Papel del miocrobioma en los trastornos del neurodesarrollo

J. Antoni Ramos-Quiroga

Departamento de Psiquiatría. CIBERSAM
Hospital Universitari Vall d'Hebron
Universitat Autònoma de Barcelona

UAB Universitat Autònoma de Barcelona

Vall d'Hebron Barcelona Campus Hospitalari

cibersam Centro de Investigación Biomédica En Red de Salud Mental

Declaración de intereses

Company	Speaker	Consultant	Grants
Janssen-Cilag	X	X	X
Lilly	X	X	X
Shire	X	X	X
Novartis	X		
Laboratorios Rubió	X	X	X
Almirall		X	
Rovi			X
Ferrer	X	X	X
Lundbeck		X	X
Alicia Koplowitz Foundation, PSIOUS, BGAZE			X
Instituto Carlos III-EU FP7-H2020		X	X

INDICE

- Introducción
- Dieta y TDAH
- Microbioma y TDAH
- Proyecto Vall d'Hebron
- Conclusiones

INDICE

- Introducción
- Dieta y TDAH
- Microbioma y TDAH
- Proyecto Vall d'Hebron
- Conclusiones

TRASTORNOS DEL NEURODESARROLLO

- Trastornos del espectro autista.
- Trastornos del desarrollo intelectual / discapacidad intelectual
- Trastorno por déficit de atención e hiperactividad.
- Trastornos motores (de tics).
- Trastornos de la comunicación.
- Trastornos específicos del aprendizaje.

TRASTORNOS DEL NEURODESARROLLO

- Déficits cognitivos de instauración rápida y continuada.
- Trastornos del desarrollo neurológico.
- Similitudes entre ellos respecto factores de riesgo y clínicos.
- Fenotipo genético común.
- Entre ellos existe una comorbilidad común.

TRASTORNOS DEL NEURODESARROLLO

- Trastornos del espectro autista.
- Trastornos del desarrollo intelectual / discapacidad intelectual
- Trastorno por déficit de atención e hiperactividad.
- Trastornos motores (de tics).
- Trastornos de la comunicación.
- Trastornos específicos del aprendizaje.

TRASTORNOS DEL NEURODESARROLLO

- Trastornos del espectro autista.
- Trastornos del desarrollo intelectual / discapacidad intelectual
- **Trastorno por déficit de atención e hiperactividad.**
- Trastornos motores (de tics).
- Trastornos de la comunicación.
- Trastornos específicos del aprendizaje.

TDAH: RETRASO MADURACIÓN CORTICAL

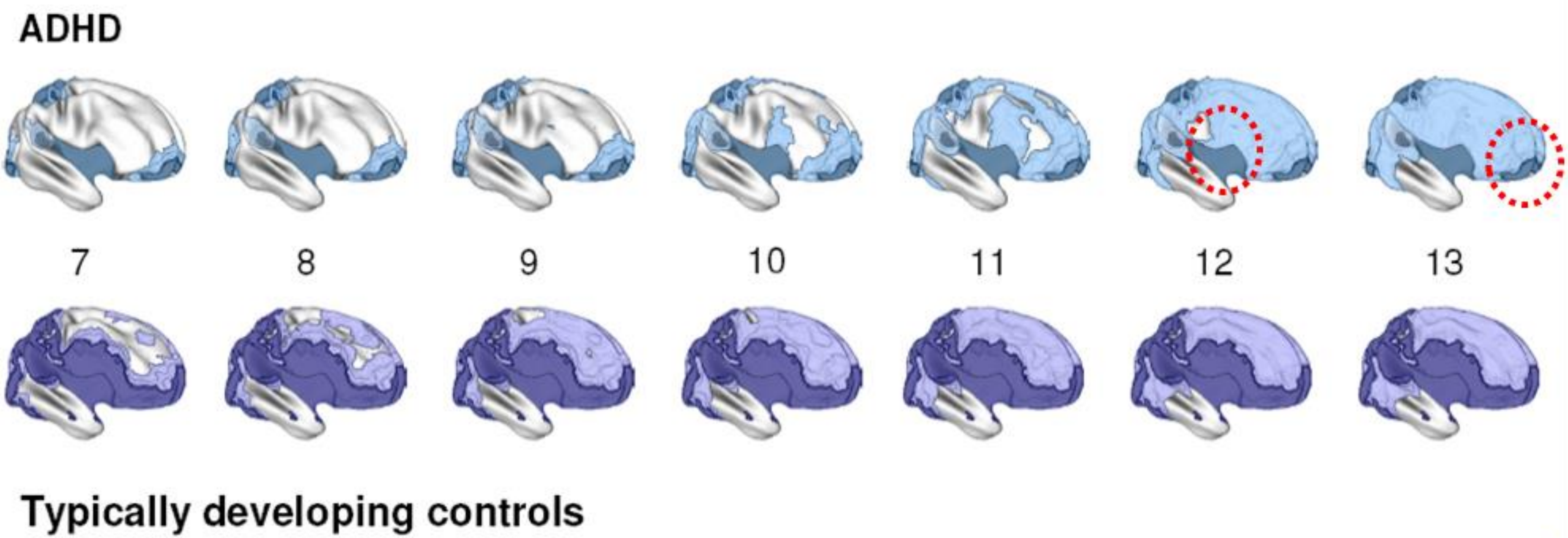


Figure 1b: right lateral view of the cortical regions where peak thickness was attained at each age (shown age 7 through 13). Again, the delay in ADHD group in attaining peak cortical thickness is apparent.

Shaw et al., 2007

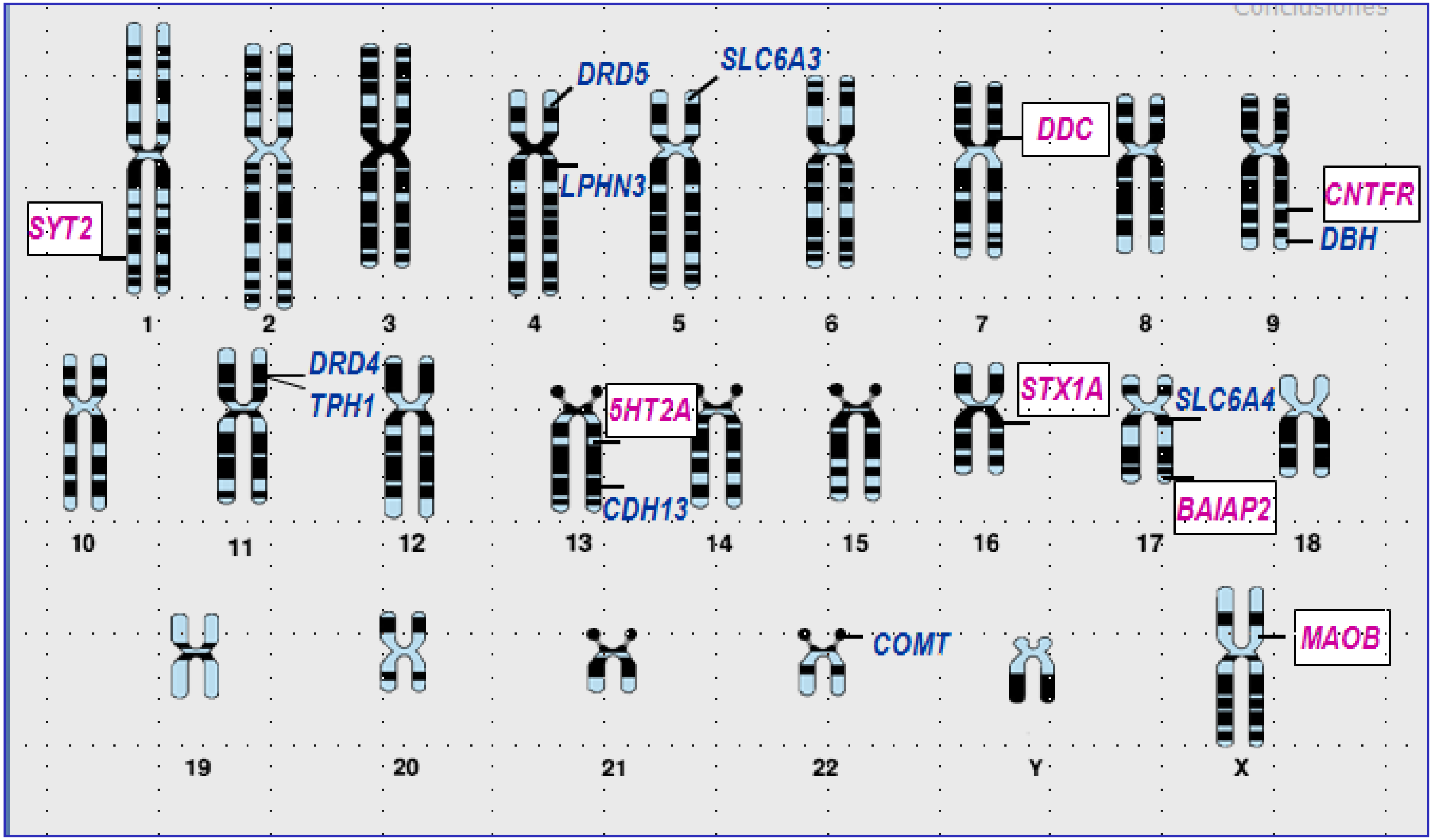
Factores

Ambientales

TDAH

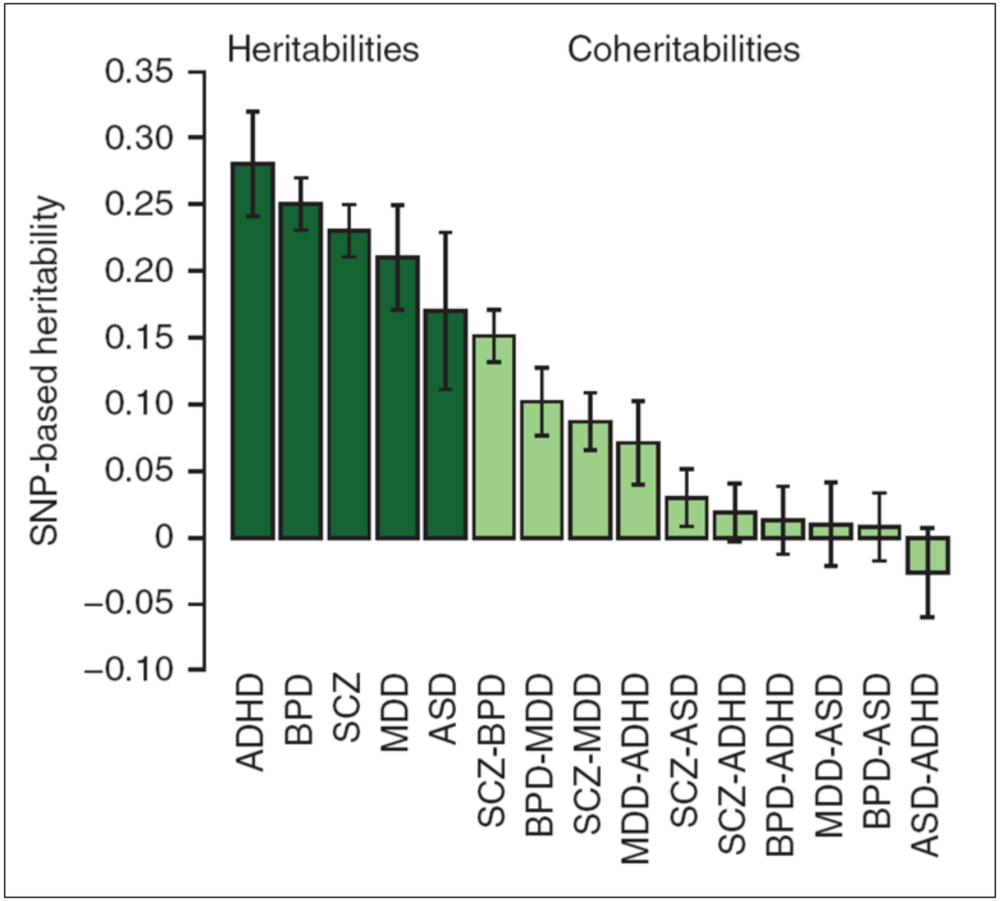
N genes de riesgo

GENETICA Y TDAH



Ribasés M. *Biol Psychiatry* 63(10):935-45 (2008).
Ribasés M. *Mol Psychiatry* 14(1):71-85 (2009).
Ribasés M, et al. *Biol Psychiatry* 15;66(10):926-34 (2009).
Sánchez-Mora et al. *Am J Med Genet B* 153B(2):512-23 (2010).
Sánchez-Mora et al. Am J Med Genet B 156(5):600-12 (2011).
Ribasés et al. World J Biol Psychiatry. 2012
Ribasés et al. Psychiatric Genetics. 2012.

TDAH: componente genético



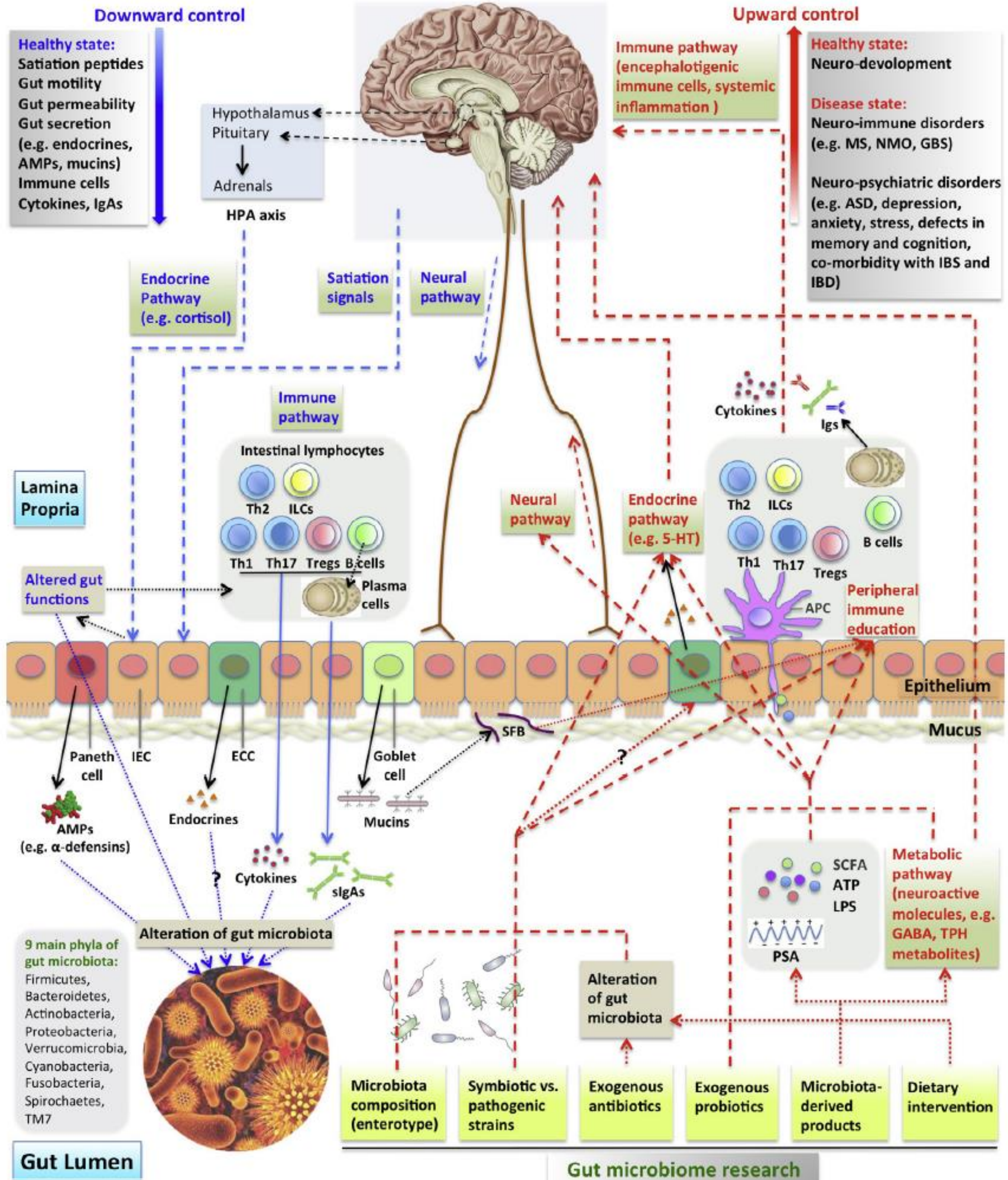
ADHD
Bipolar Disorder
Schizophrenia
Major Depression
Autism

$h^2_{SNP} = 28\%$

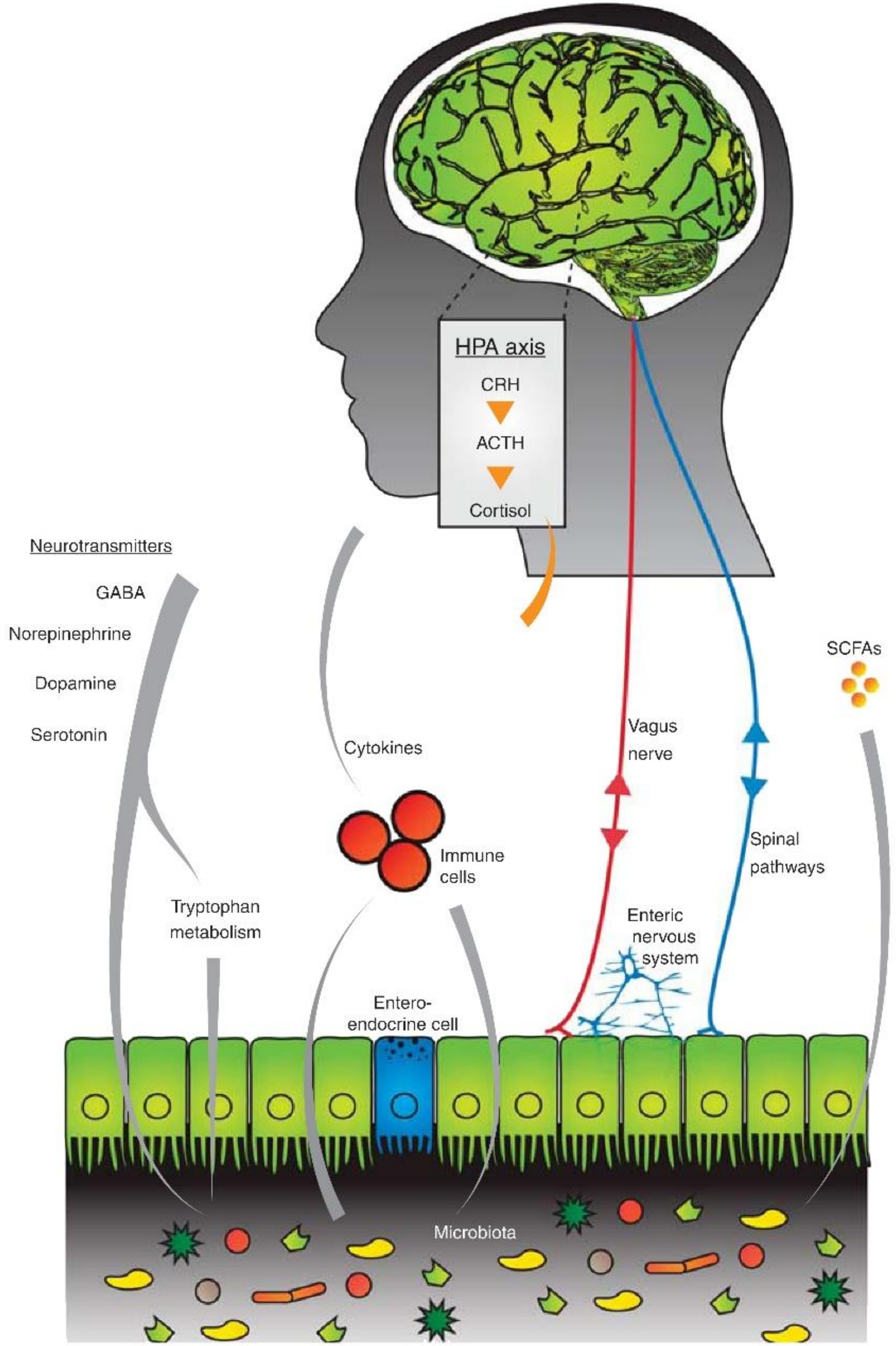
$\lambda_{SNP} = 1.71$

Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disorder Group of the Psychiatric Genomics Consortium. Nature Genetics;45(9):984-94(2013)



Downward control
Healthy state:
Satiation peptides
Gut motility
Gut permeability
Gut secretion
(e.g. endocrines, AMPs, mucins)
Immune cells
Cytokines, IgAs
Hypothalamus
Pituitary
Adrenals
HPA axis
Upward control
Immune pathway (encephalotigenic immune cells, systemic inflammation)
Healthy state:
Neuro-development
Disease state:
Neuro-immune disorders (e.g. MS, NMO, GBS)
Neuro-psychiatric disorders (e.g. ASD, depression, anxiety, stress, defects in memory and cognition, co-morbidity with IBS and IBD)
Endocrine Pathway (e.g. cortisol)
Satiation signals
Neural pathway
Immune pathway
Intestinal lymphocytes
Th2
ILCs
Th1
Th17
Tregs
B cells
Plasma cells
Lamina Propria
Altered gut functions
Neural pathway
Endocrine pathway (e.g. 5-HT)
Cytokines
Igs
B cells
APC
Peripheral immune education
Epithelium
Mucus
SFB
Paneth cell
IEC
ECC
Goblet cell
AMPs (e.g. α-defensins)
Endocrines
Mucins
Cytokines
sIgAs
?
Alteration of gut microbiota
9 main phyla of gut microbiota:
Firmicutes,
Bacteroidetes,
Actinobacteria,
Proteobacteria,
Verrucomicrobia,
Cyanobacteria,
Fusobacteria,
Spirochaetes,
TM7
Gut Lumen
SCFA
ATP
LPS
PSA
Metabolic pathway (neuroactive molecules, e.g. GABA, TPH metabolites)
Alteration of gut microbiota
Microbiota composition (enterotype)
Symbiotic vs. pathogenic strains
Exogenous antibiotics
Exogenous probiotics
Microbiota-derived products
Dietary intervention
Gut microbiome research



HPA axis
CRH
ACTH
Cortisol
Neurotransmitters
GABA
Norepinephrine
Dopamine
Serotonin
Cytokines
SCFAs
Vagus nerve
Spinal pathways
Immune cells
Tryptophan metabolism
Enteric nervous system
Entero-endocrine cell
Microbiota

INDICE

IMPACTO DE LA DIETA

Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial

Lidy M Pelsser, Klaas Frankena, Jan Toorman, Huub F Savelkoul, Anthony E Dubois, Rob Rodrigues Pereira, Ton A Haagen, Nanda N Rommelse, Jan K Buitelaar

- The Impact of Nutrition on Children with ADHD (INCA) study was a randomised controlled trial that consisted of an open-label phase with masked measurements followed by a double-blind crossover phase.

IMPACTO DE LA DIETA

- In the open-label phase (first phase), children aged 4–8 years who were diagnosed with ADHD were randomly assigned to 5 weeks of a restricted elimination diet (diet group) or to instructions for a healthy diet (control group).

- The clinical responders (those with an improvement of at least 40% on the ADHD rating scale [ARS]) from the diet group proceeded with a 4-week double-blind crossover food challenge phase (second phase), in which high-IgG or low-IgG foods (classified on the basis of every child's individual IgG blood test results) were added to the diet.

IMPACTO DE LA DIETA

	Diet group (parent n=50; teacher n=37)						Control group (parent n=50; teacher n=40)						End rating*	
	Start	End (week 9)	Difference (95% CI)	p value†	Scale reduction (%)	Cohen's d	Start	End (week 13)	Difference (95% CI)	p value†	Scale reduction (%)	Cohen's d	Difference (95% CI)	p value†
ADHD rating scale														
Parent total score (JT; 0–54)	45·3 (4·7)	21·1 (16·8)	24·2 (19·5–29·0)	<0·0001	53·4	2·0	47·6 (4·1)	46·2 (5·8)	1·3 (0·2 to 2·5)	0·023	2·7	0·28	23·7 (18·6–28·8)	<0·0001
Teacher total score (LP; 0–54)	34·4 (6·7)	20·1 (10·1)	14·3 (11·6–17·1)	<0·0001	41·6	1·67	39·2 (7·8)	39·6 (8·6)	–0·4 (–1·7 to 1·0)	0·580	–1·0	–0·05	15·3 (12·0–18·6)	<0·0001
Parent inattention score (JT; 0–27)	21·2 (4·1)	9·9 (9·0)	11·3 (8·9–13·8)	<0·0001	53·3	1·62	23·2 (3·5)	22·9 (3·6)	0·2 (–0·4 to 0·8)	0·433	0·9	0·09	11·8 (9·1–14·4)	<0·0001
Teacher inattention score (LP; 0–27)	15·1 (5·7)	8·6 (6·1)	6·5 (4·9–8·2)	<0·0001	43·0	1·10	19·5 (5·2)	19·3 (5·2)	0·3 (–0·6 to 1·1)	0·587	1·5	0·04	7·4 (5·4–9·4)	<0·0001
Parent hyperactivity and impulsivity score (JT; 0–27)	24·1 (3·5)	11·2 (8·6)	12·9 (10·5–15·3)	<0·0001	53·5	1·96	24·4 (3·1)	23·3 (4·5)	1·1 (0·2 to 2·0)	0·012	4·5	0·28	11·9 (9·3–14·5)	<0·0001
Teacher hyperactivity and impulsivity score (LP; 0–27)	19·3 (5·0)	11·5 (6·0)	7·8 (6·2–9·5)	<0·0001	40·4	1·41	19·7 (6·6)	20·3 (6·3)	–0·6 (–1·4 to 0·2)	0·128	–3·0	–0·09	8·5 (6·8–10·3)	<0·0001
Abbreviated Conners' scale														
Parent (LP; 0–30)	23·7 (3·4)	11·7 (8·7)	12·0 (9·4–14·6)	<0·0001	50·7	1·82	23·5 (3·9)	23·4 (4·7)	0·1 (–0·7 to 0·8)	0·828	0·3	0·02	11·8 (9·2–14·5)	<0·0001
Teacher (LP; 0–30)	18·5 (3·8)	11·9 (6·7)	6·6 (4·9–8·4)	<0·0001	35·9	1·22	19·1 (4·5)	19·9 (4·6)	–0·8 (–1·4 to –0·3)	0·003	–4·3	–0·18	7·5 (5·9–9·2)	<0·0001
Structured psychiatric interview														
Parent ODD score (JT; 0–8)‡	5·5 (1·1)	1·9 (2·3)	3·6 (2·5–4·6)	<0·0001	65·4	2·00	5·5 (1·2)	5·3 (1·4)	0·2 (–0·3 to 0·7)	0·488	3·6	0·15	3·6 (2·5–4·8)	<0·0001
Teacher ODD score (LP; 0–8)§	4·9 (1·1)	2·1 (2·9)	2·8 (1·5–4·0)	<0·0001	57·1	1·28	5·2 (1·1)	5·0 (1·7)	0·2 (–0·4 to 0·9)	0·501	3·8	0·14	2·0 (0·2–3·9)	0·0320

Data are mean (SD). All data are masked, except for the teacher ratings and the abbreviated Conners' scale ratings. ADHD=attention-deficit hyperactivity disorder. JT=masked paediatrician. LP=unmasked researcher. ODD=oppositional defiant disorder. *Adjusted for score at start and block. The interaction between block and group was not significant (generalised linear model) and the link test showed sufficient fit in all analyses. †Generalised linear model. ‡Diet group n=20, control group n=27. §Diet group n=8, control group n=13.

***Table* 3: ADHD rating scale, abbreviated Conners' scale, and structured psychiatric interview scores at start and end of the first phase**

IMPACTO DE LA DIETA

Article

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

Edmund J.S. Sonuga-Barke, Ph.D.
Daniel Brandeis, Ph.D.
Samuele Cortese, M.D., Ph.D.
David Daley, Ph.D.
Maite Ferrin, M.D., Ph.D.
Martin Holtmann, M.D.
Jim Stevenson, Ph.D.
Marina Danckaerts, M.D., Ph.D.
Saskia van der Oord, Ph.D.
Manfred Döpfner, Ph.D.
Ralf W. Dittmann, M.D., Ph.D.
Emily Simonoff, M.D.
Alessandro Zuddas, M.D.
Tobias Banaschewski, M.D., Ph.D.
Jan Buitelaar, M.D., Ph.D.
David Coghill, M.D.
Chris Hollis, M.D.
Eric Konofal, M.D., Ph.D.
Michel Lecendreux, M.D.
Ian C.K. Wong, Ph.D.
Joseph Sergeant, Ph.D.
European ADHD Guidelines Group

Objective: Nonpharmacological treatments are available for attention deficit hyperactivity disorder (ADHD), although their efficacy remains uncertain. The authors undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments.

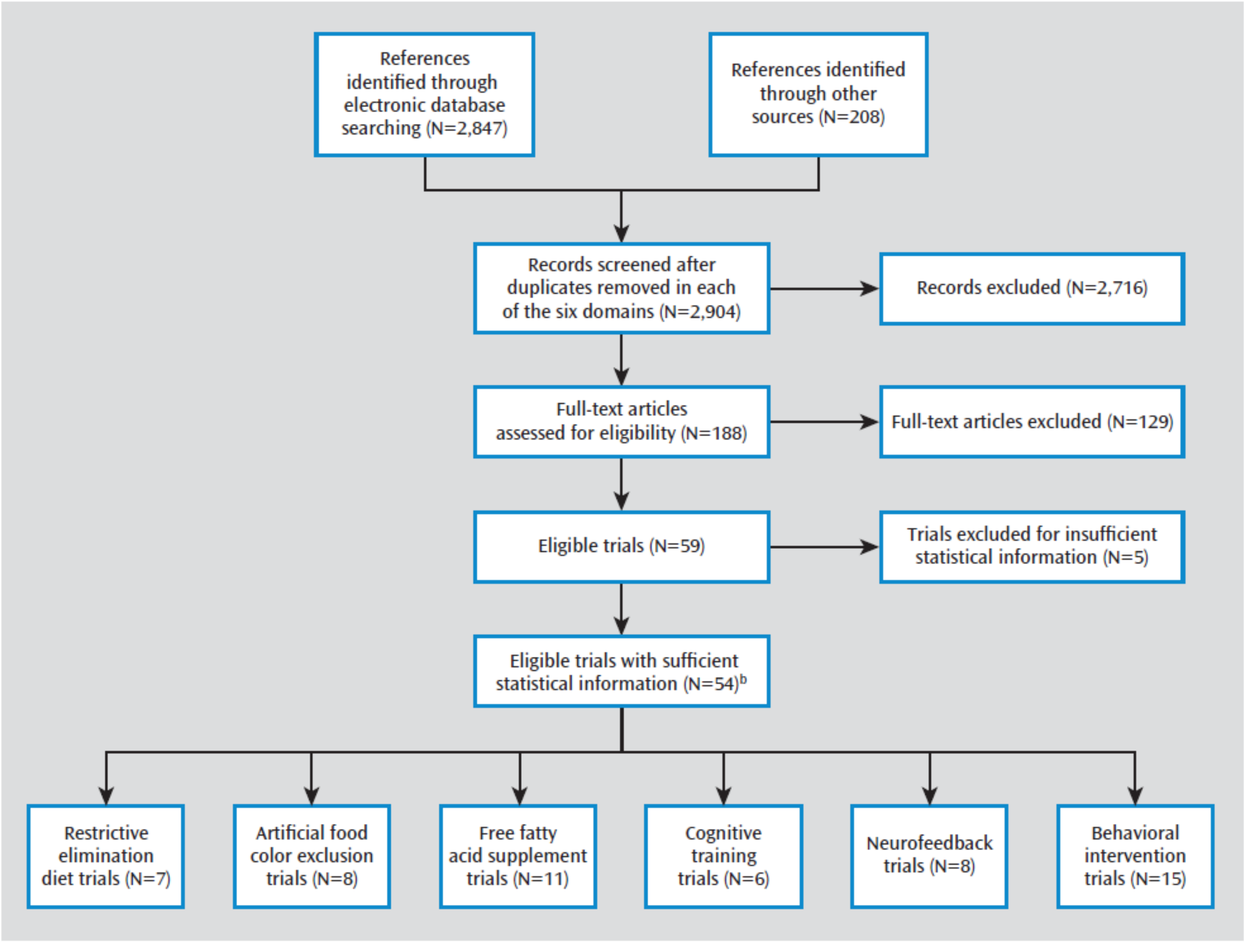
Method: Using a common systematic search and a rigorous coding and data extraction strategy across domains, the authors searched electronic databases to identify published randomized controlled trials that involved individuals who were diagnosed with ADHD (or who met a validated cutoff on a recognized rating scale) and that included an ADHD outcome.

Results: Fifty-four of the 2,904 nonduplicate screened records were included in the analyses. Two different analyses were performed. When the outcome measure was based on ADHD assessments by raters closest to the therapeutic setting, all dietary (standardized mean differences=0.21–0.48) and psychological (standardized mean differences=0.40–0.64) treatments produced statistically significant effects. However, when the best probably blinded assessment was employed, effects remained significant for free fatty acid supplementation (standardized mean difference=0.16) and artificial food color exclusion (standardized mean difference=0.42) but were substantially attenuated to nonsignificant levels for other treatments.

Conclusions: Free fatty acid supplementation produced small but significant reductions in ADHD symptoms even with probably blinded assessments, although the clinical significance of these effects remains to be determined. Artificial food color exclusion produced larger effects but often in individuals selected for food sensitivities. Better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptoms.

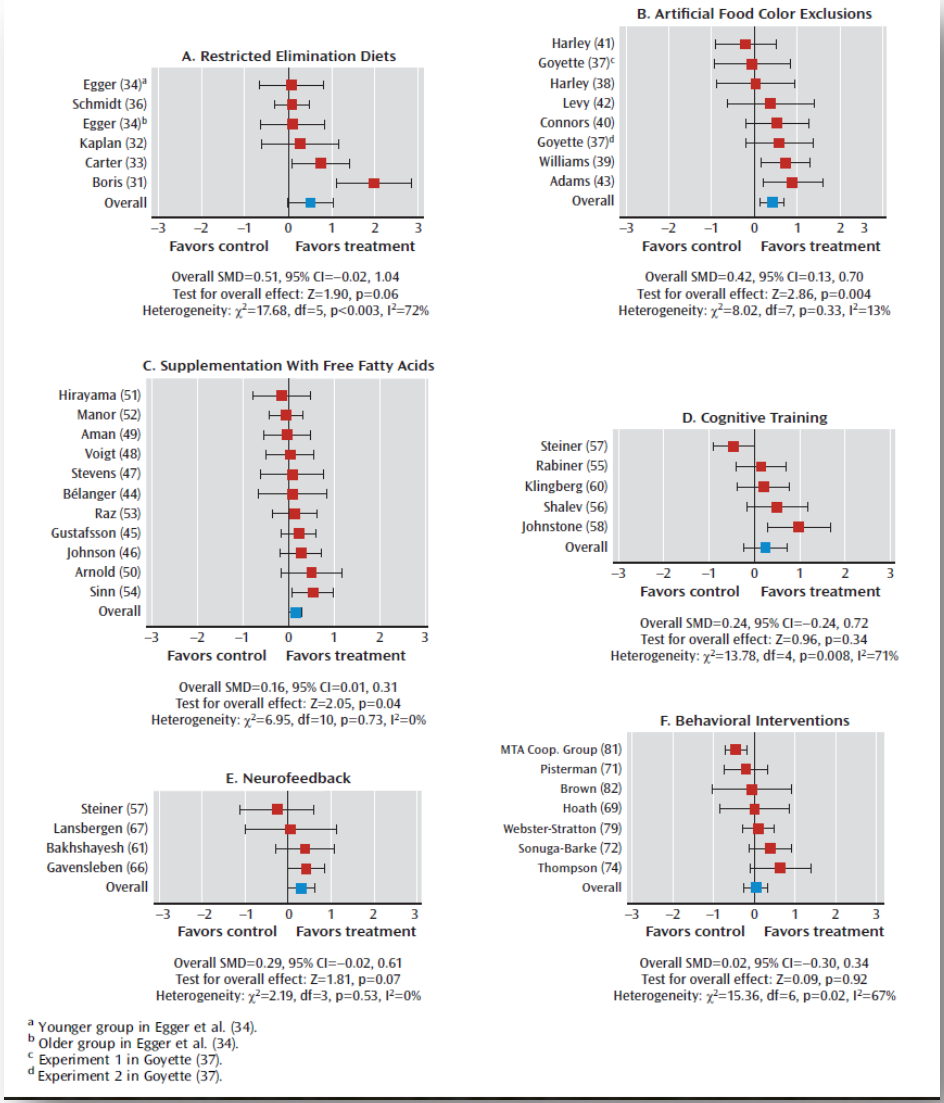
IMPACTO DE LA DIETA

FIGURE 1. Combined PRISMA Flow Chart for All Six Treatment Domains Systematically Reviewed[a]



[a] PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).
[b] Data from one three-arm trial are included in both neurofeedback and cognitive training analyses.

IMPACTO DE LA DIETA



INDICE

- Introducción
- Dieta y TDAH
- Microbioma y TDAH
- Proyecto Vall d'Hebron
- Conclusiones

IMPACTO DEL MICROBIOMA EN SNC

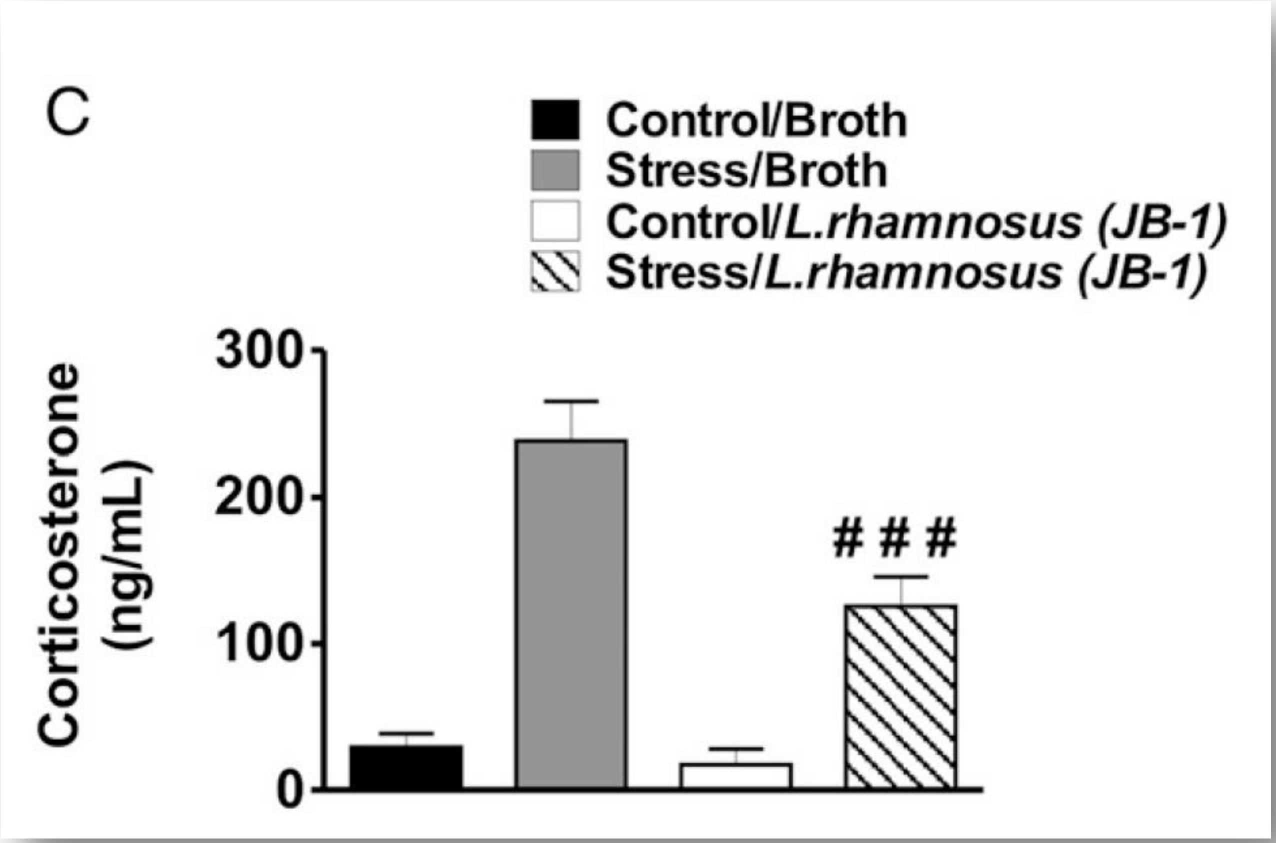
Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

Javier A. Bravo[a,1], Paul Forsythe[b,c,1], Marianne V. Chew[b], Emily Escaravage[b], Hélène M. Savignac[a,d], Timothy G. Dinan[a,e], John Bienenstock[b,f,2], and John F. Cryan[a,d,g,2]

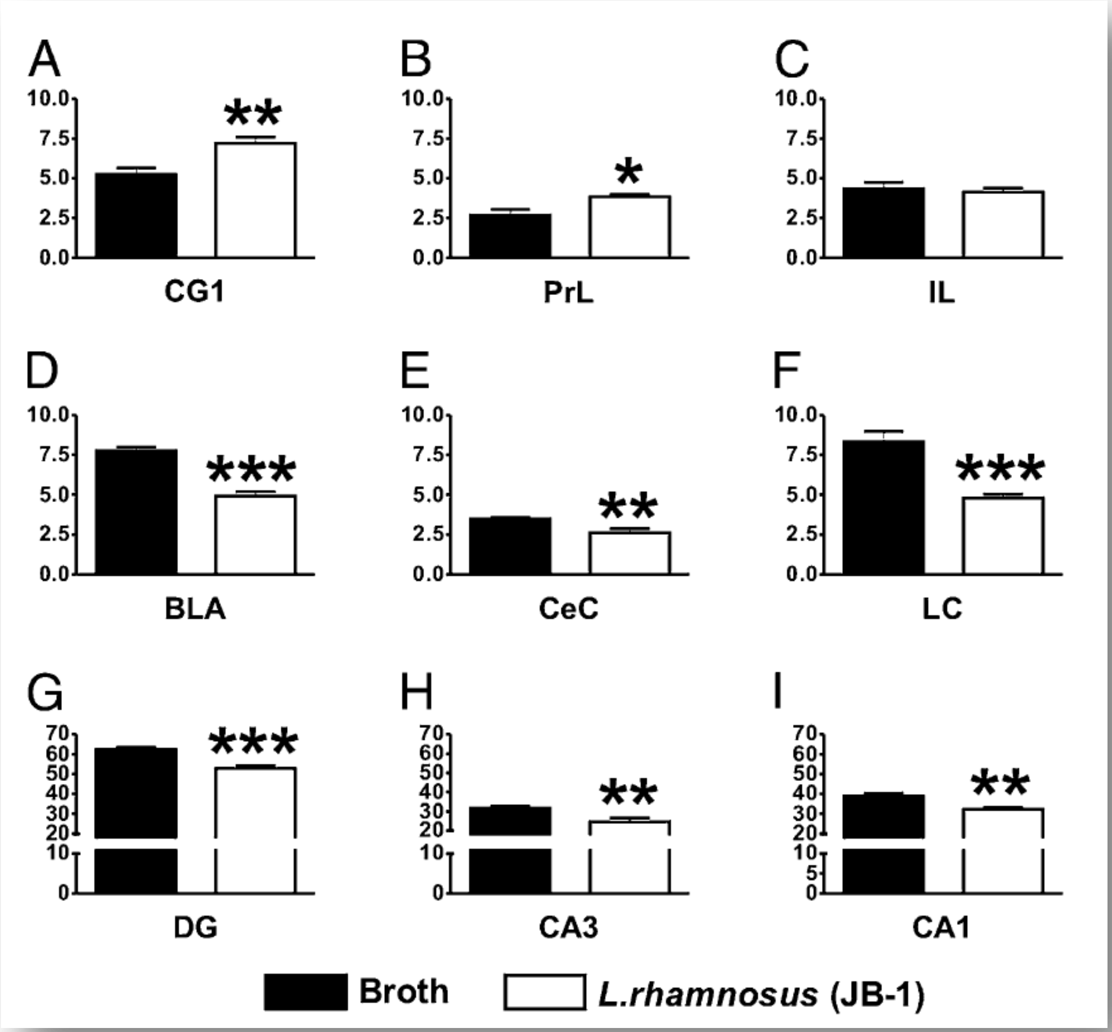
[a]Laboratory of NeuroGastroenterology, Alimentary Pharmabiotic Centre, [d]School of Pharmacy, and Departments of [e]Psychiatry and [g]Anatomy, University College Cork, Cork, Ireland; [b]The McMaster Brain–Body Institute, St. Joseph's Healthcare, Hamilton, ON, Canada L8N 4A6; and Departments of [c]Medicine and [f]Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada L8S 4L8

Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved July 27, 2011 (received for review February 27, 2011)

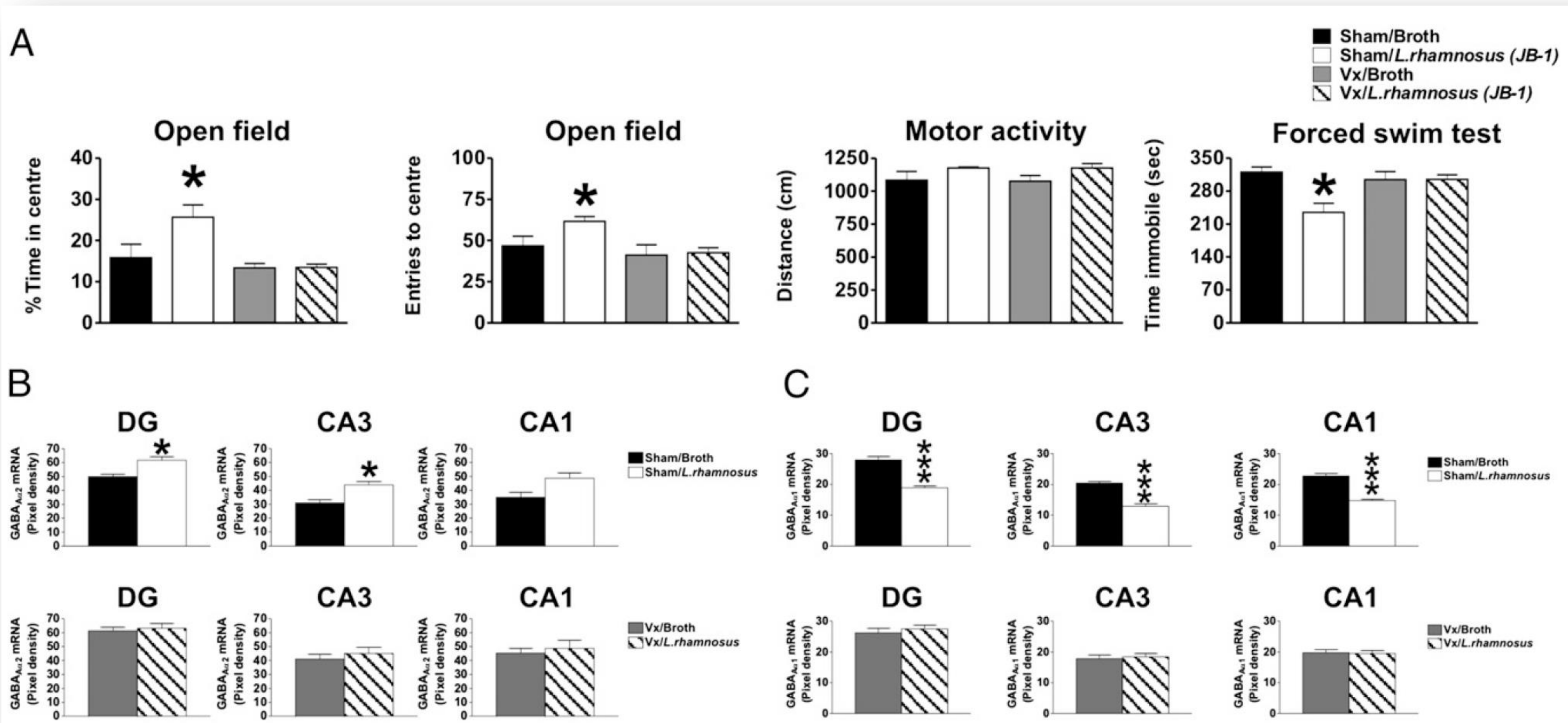
IMPACTO DEL MICROBIOMA EN SNC



IMPACTO DEL MICROBIOMA EN SNC



IMPACTO DEL MICROBIOMA EN SNC



IMPACTO DEL MICROBIOMA EN SNC

GASTROENTEROLOGY 2013;144:1394–1401

Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity

KIRSTEN TILLISCH,[1] JENNIFER LABUS,[1] LISA KILPATRICK,[1] ZHIGUO JIANG,[1] JEAN STAINS,[1] BAHAR EBRAT,[1] DENIS GUYONNET,[2] SOPHIE LEGRAIN–RASPAUD,[2] BEATRICE TROTIN,[2] BRUCE NALIBOFF,[1] and EMERAN A. MAYER[1]

[1]Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California; and [2]Danone Research, Palaiseau, France

- The FMPP contained Bifidobacterium animalis subsp Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis subsp Lactis

IMPACTO DEL MICROBIOMA EN SNC

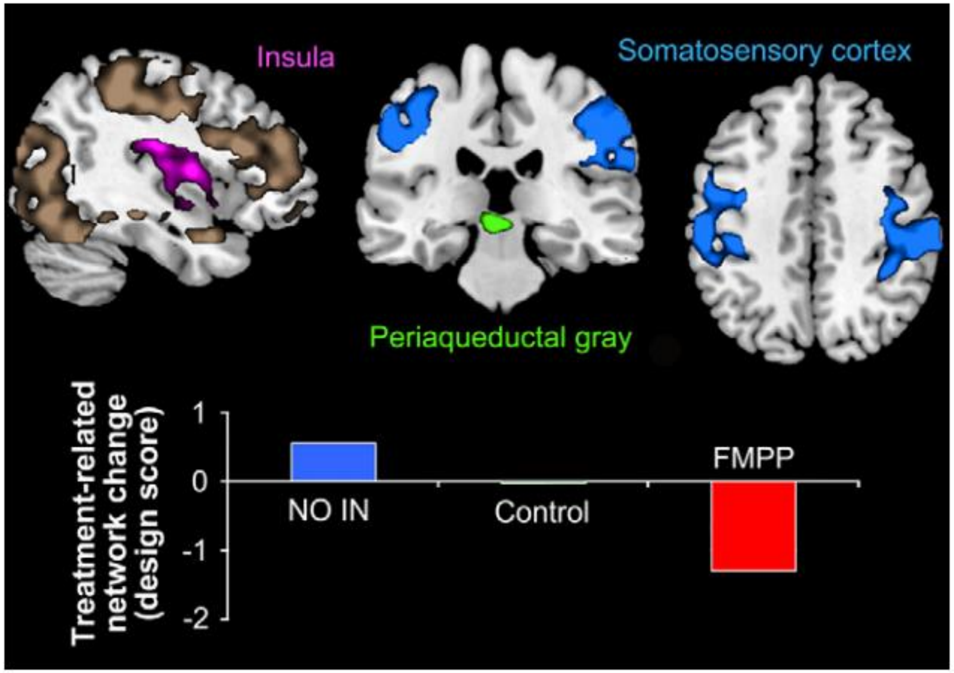


Figure 1. A distributed network of brain regions showing decreases in the FMPP group during the emotional faces attention task is shown in the shaded regions. Three regions of interest selected from the network for study in the resting state are highlighted in *pink* (insula), *green* (periaqueductal gray), and *blue* (somatosensory regions). The change in network strength with intervention is depicted graphically.

IMPACTO DEL MICROBIOMA EN SNC

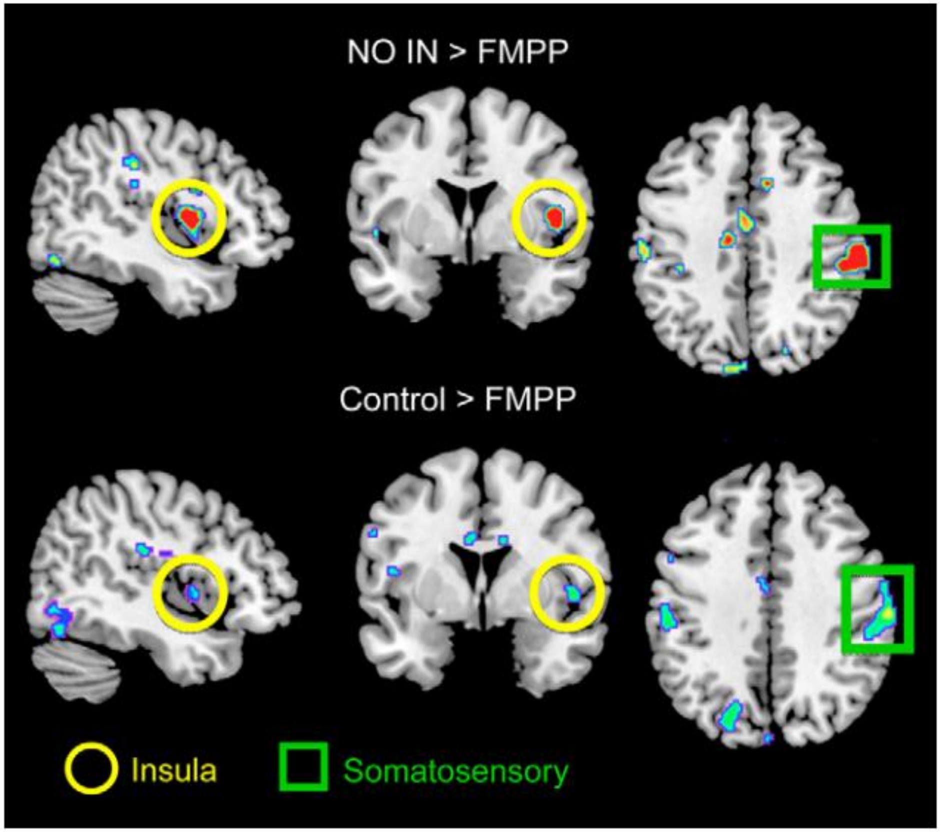
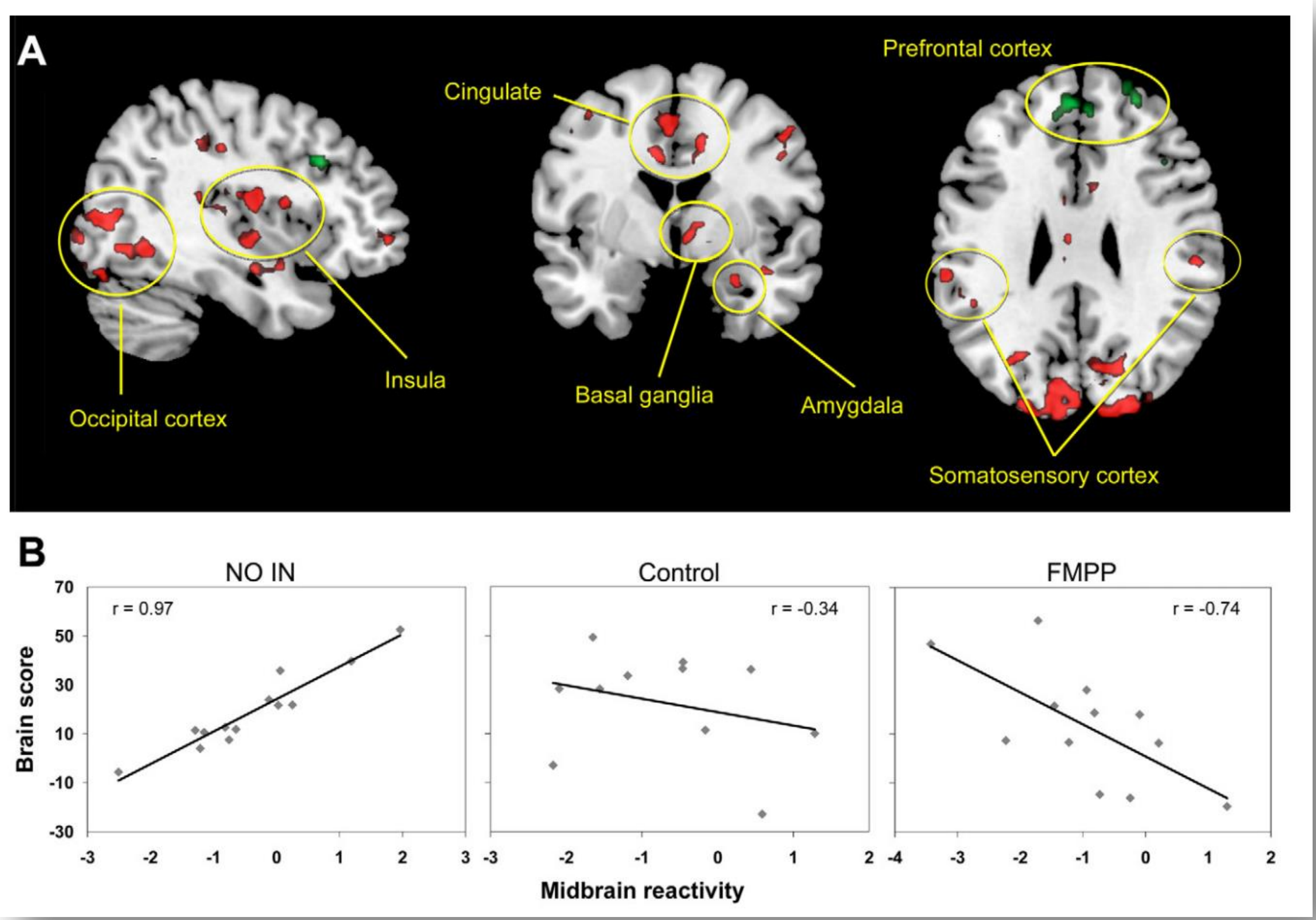


Figure 2. Regions showing reduced activity in response to an emotional faces attention task after FMPP intervention are shown, with significant regions demarcated.

IMPACTO DEL MICROBIOMA EN SNC



IMPACTO DEL MICROBIOMA EN SNC

25

Colonization with human ADHD gut microbiota influences brain structure and function in mice

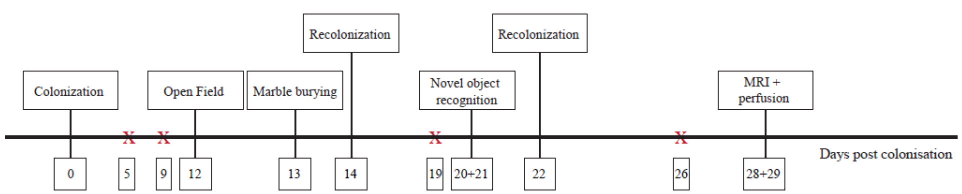
Anouk C Tengeler[1], Maximilian Wiesmann[1], Alejandro Arias Vasquez[2,3,4], Barbara Franke[2,3], Arend Heerschap[5], Tamas L Kozicz*[1], Amanda J Kiliaan*[1]

1 Department of Anatomy, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
2 Department of Psychiatry, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
3 Department of Human Genetics, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
4 Department of Cognitive Neurosciences, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
5 Department of Radiology & Nuclear Medicine, Radboud university medical center, Nijmegen, The Netherlands
*Shared last authorship

DONDERS INSTITUTE

Material & Methods

Young (38 ± 0.5 days old) male germ-free C57BL/6JOlaHsd mice were colonized with microbiota from persons with ADHD (ADHD-mice) or gender- and age-matched healthy controls (control mice). Mice were recolonized with the same microbiota twice during the experiment. Several behavioral tests were conducted such as the open field, marble burying and object recognition test. Mice were group-housed in, and behavioral tests were performed inside gnotobiotic isolators. Fecal pellets were collected at several timepoints during the experiment (see Figure 1 for a detailed schematic overview). Four weeks after the first colonization, RsfMRI, DTI, and FAIR-ASL were measured with the 11.7T scanner after which the animals were sacrificed via transcardial perfusion-fixation. Brains were collected and used for immunohistochemical assays. All the graphs show preliminary data of the mean ±SEM unless stated otherwise.



IMPACTO DEL MICROBIOMA EN SNC

Colonization with human ADHD gut microbiota influences brain structure and function in mice

Anouk C Tengeler[1], Maximilian Wiesmann[1], Alejandro Arias Vasquez[2,3,4], Barbara Franke[2,3], Arend Heerschap[5], Tamas L Kozicz*[1], Amanda J Kiliaan*[1]

1 Department of Anatomy, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
2 Department of Psychiatry, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
3 Department of Human Genetics, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
4 Department of Cognitive Neurosciences, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
5 Department of Radiology & Nuclear Medicine, Radboud university medical center, Nijmegen, The Netherlands
*Shared last authorship

DONDERS INSTITUTE

Anxiety-related behavior

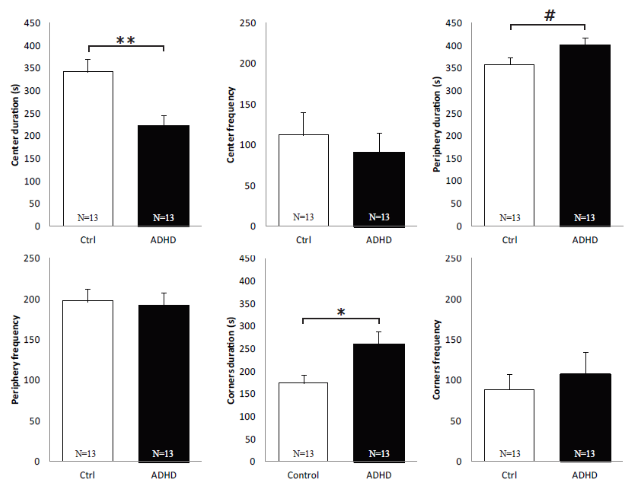


Figure 3. Anxiety-related behavior during 15 minutes in the open field test (40 cm x 40 cm). The time spent in the center (20 cm x 20 cm) is decreased in ADHD-mice compared to control mice (A). Time spent in the corners (10 cm x 10cm) is increased iin ADHD-mice (B). *P=0.017; **P=0.004; #P=0.059.

IMPACTO DEL MICROBIOMA EN SNC

Colonization with human ADHD gut microbiota influences brain structure and function in mice

Anouk C Tengeler[1], Maximilian Wiesmann[1], Alejandro Arias Vasquez[2,3,4], Barbara Franke[2,3], Arend Heerschap[5], Tamas L Kozicz*[1], Amanda J Kiliaan*[1]

1 Department of Anatomy, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
2 Department of Psychiatry, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
3 Department of Human Genetics, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
4 Department of Cognitive Neurosciences, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
5 Department of Radiology & Nuclear Medicine, Radboud university medical center, Nijmegen, The Netherlands
*Shared last authorship

DONDERS INSTITUTE

Resting-state functional connectivity changes

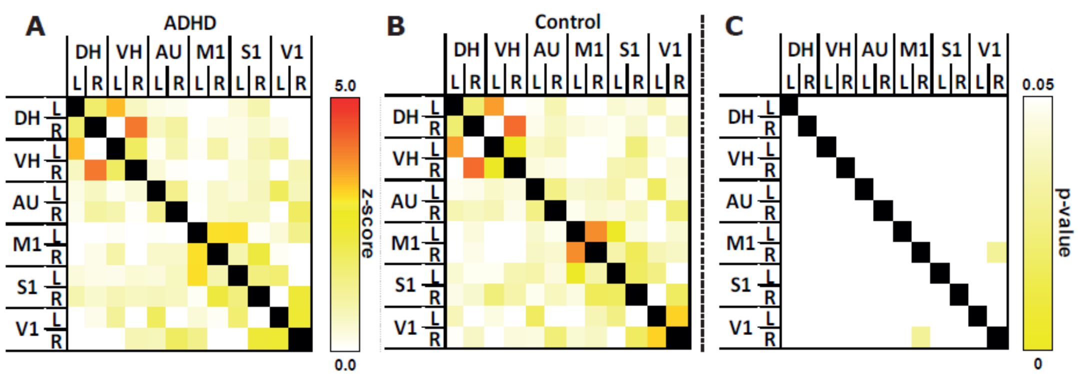


Figure 5. Resting-state FC based on partial correlation analyses of 12 ROIs. Partial correlation matrices of ADHD-mice; n=8 (A) and control mice; n=8 (B). Statistical analyses of FC reveals a significant lower FC between the right motor cortex and right visual cortex in ADHD-mice (C). DH=dorsal hippocampus; VH=ventral hippocampus; AU=auditory cortex; M1=motor cortex; S1=somatosensory cortex; V1=visual cortex; L=left; R=right.

IMPACTO DEL MICROBIOMA EN SNC

25

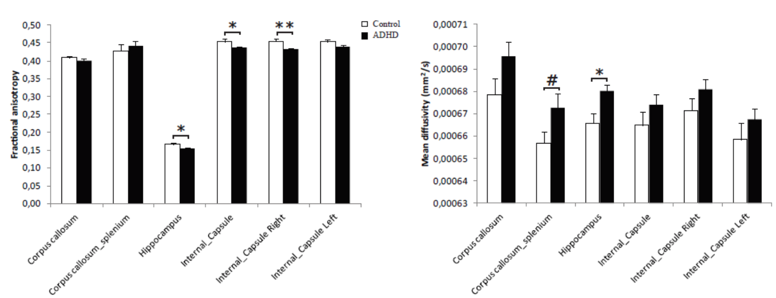
Colonization with human ADHD gut microbiota influences brain structure and function in mice

Anouk C Tengeler[1], Maximilian Wiesmann[1], Alejandro Arias Vasquez[2,3,4], Barbara Franke[2,3], Arend Heerschap[5], Tamas L Kozicz*[1], Amanda J Kiliaan*[1]

1 Department of Anatomy, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
2 Department of Psychiatry, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
3 Department of Human Genetics, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
4 Department of Cognitive Neurosciences, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
5 Department of Radiology & Nuclear Medicine, Radboud university medical center, Nijmegen, The Netherlands
*Shared last authorship

DONDERS INSTITUTE

Diffusion tension imaging



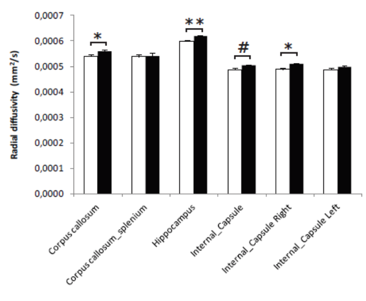


Figure 6. Quantitative assessment of diffusion tensor derived indices. ADHD-mice showed decreased fractional anisotropy (FA) in the hippocampus (P0.025), right internal capsule (P0.028) and whole internal capsule (P=0.007). In the mean diffusivity (MD), differences were detected in the hippocampus (P0.011). ADHD-mice had a higher radial diffusivity (RD) in the corpus callosum (P0.041), hippocampus (P0.004) and right internal capsule (P0.014). #P<0.08. Control n=11; ADHD n=11. Data are presented as mean ± SEM.

IMPACTO DEL MICROBIOMA EN SNC

Colonization with human ADHD gut microbiota influences brain structure and function in mice

Anouk C Tengeler[1], Maximilian Wiesmann[1], Alejandro Arias Vasquez[2,3,4], Barbara Franke[2,3], Arend Heerschap[5], Tamas L Kozicz*[1], Amanda J Kiliaan*[1]

1 Department of Anatomy, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
2 Department of Psychiatry, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
3 Department of Human Genetics, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
4 Department of Cognitive Neurosciences, Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.
5 Department of Radiology & Nuclear Medicine, Radboud university medical center, Nijmegen, The Netherlands
*Shared last authorship

DONDERS INSTITUTE

Conclusions

- Mice colonized with ADHD microbiota did not differ in locomotion activity, but were more anxious than control mice.
- ADHD-microbiota mice showed decreased functional connectivity between right motor cortex and right visual cortex.
- ADHD mice showed differences in diffusivity in the hippocampus and right internal capsule.

- These data showed that human ADHD gut microbiota induces anxiety, a common comorbidity of ADHD, and alters brain structure and connectivity in regions known to be altered in human ADHD patients.

¿PREVENCIÓN CON PROBIÓTICOS?

nature publishing group

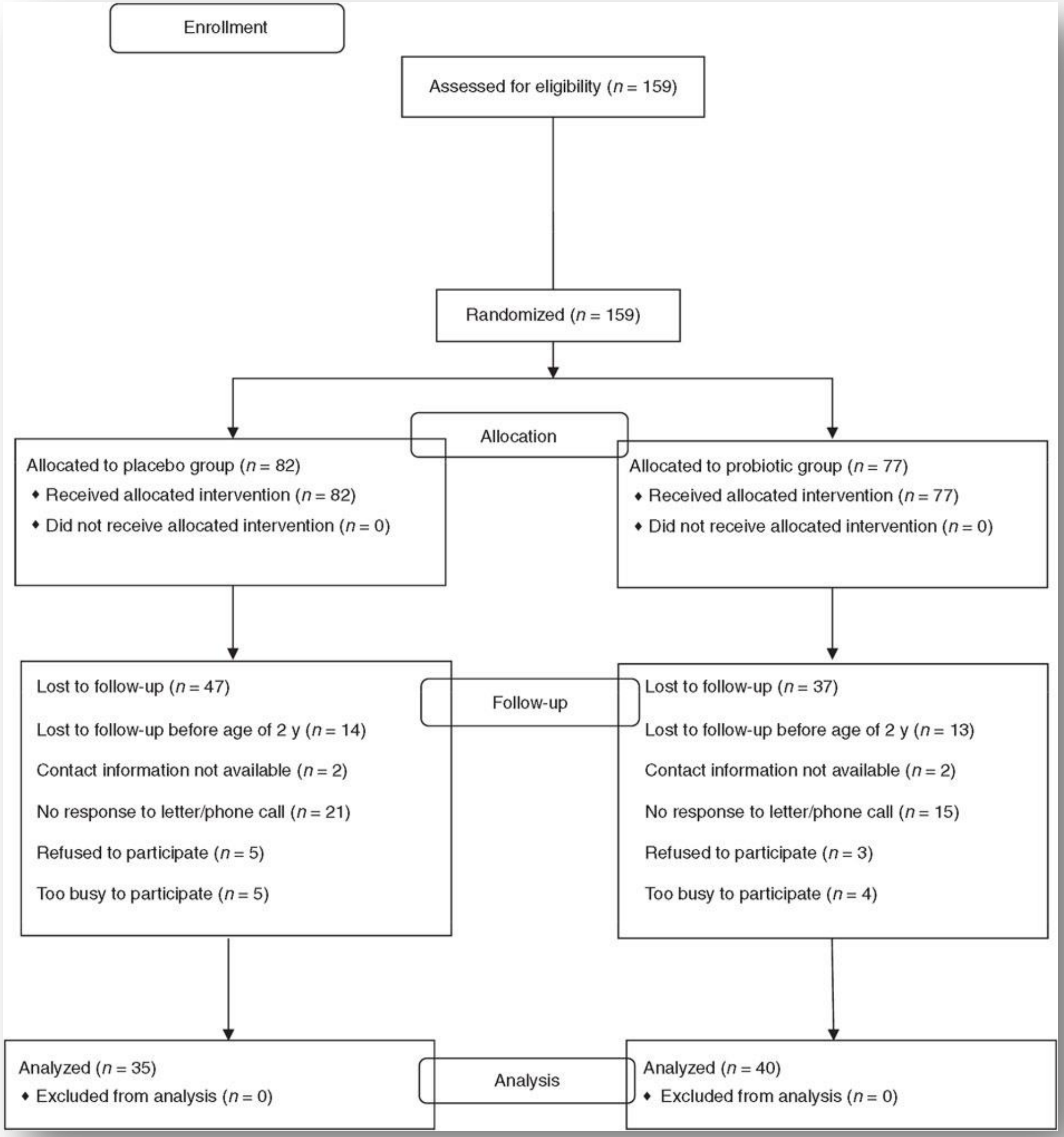
Clinical Investigation | Articles

A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial

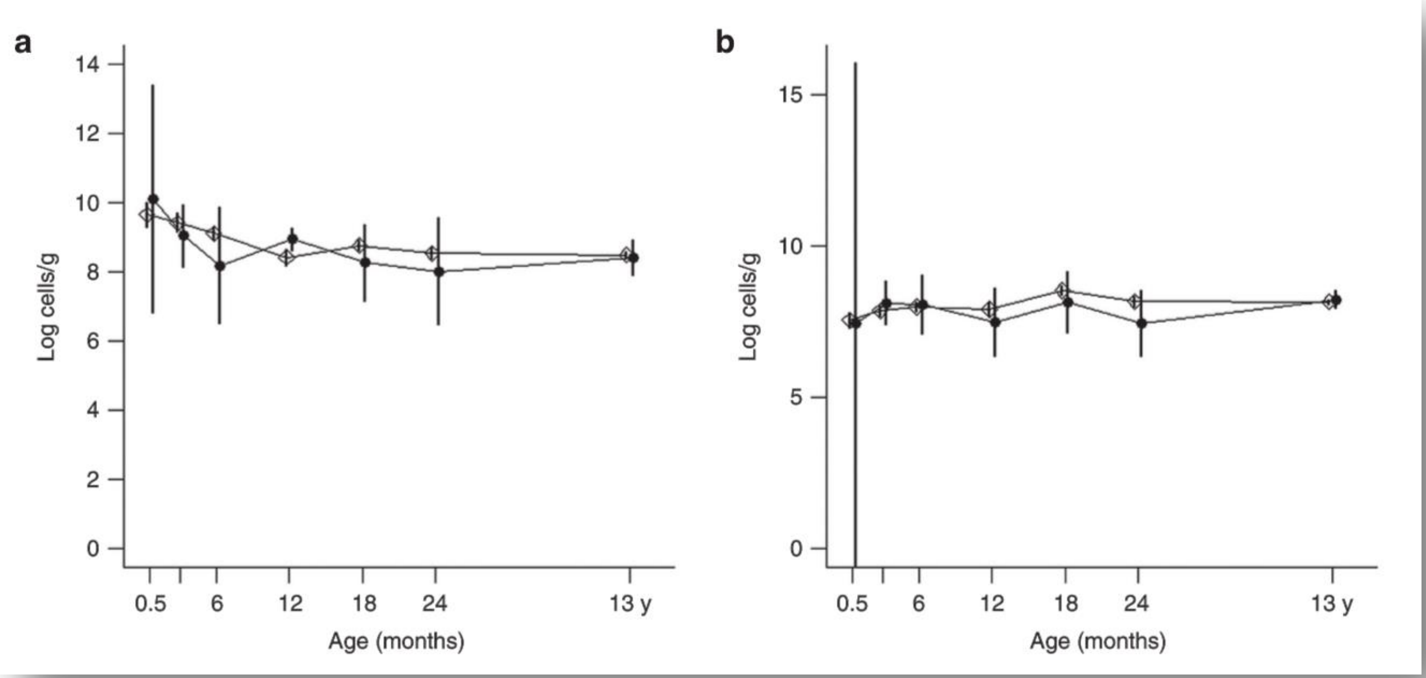
Anna Pärtty[1], Marko Kalliomäki[1], Pirjo Wacklin[2], Seppo Salminen[3] and Erika Isolauri[1]

Pediatr Res. 2015 Jun;77(6):823-8

¿PREVENCIÓN CON PROBIÓTICOS?

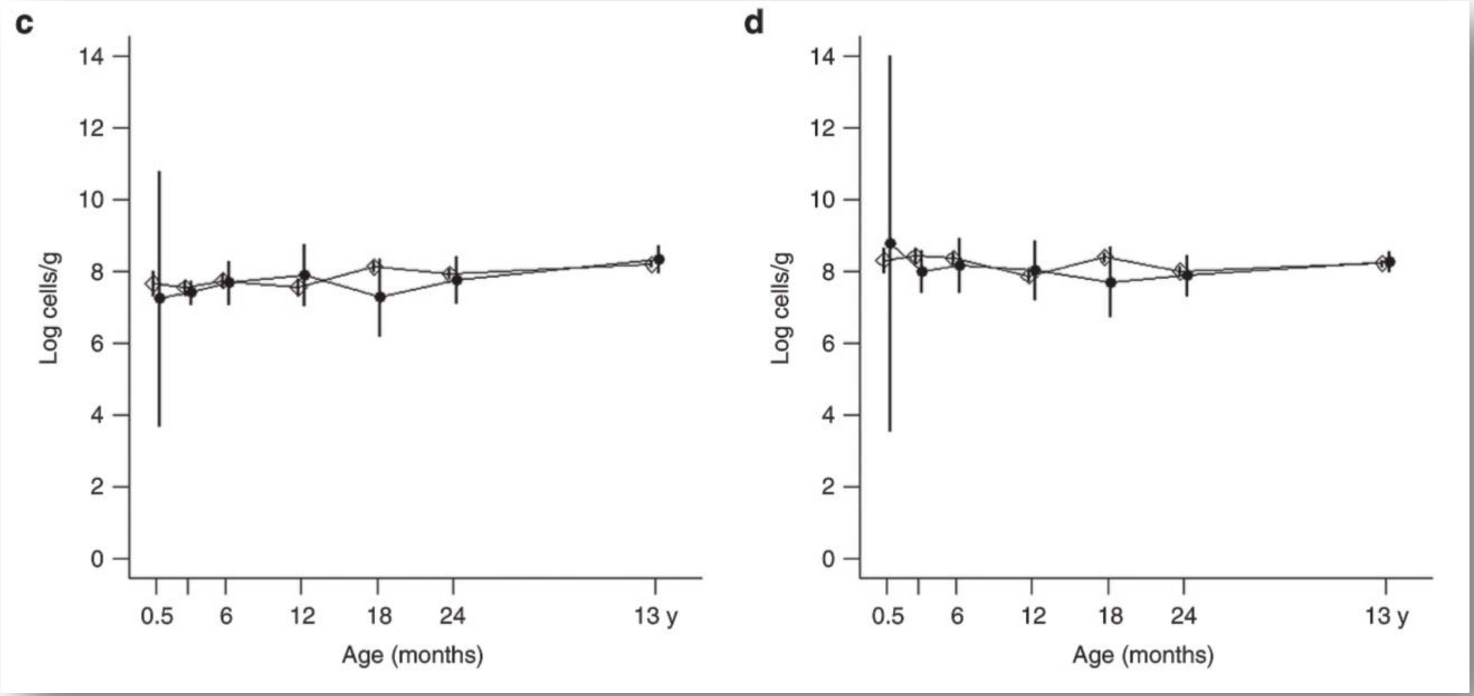


¿PREVENCIÓN CON PROBIÓTICOS?



Bifidobacterium **Clostridium histolitycum**

¿PREVENCIÓN CON PROBIÓTICOS?



Bacteroides-Prevotella **Lactobacilus Enterococus**

¿PREVENCIÓN CON PROBIÓTICOS?

Table 1. Clinical characteristics of the study subjects

	Probiotic, *n* = 40	Placebo, *n* = 35
Male	24 (60)	16 (46)
Vaginal delivery	33 (83)	29 (83)
Gestational age at birth (wk)[a]	40 (2)	40 (2)
Birth weight (g)[a]	3,493 (573)	3,694 (574)
Birth length (cm)[a]	51 (2)	51 (2)
Apgar score at 5 min[a]	9 (1)	9 (1)
Exclusively breast-fed (months)[a]	3(2)	3 (2)
Antibiotic treatment during the first 6 mo of life	13 (33)	7 (20)
Weight at age of 13 y (kg)[a]	56 (12)	57 (12)
Length at age of 13 y (cm)[a]	165 (9)	165 (9)
Systolic blood pressure at the age of 13 (mmHg)[a]	104 (10)	106 (11)
Waist circumference (cm)[a]	70 (8)	72 (10)

Results are given as mean (SD)[a] or as number (%) of subjects. Clinical characteristics of the study population were comparable between the groups ($P > 0.05$ in all the comparisons).

¿PREVENCIÓN CON PROBIÓTICOS?

Table 2. Clinical characteristics of the children completing and not completing the present study

	Children completing the study, $n = 75$	Dropouts, $n = 83$
Male	40 (53)	53 (64)
Vaginal delivery	62 (83)	70 (84)
Gestational age at birth (wk)[a]	40 (2)	40 (1)
Birth weight (g)[a]	3,585 (582)	3,631 (435)
Birth length (cm)[a]	51 (2)	51 (2)
Apgar score at 5 min[a]	9 (1)	9 (1)
Exclusively breast-fed (months)[a]	3(2)	2 (2)
Antibiotic treatment during the first 6 mo of life	20 (27)	16 (24)

Results are given as mean (SD)[a] or as number (%) of subjects. Clinical characteristics of the study population were comparable between the groups ($P > 0.05$ in all the comparisons), except for length of exclusive breast-feeding ($P = 0.03$).

¿PREVENCIÓN CON PROBIÓTICOS?

Table 3. Clinical characteristics of children with and without ADHD or AS

	Healthy, $n = 69$	ADHD/AS, $n = 6$	P value
Early probiotic supplementation	40 (58)	0 (0)	$P = 0.008$
Male	34 (49)	6 (100)	$P = 0.03$
Vaginal birth	58 (84)	4 (67)	$P = 0.28$
Exclusively breast-fed (months)[a]	3 (2)	2 (2)	$P = 0.16$
Antibiotic treatment during the first 6 mo of life	19 (28)	1 (17)	$P = 1.00$
Total distress during the 7th week (min/day)[a,b]	107 (73)	101 (87)	$P = 0.87$
Total distress during the 12th week (min/day)[a,c]	68 (46)	50 (50)	$P = 0.42$
Weight at age of 13 y (kg)[a]	54 (12)	57 (12)	$P = 0.64$
Length at age of 13 y (cm)[a]	165 (9)	163 (10)	$P = 0.48$
Systolic blood pressure at age of 13 y (mmHg)[a]	105 (10)	105 (14)	$P = 0.92$

Results are given as mean (SD)[a], or as numbers (%) of subjects. [b]The sum of colic type, other cry, and fussing reported by parents; $n = 47$ for healthy and $n = 5$ for ADHD/AS. [c]The sum of colic type, other cry, and fussing reported by parents; $n = 45$ for healthy and $n = 5$ for ADHD/AS.

INDICE

- Introducción
- Dieta y TDAH
- Microbioma y TDAH
- Proyecto Vall d'Hebron
- Conclusiones

PROYECTO VALL D'HEBRON

Estudio de asociación a escala metagenómica (MGWAS) en adultos con TDAH a través de secuenciación masiva de ADN de muestras fecales

- **HIPÓTESIS:**
  - Los pacientes con TDAH presentan alteraciones en el perfil de microbiota intestinal en relación a individuos sin TDAH.
  - Diferenciar perfiles clínicos: sintomas, gravedad y funciones cognitivas.

PROYECTO VALL D'HEBRON

Estudio de asociación a escala metagenómica (MGWAS) en adultos con TDAH a través de secuenciación masiva de ADN de muestras fecales

- **METODOLOGÍA:**
  - 100 pacientes con TDAH vs 100 individuos sin TDAH.
  - Estudio de asociación metagenómico.
  - Correlacionar la composición bacteriana intestinal con subtipos clínicos del TDAH.
  - Fase de replica con 200 adultos de Radbound University Medical Centre (Holanda).

INDICE

- Introducción
- Dieta y TDAH
- Microbioma y TDAH
- Proyecto Vall d'Hebron
- Conclusiones

CONCLUSIONES

- El estudio del microbioma intestinal puede ayudarnos a entender mejor el TDAH.
- La modulación de la dieta puede tener un impacto en la intensidad del TDAH.
- El microbioma intestinal se ha asociado a cambios a nivel del SNC.
- La modulación del microbioma intestinal con probióticos puede tener efectos terapéuticos en el TDAH.

AGRADECIMIENTOS

Vall d'Hebron
Barcelona Campus Hospitalari

Papel del miocrobioma en los trastornos del neurodesarrollo

J. Antoni Ramos-Quiroga

@ramosquiroga2

Servicio de Psiquiatría. CIBERSAM
Hospital Universitari Vall d'Hebron
Universitat Autònoma de Barcelona