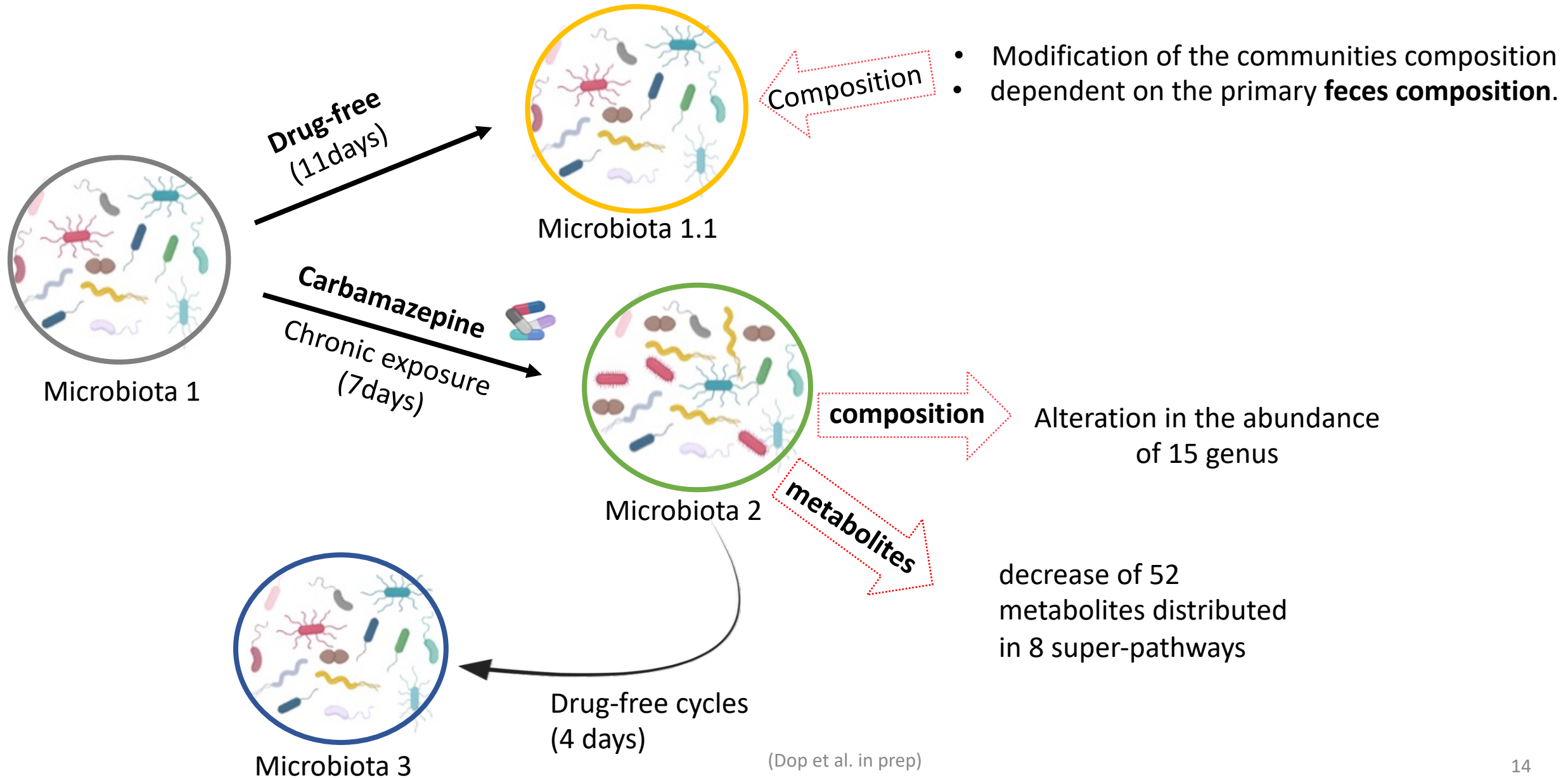
- A
- B
- C
- D

The **Drug-free cycles** allow the microcosm to **partially overcome** the carbamazepine repeated exposure

Feces A (PCA)



Take home message





Collaborators :

Pr. Stéphane Auvin
(APHP, Robert Debré
University Hospital; INSERM)

FInE team:

Nicolas Lapaque
Fabienne Béguet-Crespel



Patricia Lepage
Zehra Esra Ilhan
Constance Patin
Karine Le Roux
Hiba Yazbek
Solène Blin
Delpine Gibert
Emilie Rezer



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Where to join us!

PhylHom Team :
camille.dop@inrae.fr ;
Patricia.lepage@inrae.fr



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