Microbial Dysbiosis and probiotic treatment in a genetic model of Autism

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ARTICLE IN PRESS

Brain, Behavior, and Immunity xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders

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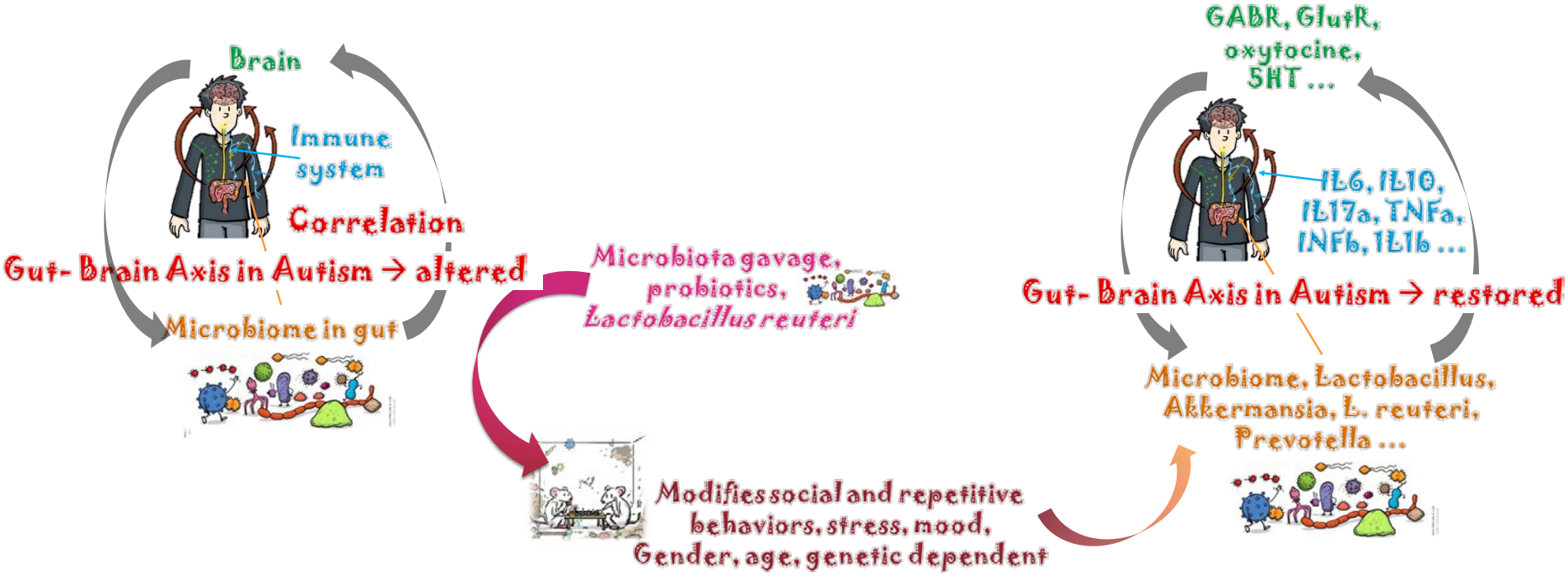
This study highlights the role of genetics in establishing the microbiome, help us understand the role of the microbiome in autism and if probiotics may helpful in a subset of affected individuals.

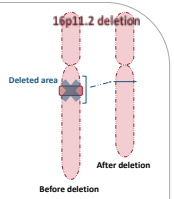
We can we can advance the hypothesis that there is a close link between microbiome in the gut and the synaptic regulation in specific brain regions.



Why would we expect a role for microbiota in ASD ? What would be the role of microbiota in the establishment of ASD ?

16p11.2 Deletion Microbiome Project

- Mice samples (n=100)



- Human samples

97 individuals recruited into microbiome study.
→ 51 individuals with chromosome 16p11.2 deletion and 46 siblings

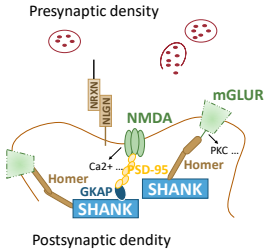
Gut microbiome analysis

https://simonsvipconnect.org/participate-in-research/other-vip-approved-research-opportunities/16p-microbiome-project.html

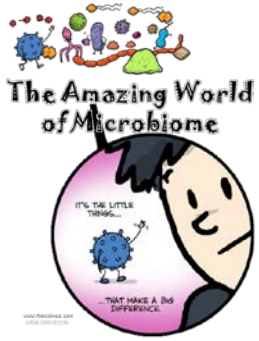
SHANK3 mutation mice samples

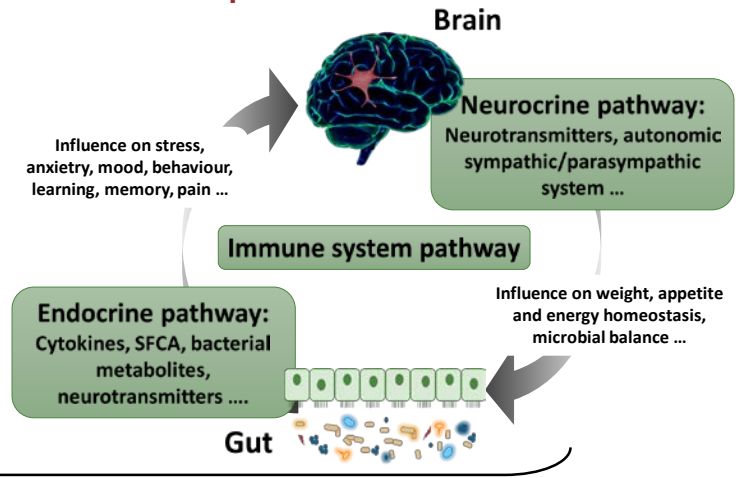
(SH3 and multiple ankyrn repeat domains 3)

- Mice samples
(n=99 → M=50; F=49)



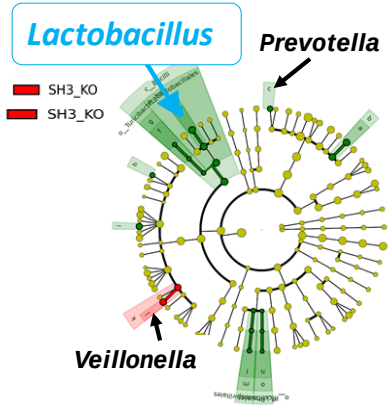
The Gut-Brain Axis concept …

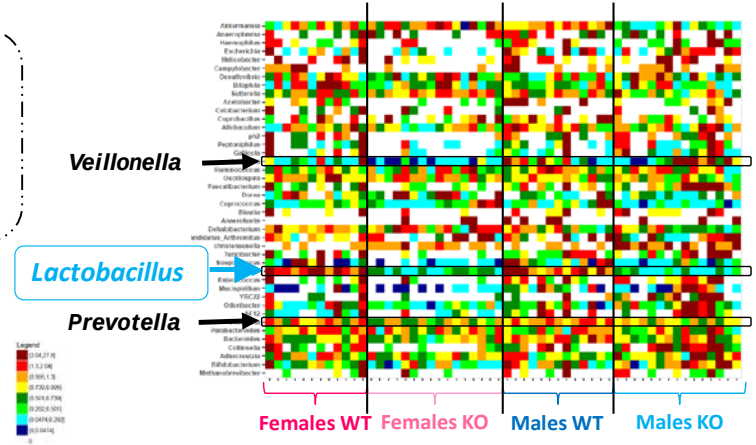




How does the gut influence the brain in ASD ?
Is this Gut- Brain Axis dysregulated in ASD ?

Can genetic susceptibility to autism induce dysregulation of the microbiome?





AgroParisTech INRA MIA Paris
UMR Mia (Morse)
Timothée Tabouy PhD student

Why Lactobacillus reuteri ?

Cell

Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring

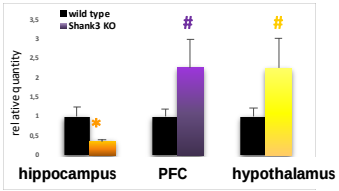
Promotes social behavior, link with stress, behavior, oxytocin, GABA, GABR and autism

Lactobacillus produces and secretes GABA and increased *Lactobacillus* has been associated with more GABR → regulates GABR expression in brain

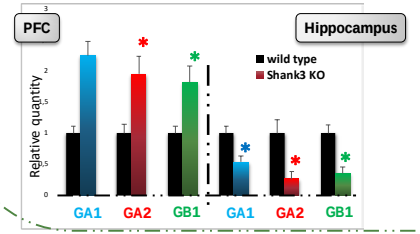
Autism and oxytocin // GABA and oxytocin → role in social and emotional behaviors

GABR, Glutamate and oxytocin study in Brain

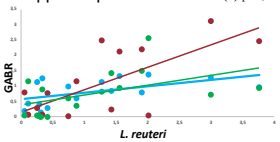
Dysregulation of **oxytocin** gene expression in **PFC, hippocampus** and **hypothalamus**



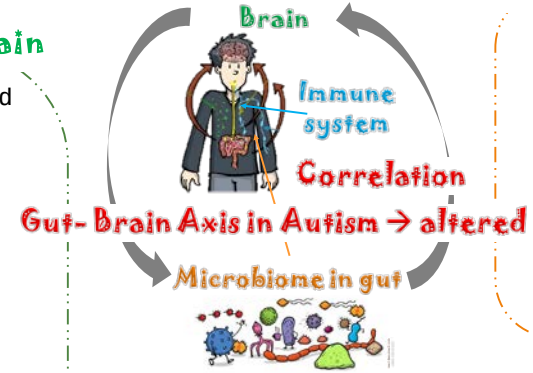
Dysregulation of **GABRA1, GABRA2, GABRB1** gene expression in brain



Correlation **GABR expression / *L. reuteri*** in hippocampus of Females (*) p<0,05

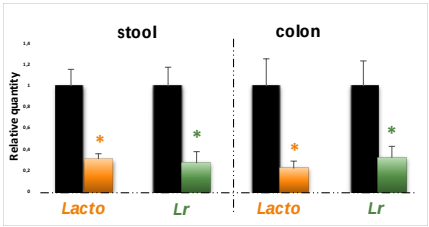


GABRA1 R* = 0,525 / GABRA2 R* = 0,723 / GABRB1 R* = - 0,500



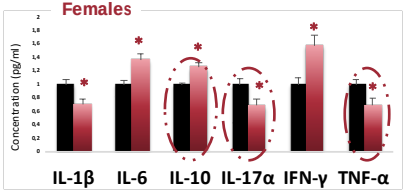
Microbiome study in stool and colon

Dysregulation of ***Lactobacillus (Lacto)*** and ***L. reuteri (Lr)*** expression



Immune system study in blood

Dysregulation of immune system in blood of both **females** and **males**



Treatment with *L. reuteri* →

Females and males Shank3 KO and controls mice

Gavage for 4 weeks

Lactobacillus reuteri

Behavior test for 1 week

Social Behavior | Marble burying | Repetitive Behavior

Open field | Elevated plus maze | Hyperactivity and anxiety

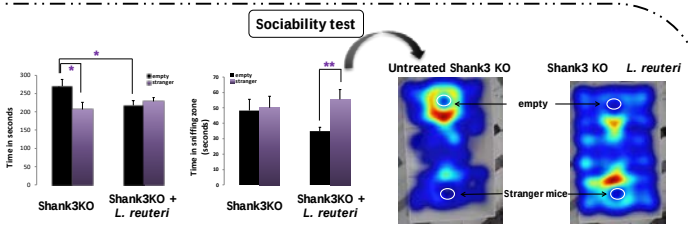
GABR and oxytocin study in Brain

Immune system study in blood

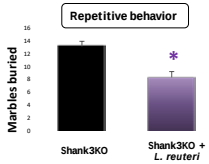
Microbiome study in stool

Behavioral studies

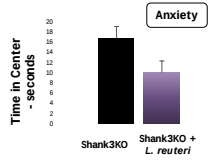
- In males attenuate social deficits and reduce repetitive behaviors, without affecting anxiety behavior



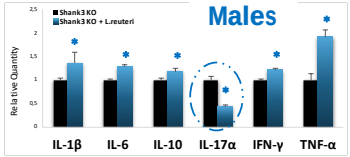
sex dependent



- In females reduce repetitive behaviors, without affecting social deficits and anxiety behavior significantly

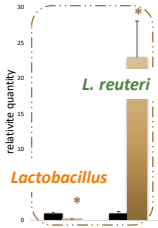


Immune system study in blood

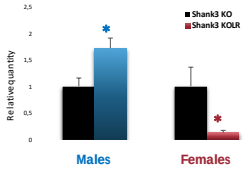


induces changes in plasma **cytokine levels** in blood

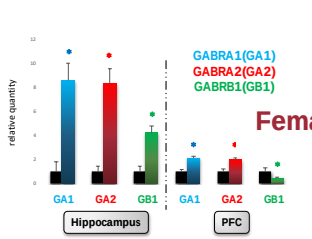
Microbiome study in stool

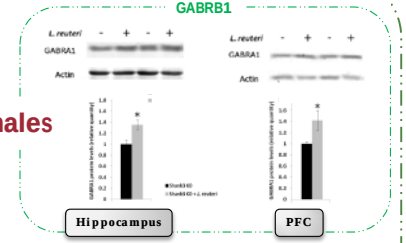


GABR and oxytocin study in Brain



changes levels of **oxytocin** gene expression in hypothalamus





changes levels of GABR subunit gene expression and **GABRB1** protein levels in brain

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The Amazing World of Microbiomes

Bar-Ilan University The Azrieli Faculty of Medicine

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SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

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