Effect of the microbiota of children with autism spectrum disorder(ASD) on behavior and various biological parameters in germ-free mice

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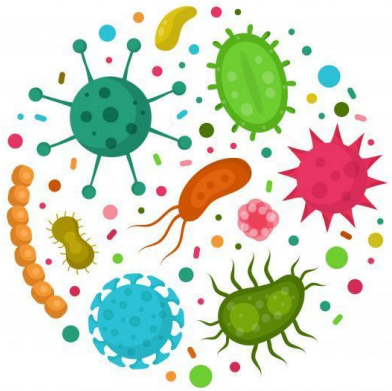
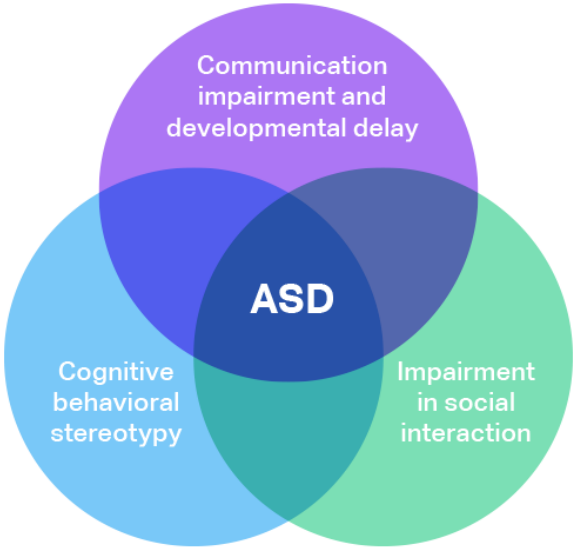
Effect of the microbiota of children with autism spectrum disorder(ASD) on behavior and various biological parameters in germ-free mice

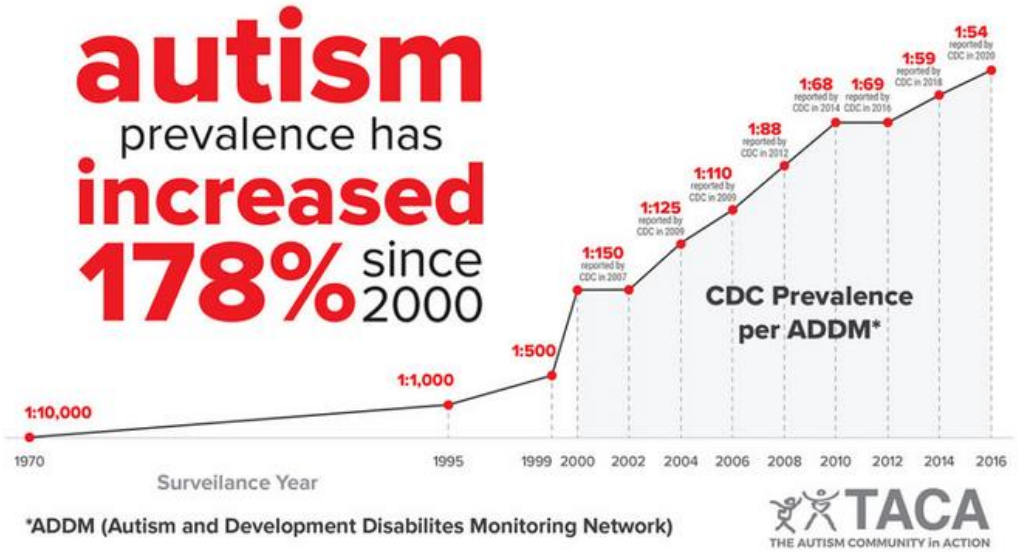


Léa Roussin

Autism spectrum disorder



embracingasd.com



tacanow.org

- Studies show a rate of heritability lower than 50%, highlighting an important impact of environnement on the disorder

- It is important to characterize and better understand these environmental factors

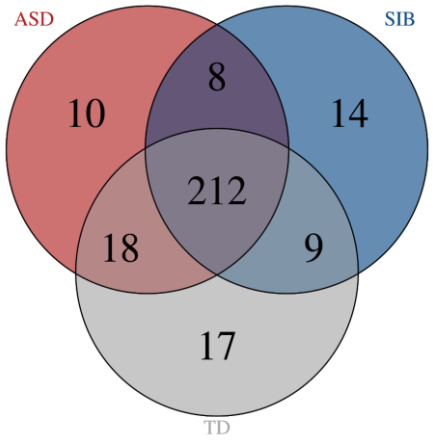
- Notably: Prevalence of GI symptoms 4X higher in ASD patients→implication of the Gut-microbiota-brain axis

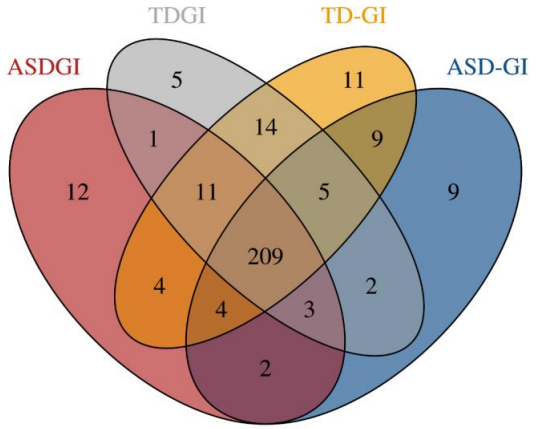
Microbiota-gut-brain axis in ASD

Difference in microbiota composition

•Many studies in the past decade show a difference in microbiota composition in ASD patients compared to neurotypical individuals

•However, there is great variability in the results that could be in part caused by the impact of environment and alimentation on microbiota, or differences in the choice of patients and control groups:





From Dr. Ruth Ann Luna's presentation at the 74th Annual Meeting Society of Biological Psychiatry,Chicago (May 2019)

→Controls groups used: difference in microbiota composition in unrelated neurotypical controls compared to neurotypical siblings of ASD individuals.

→ GI symptoms: difference in microbiota composition depending on presence or absence of GI symptoms

Our project

ASD (A) → Stool sampling and preservation

Their siblings (S-A) → Stool sampling and preservation

ASD+GI (AG) → Stool sampling and preservation

Their siblings (S-AG) → Stool sampling and preservation

FMT of pooled samples from each group to mice

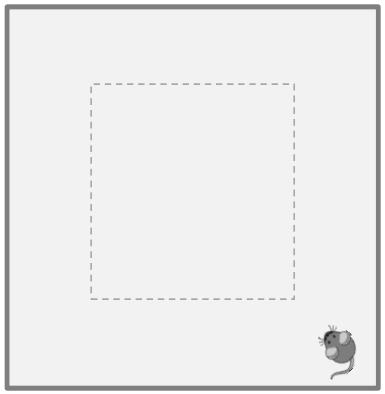
INRAE

Germ-free mice (two strains)

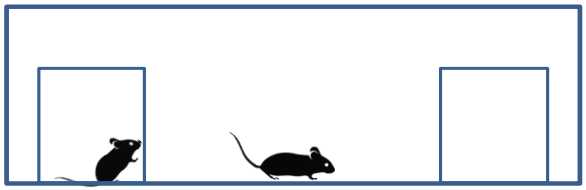
Analysis of **behavior** (8 weeks after FMT) and various biological parameters

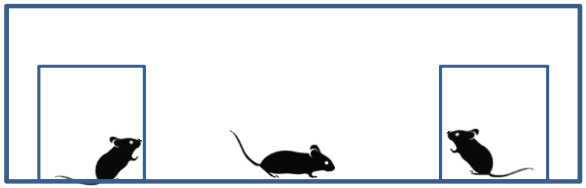
3 mouse models of ASD:
-CMA model
-VPA model
- *PCDH9* KO

Behavioral tests

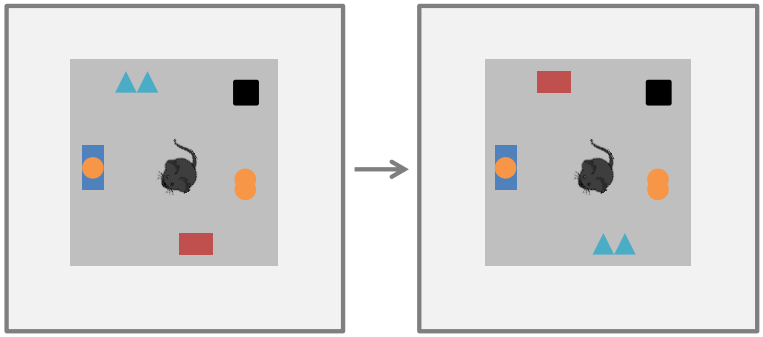


Anxiety: Open field





Social interaction and novelty



Cognition: spatial memory

Repetitive behaviors (grooming)

Hypothesis:

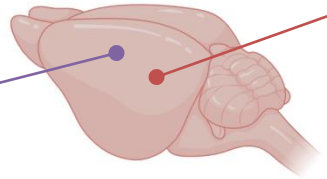
- **Altered behavior in the ASD groups compared to their respective sibling groups.**
- **Potential differences between A and AG groups**

Our project

Biological parameters

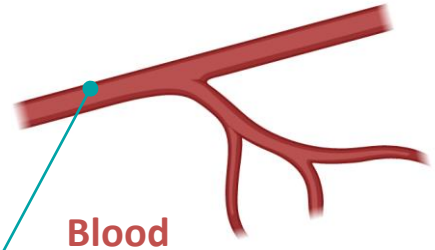
Neuroinflammation (microglia)

5-HT neurons



Brain

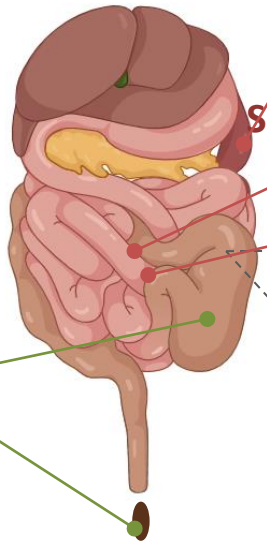
T cell populations



Blood

Gut permeability

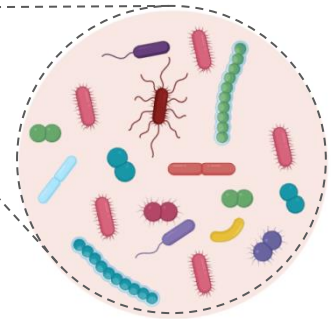
KYN/TRP ratio



Spleen

Gut inflammation

Gut



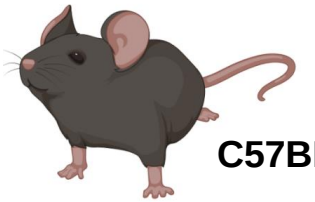
Microbiota

Microbiota composition and activity

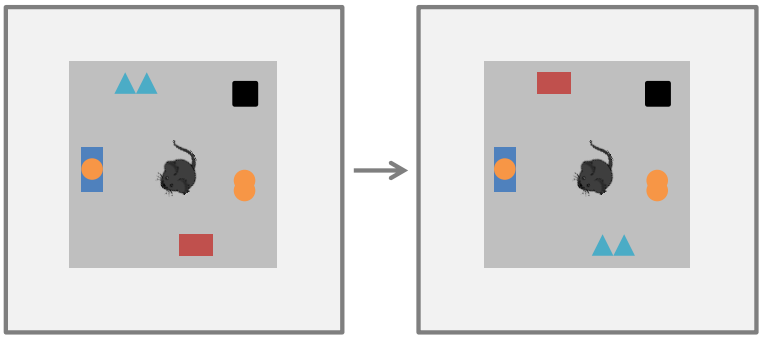
Images: biorender.com

First results

Behavior



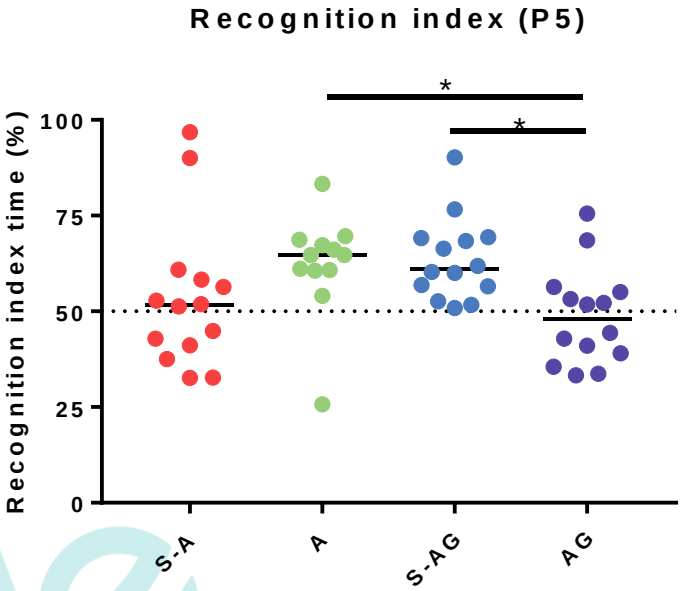
C57BL/6JCrl



Cognition: spatial memory

Recognition index (%)= DO/(DO+NDO)*100

DO=mean time interacting with **displaced objets**
NDO=mean time interacting with **non displaced objets**



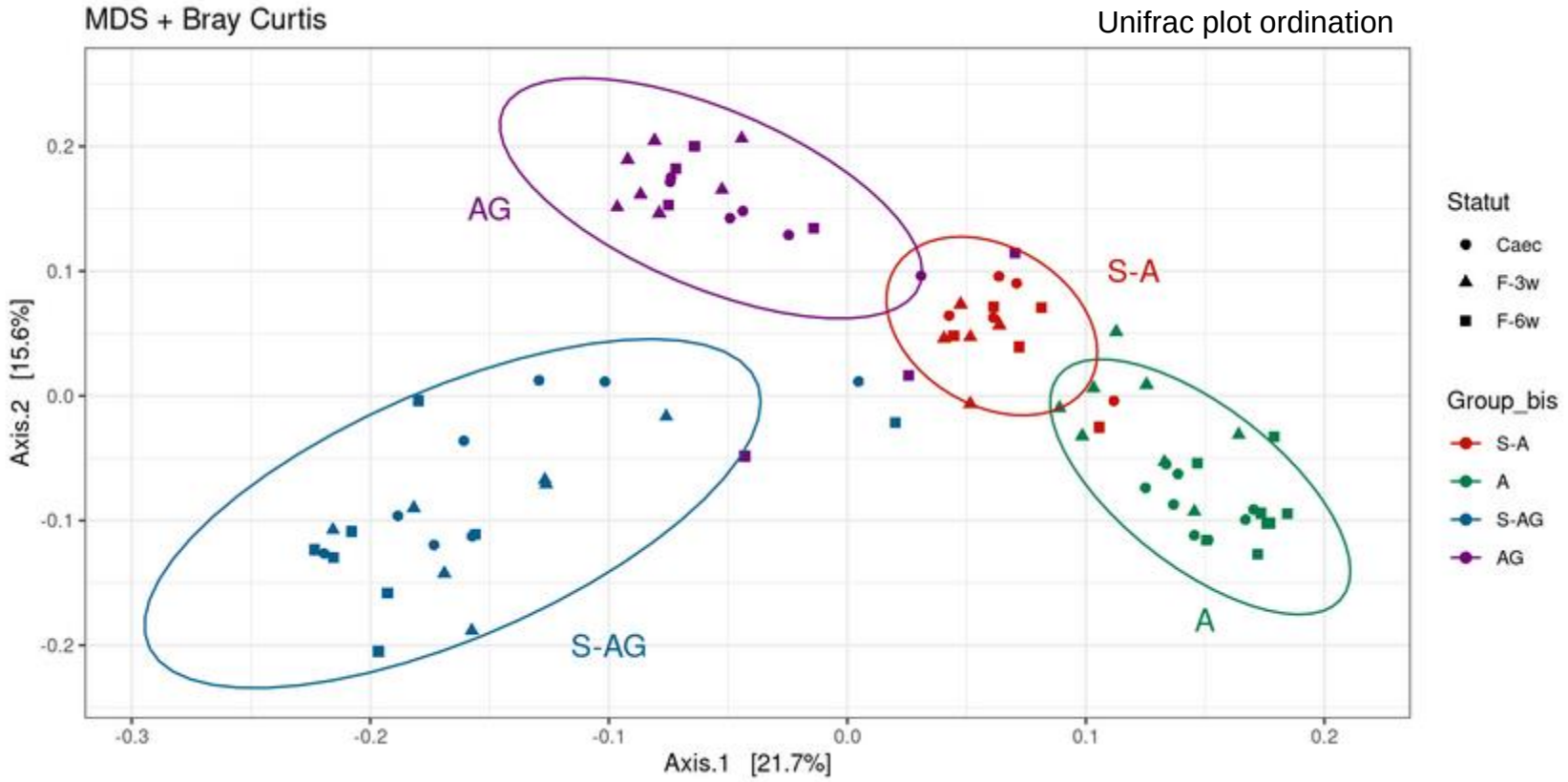
•Decreased recognition index in the AG group compared to S-AG and A.

→ Microbiota from children with ASD and GI symptoms can impact spatial memory in germ-free mice

First results

Analysis of microbiota composition

Principal coordinate Analysis (PcoA):



→Microbiota from each group forms a distinct cluster in PcoA analysis, highlighting that our 4 groups form distinct microbiota populations

Conclusions and perspectives

Behavior:

•Altered spacial memory in germ-free C57BL/6 mice that received microbiota from the AG group

No differences between groups for the other behavioral tests.

•Another study is planned to study behavior of Germ-free mice (2022)

Other parameters:

•Some differences in SFCAs profiles and T cell populations (analysis still ongoing)

• A lot left to analyse (gut inflammation/permeability, neuroinflammation, 5-HT etc).

1 month stay at Utrecht University for some of the experiments!

Thanks for your attention!

PhD supervisors:
Laurent Naudon
Sylvie Rabot


Utrecht Team:
Aletta Kraneveld
Paula-Perez Pardo
Naika Prince



The Amipem team:

Thanks to the Anaxem animal facility

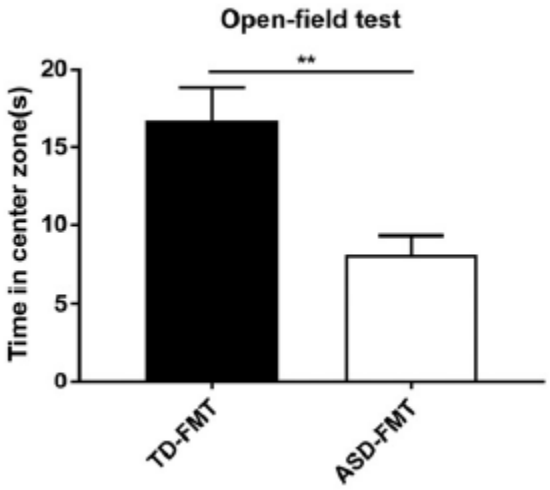
Extras

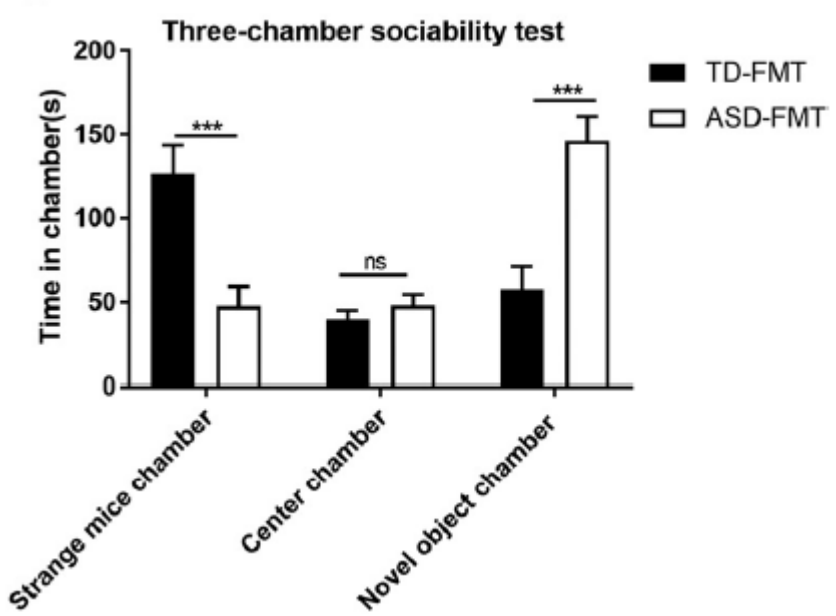
Preclinical studies

FMT from ASD patients to germ-free mice

Xiao et al. 2021:

ASD children or NT controls→pool of stool samples→ transplantation to mice





In ASD-FMT mice compared to TD-FMT:

→Increased anxiety (time in center of open-field)

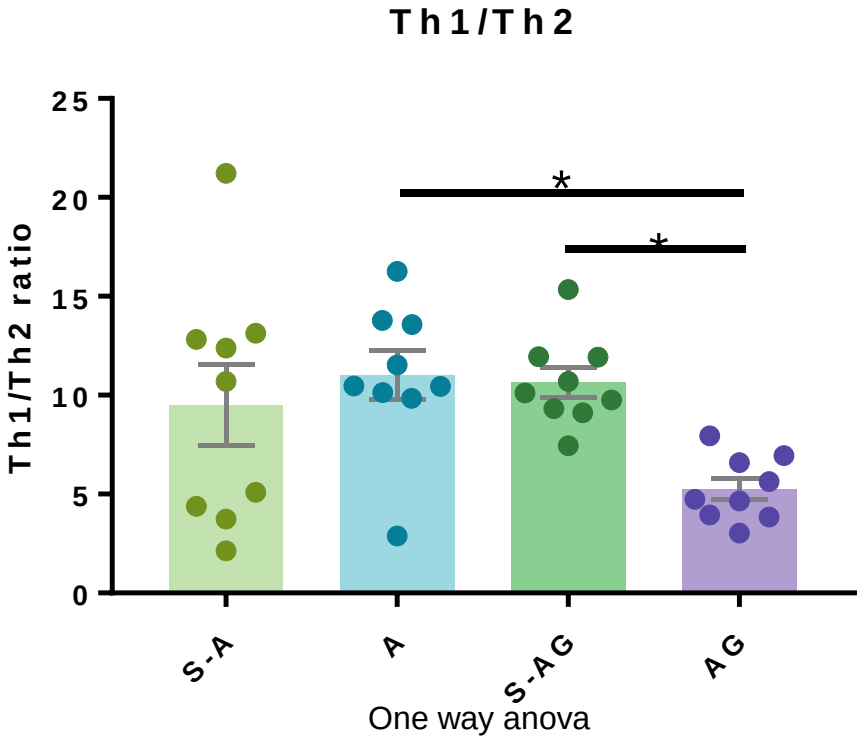
→Altered social behavior

Microbiota from ASD patients can transfer altered behaviors to mice

T cell analysis in sleep (flow cytometry)

Expressed in % of CD4+ cells

C57BL/6 (2nd cohort)



•Th1/Th2 ratio is lower in the AG group, highlighting a less inflammatory profile in those mice compared to S-AG and AG groups.