VIII CONGRESSO NAZIONALE

SINut Società Italiana di Nutraceutica

Fondazione V S M

Probiotici ed autismo: una speranza per il futuro?

Enzo Grossi

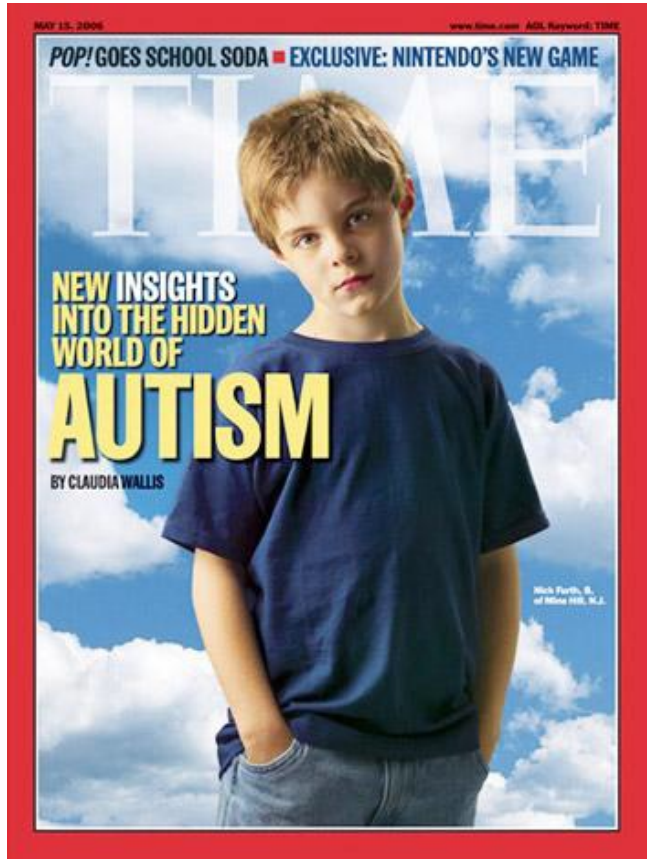
Fondazione Villa Santa Maria, Tavernerio(Como)

Bologna, 16 Giugno 2018

WHAT IS AUTISM ?

Autism is a severe organic brain disease with loss of normal cortical architecture and synapses loss characterized by a complex spectrum of deficits:

- Social communication and social interaction
- Verbal communication
- Intellectual ability
- Restricted nutrition
- Stereotyped motor movements
- Highly restricted interests



Menu | I migliori 10 ristoranti: Sca | Posta in arrivo (59) - anna | autism probiotics - PubMe | Autismo, negli anni 70 un
www.dire.it/11-06-2018/210640-autismo-negli-anni-70-un-caso-su-5-000-oggi-1-su-110/

DiRE
AGENZIA DI STAMPA NAZIONALE

Sanità

ROMA – "C'è un'escalation preoccupante delle diagnosi di autismo non solo in Italia ma

Epidemiology of ASD in USA

Center for Disease Control and Prevention (USA):

2009 = 1 in 110 US children

2012 = 1 in 88 US children

2014 = 1 in 68 US children

King & Bearman. *Am. Soc.Rev. (2011)*

GI symptoms are common at the onset of ASD and often persist

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American Academy of Pediatrics
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Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis

Barbara O. McElhanon, Courtney McCracken, Saul Karpen and William G. Sharp

Pediatrics; originally published online April 28, 2014;
DOI: 10.1542/peds.2013-3995

Gastrointestinal disturbances in ASD

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Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis
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Pediatrics; originally published online April 28, 2014;
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Study	OR	95% CI
Black et al[33]	1.03	(0.48–2.20)
Gondalia et al[43]	14.91	(4.68–47.52)
Horvath & Perman[40]	12.1	(6.00–24.41)
Ibrahim et al[37]	1.15	(0.71–1.86)
Mouridsen et al[38]	0.39	(0.22–0.69)
Parracho et al[a23]	48.25	(11.83–196.85)
Smith et al[42]	11.67	(4.02–33.86)
Valicenti-McDermott et al[41]	6.00	(2.53–14.24)
Wang et al[24]	5.24	(3.19–8.60)
Wang et al[36]	4.07	(2.04–8.11)
Overall Estimate	**4.42**	**(1.90–10.28)**

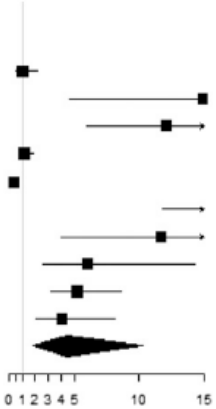

FIGURE 2
Forest plot of general GI concerns with 95% CIs. [a]OR outside of range.

McElhanon et al. *Pediatrics (2014)*

CONCLUSIONs

✓ Children with ASD present a significant increase of gastrointestinal symptoms in comparison to typically developing children with a OR of4.42 (95% CI 1.90-10.28).

Correlation between autism severity and gastrointestinal symptoms

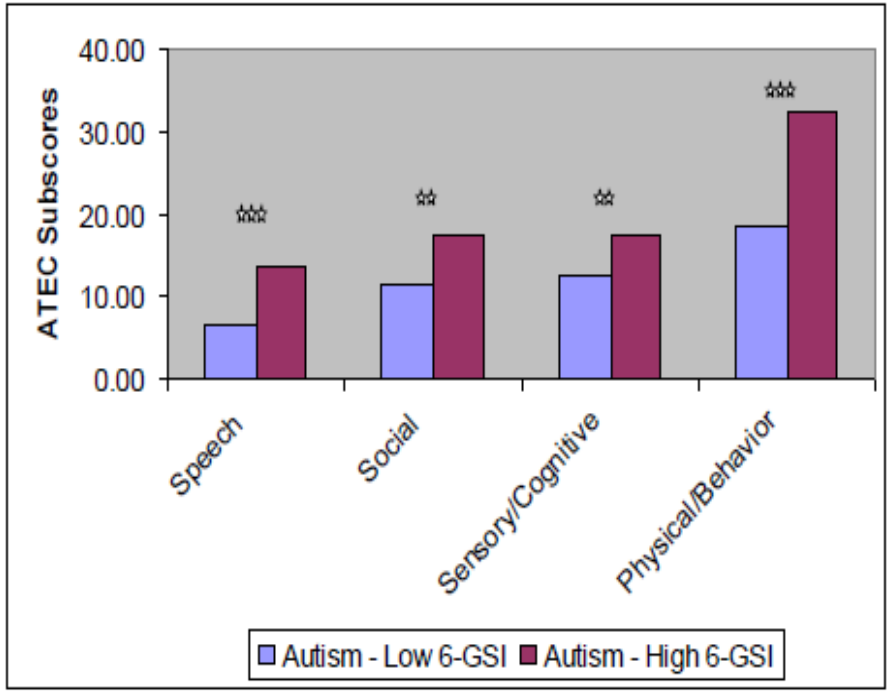

Figure 2 Comparison of ATEC subscores for the Autism-Low 6-GSI group (few GI problems) and the Autism High 6-GSI group (ma GI problems); the stars indicate the significance (*** $p < 0.001$, ** $p < 0.01$).

Adams et al. BMC Gastroenterology 2011, 11:22
http://www.biomedcentral.com/1471-230X/11/22

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Gastrointestinal flora and gastrointestinal status in children with autism–comparisons to typical children and correlation with autism severity

James B Adams[1*], Leah J Johansen[1], Linda D Powell[1], David Quig[2] and Robert A Rubin[3]

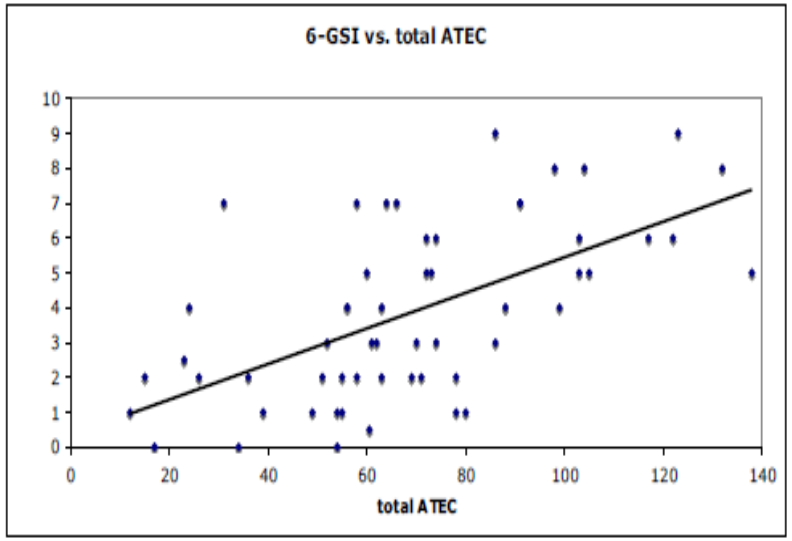

Figure 3 6-Item Gastrointestinal Severity Index (6-GSI) vs. total ATEC score

Adams et al. *BMC Gastroenterology (2011)*

J Autism Dev Disord
DOI 10.1007/s10803-017-3271-5

ORIGINAL PAPER

Behavioral Phenotype of ASD Preschoolers with Gastrointestinal Symptoms or Food Selectivity

Margherita Prosperi[1] · Elisa Santocchi[1] · Giulia Balboni[2] · Antonio Narzisi[1] · Margherita Bozza[3] · Francesca Fulceri[1] · Fabio Apicella[1] · Roberta Igliozzi[1] · Angela Cosenza[1] · Raffaella Tancredi[1] · Sara Calderoni[1,4] · Filippo Muratori[1,4]

© Springer Science+Business Media, LLC 2017

Variables	ASD GI+ ($n=42$) Mean ± *SD*	ASD GI− ($n=121$) Mean ± *SD*	Student *t* test (*t* value)
ADOS CSS	7.12 ± 1.71	6.39 ± 1.77	2.30*
CBCL syndrome scales			
Emotionally Reactive	59.86 ± 10.56	56.56 ± 8.15	2.08*
Anxious/Depressed	58.41 ± 7.87	55.90 ± 6.74	1.98*
Somatic Complaints	51.33 ± 2.49	50.81 ± 2.53	1.16
Withdrawn	71.74 ± 10.03	68.83 ± 10.02	1.62
Sleep Problems	59.14 ± 10.50	54.65 ± 5.86	3.43***
Attention Problems	64.69 ± 7.61	61.58 ± 8.19	2.16*
Aggressive Problems	56.79 ± 6.31	54.04 ± 5.50	2.68**
CBCL Summary Scales			
Internalizing Problems	60.98 ± 8.92	57.01 ± 8.97	2.47*
Externalizing Problems	57.69 ± 8.64	53.43 ± 8.46	2.80**
Total Problems	63.60 ± 10.43	56.21 ± 9.84	4.13***

Journal

Adams *et al. BMC Gastroenterology* 2011, **11**:22
http://www.biomedcentral.com/1471-230X/11/22

RESEARC

Gastroi
in chilc

Dig Dis Sci
DOI 10.1007/s10620-012-2167-7

ORIGINAL ARTICLE

Elevated Fecal Short Chain Fatty Acid and Ammonia

National Research FLAGSHIPS Preventative Health

CSIRO

FAECAL MICROBIOTA AND FERMENTATION PRODUCTS ARE ALTERED IN CHILDREN WITH AUTISM SPECTRUM DISORDER

UniSA | Sansom Institute

L. Wang[1], C.T. Christophersen[2], M.J. Sorich[1], C.P. Gerber[1], M.T. Angley[1] and M.A. Conlon[2]

1 Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA
2 Preventative Health National Research Flagship, CSIRO Food and Nutritional Sciences, Adelaide, SA

Introduction

- Autism Spectrum Disorder (ASD) is a is a complex neurodevelopmental condition and gastrointestinal (GI) factors have been implicated in its aetiology.
- Evidence is emerging that the profiles of GI microbiota [Song et al. 2004; Finegold et al. 2010] and fermentation products [Yap et al. 2010] in individuals with ASD are different from those without ASD.
- Williams et al. [2012] have recently shown that numbers of gastrointestinal mucosal *Sutterella spp.* Are elevated in children with ASD.
- Bacterial fermentation products such as short chain fatty acids (SCFA) are closely linked with gut health and contribute to various neurological processes [MacFabe et al 2008].
- It is not known if faecal SCFA profiles are altered in individuals with ASD.

Aims

- There were significantly decreased mean numbers of *Bifidobacteria* and *A. muciniphila* (p=0.032 & p= 0.016, respectively), while significantly higher mean numbers of *Sutterella* were found in ASD than CON participants (p=0.014) (Fig 2).

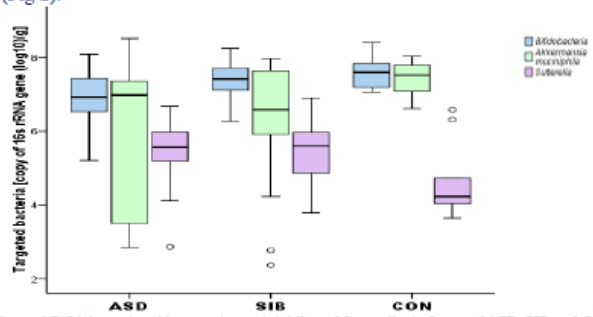

Figure 2 Numbers of *Bifidobacteria, Akkermansia muciniphila and Sutterella* in faeces of ASD, SIB and CON groups.

Growing literature about gut microbiota profile in ASD

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International Journal of Microbiology & Advanced Immunology (IJMAI)
ISSN 2329-9967

The Role of Intestinal Dysbiosis in the Pathogenesis of Autism: Minireview

Review Article

Enzo Grossi* MD & Vittorio Terruzzi MD

Villa Santa Maria Institute, NeuropsychiatricRehabilitating Center, Tavernerio (Como), Italy.

Abstract

Autism spectrum disorder is a complex neurodevelopmental disease where gastrointestinal disturbance is commonly reported. Here we review the evidence suggesting that gut microbota my play a role in this disease and summarize comparative studies we found in international literature on the topic. Discussion of results, methodology of the data collection, bias of selection and behavioral interferences lead to the conclusion that changes in the gut microbiota is a significant piece of autism spectrum disorder but further studies are needed to understand this pathogenetic role.

RESULTS

Only one study did not detect any difference
In 11 out of 12 studies significant differences evidenced

Significant increase

- *Bacteroidetes°* *(Prophyromonas, Prevotella)*
- *Firmicutes°** *(Caloramator, Clostridia)*
- *Proteobacteria°* *(Betaproteobactera, Pseudomonas, Aeromonas, Enterobacteria)*
- *Sutterella°**

Significant decrease

- *Bacteroidetes°**
- *Firmicutes°* *(Enterococcus, Lactobacillus, Streptococcus Lactococcus, Staphylococcus)*
- *Actinobacteria°* *(Bifidobacteria)*

°fecal dosage
*biopsies dosage

SUMMARY

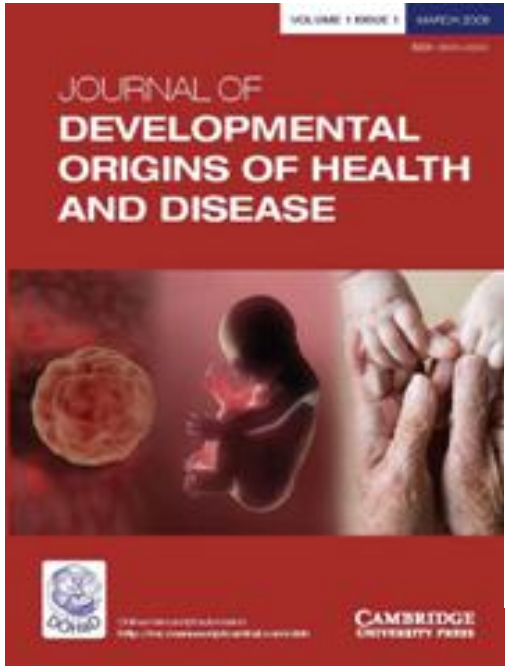
- In ASD patients there is an abnormal composition of gut microbiota
- The features of this abnormality are not yet clearly defined
- Further studies are needed with better methodological requirements, standardized method of assessment and careful recording of dietary pattern

Journal of Developmental Origins of Health and Disease

cambridge.org/doh

Received: 11 January 2018
Revised: 4 March 2018
Accepted: 14 March 2018

Original Article



Pregnancy risk factors related to autism: an Italian case–control study in mothers of children with autism spectrum disorders (ASD), their siblings and of typically developing children

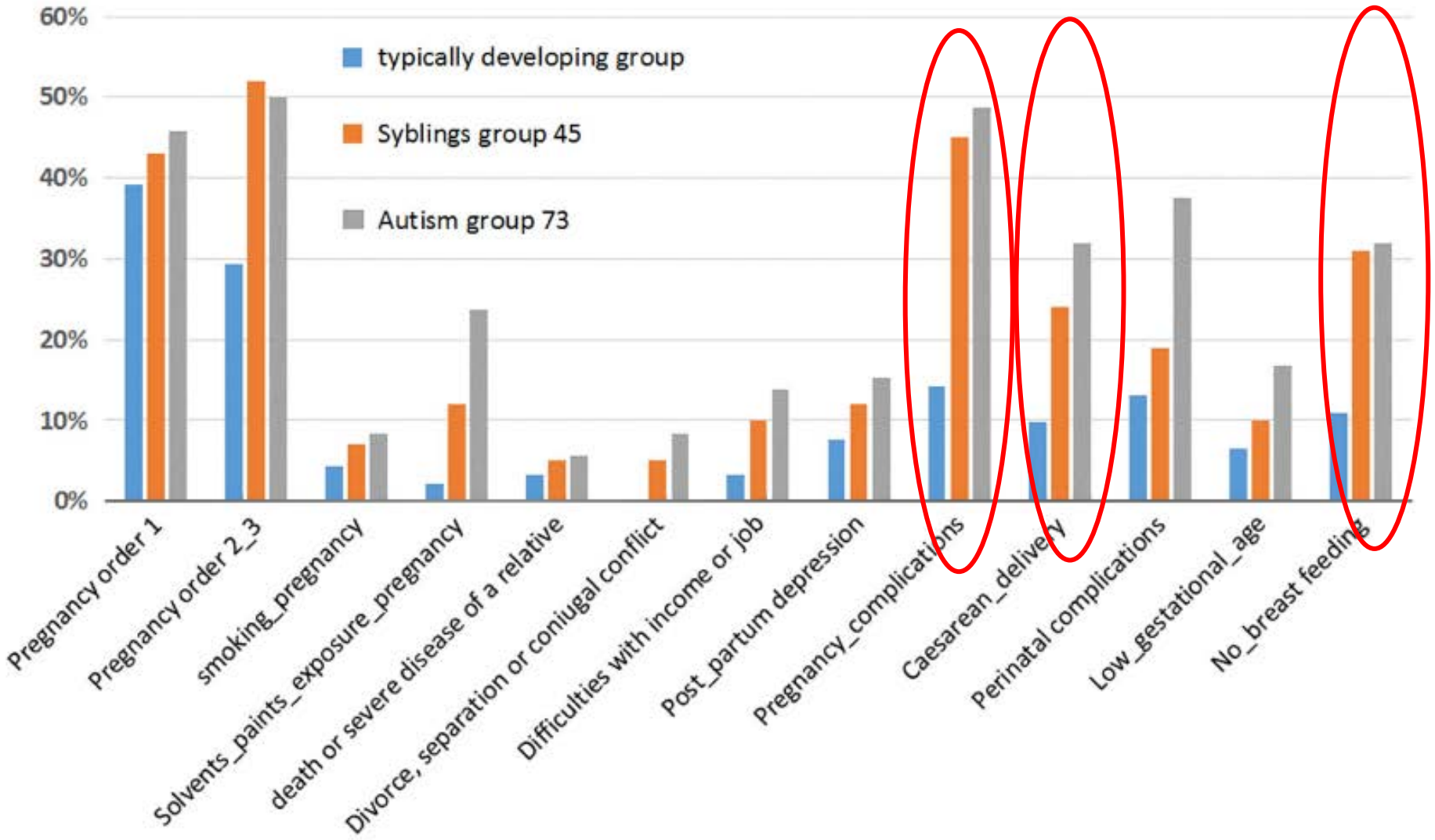
E. Grossi[1], L. Migliore[2] and F. Muratori[3,4]

[1]Department of Autism Research, Villa Santa Maria Foundation, Tavernerio, Italy, [2]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [3]Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, Calambrone, Italy and [4]Department of Developmental Neuroscience, University of Pisa, Calambrone, Italy

Abstract

This study, carried out in two Italian Institutions, assesses the frequency of 27 potential autism risk factors related to pregnancy and peri- and postnatal periods by interviewing mothers who had children with autism, children with autism and one or two typically

E. Grossi *et al.*



Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER et al.
California Institute of Technoogy, Pasadena, USA
Baylor College of Medicine, Huston, USA

Cell 2013; 155: 1-13

Impact Factor = 31,95

Please cite this article in press as: Hsiao et al., Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders, Cell (2013), http://dx.doi.org/10.1016/j.cell.2013.11.024

Cell

Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders

Elaine Y. Hsiao,[1,2,*] Sara W. McBride,[1] Sophia Hsien,[1] Gil Sharon,[1] Embriette R. Hyde,[3] Tyler McCue,[3] Julian A. Codelli,[2] Janet Chow,[1] Sarah E. Reisman,[2] Joseph F. Petrosino,[3] Paul H. Patterson,[1,4,*] and Sarkis K. Mazmanian[1,4,*]
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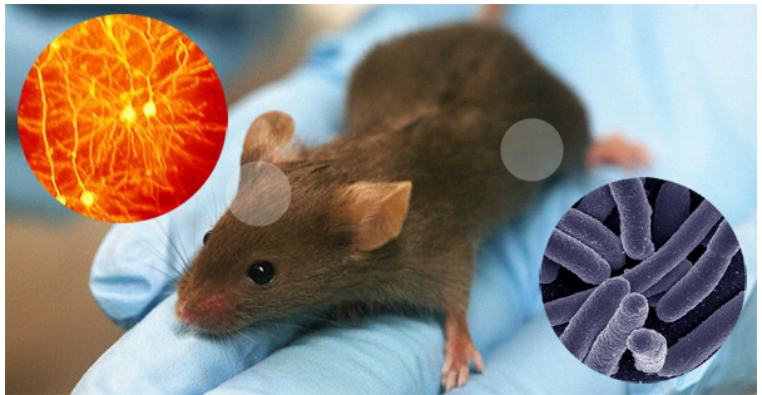
http://dx.doi.org/10.1016/j.cell.2013.11.024

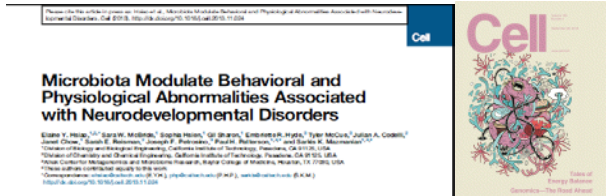


Maternal Immune Activation (MIA) autism model

Injection of a virus immune agent (poly-I:C) in pregnant mother

Autistic mouse: restricted nutrition; stereotyped motor movements; highly restricted interests; no voice communication; brain pathological changes; intestinal barrier disruption; urinary excretion of neurotoxic metabolites

Increase of clostridia genus; absence of B. fragilis



Dawson et al. BMC Microbiology 2011, 11:86
http://www.biomedcentral.com/1471-2180/11/86

BMC Microbiology

RESEARCH ARTICLE Open Access

The analysis of *para*-cresol production and tolerance in *Clostridium difficile* 027 and 012 strains

Lisa F Dawson[1], Elizabeth H Donahue[1], Stephen T Cartman[2], Richard H Barton[3,4], Jake Bundy[3], Ruth McNerney[1], Nigel P Minton[2] and Brendan W Wren[1*]

Abstract

Background: *Clostridium difficile* is the major cause of antibiotic associated diarrhoea and in recent years its increased prevalence has been linked to the emergence of hypervirulent clones such as the PCR-ribotype 027. Characteristically, *C. difficile* infection (CDI) occurs after treatment with broad-spectrum antibiotics, which disrupt the normal gut microflora and allow *C. difficile* to flourish. One of the relatively unique features of *C. difficile* is its ability to ferment tyrosine to *para*-cresol via the intermediate *para*-hydroxyphenylacetate (*p*-HPA). *P*-cresol is a phenolic compound with bacteriostatic properties which *C. difficile* can tolerate and may provide the organism with a competitive advantage over other gut microflora, enabling it to proliferate and cause CDI. It has been proposed that the *hpdBCA* operon, rarely found in other gut microflora, encodes the enzymes responsible for the conversion of *p*-HPA to *p*-cresol.

Results: We show that the PCR-ribotype 027 strain R20291 quantitatively produced more *p*-cresol *in-vitro* and was significantly more tolerant to *p*-cresol than the sequenced strain 630 (PCR-ribotype 012). Tyrosine conversion to *p*-HPA was only observed under certain conditions. We constructed gene inactivation mutants in the *hpdBCA* operon in strains R20291 and 630Δ*erm* which curtails their ability to produce *p*-cresol, confirming the role of these genes in *p*-cresol production. The mutants were equally able to tolerate *p*-cresol compared to the respective parent

Biomarkers. 2011 May;16(3):252-60. Epub 2011 Feb 18.

Urinary p-cresol is elevated in small children with severe autism spectrum disorder.

Altieri L, Neri C, Sacco R, Curatolo P, Benvenuto A, Muratori F, Santocchi E, Bravaccio C, Lenti C, Saccani M, Rigardetto R, Gandione M, Urbani A, Persico AM.

Abstract

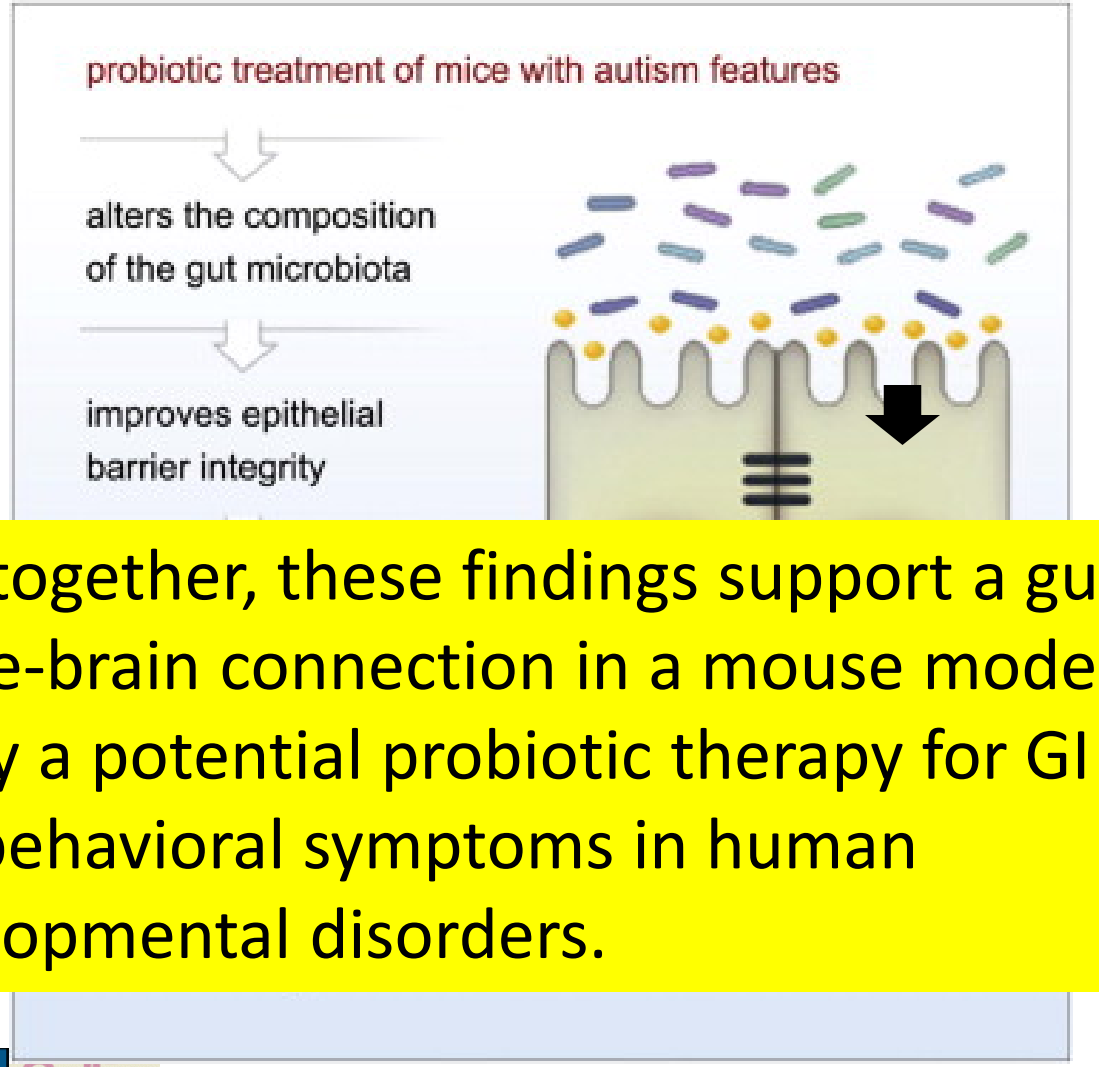
Several studies have described in autistic patients an overgrowth of unusual gut bacterial strains, able to push the fermentation of tyrosine up to the formation of p-cresol. We compared levels of urinary p-cresol, measured by high-performance liquid chromatography-ultraviolet, in 59 matched case-control pairs. Urinary p-cresol was significantly elevated in autistic children smaller than 8 years of age ($p < 0.01$), typically females ($p < 0.05$), and more severely affected regardless of sex ($p < 0.05$). Urinary cotinine measurements excluded smoking-related hydrocarbon contaminations as contributors to these differences. Hence, elevated urinary p-cresol may serve as a biomarker of autism liability in small children, especially females and more severely affected males

Alterations of the Intestinal Barrier in Patients With Autism Spectrum Disorders and in Their First-degree Relatives

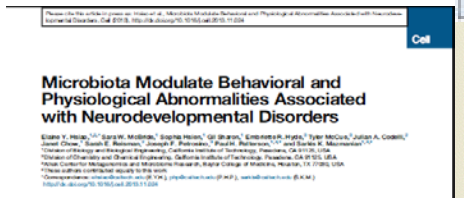
*Laura de Magistris, *Valeria Familiari, †#Antonio Pascotto, *Anna Sapone, †Alessandro Frolli, §Patrizia Iardino, ‡Maria Carteni, ‡Mario De Rosa, ¶Ruggiero Francavilla, *Gabriele Riegler, †Roberto Militerni, and ||Carmela Bravaccio

Intestinal Permeability (IPT) and Faecal Calprotectin (FC) were investigated in 90 autistic subjects and 146 first degree relatives. GI symptoms were present in 48,9% of the children. An high percentage of altered IPT values were found among autistic subjects (36,7%) and their relatives (21,2%). Autistic patients on reported gluten-casein free diet had lower IPT values than those who were on unrestricted diet. FC resulted altered in 24,4% of autistic and in 11,6% of their relatives, indicating the presence of intestinal inflammation. The obtained results are in keeping with the leaky gut hypothesis; the IPT alteration of patients and their first degree relatives represents a strong indication of the presence of an intestinal hereditary factor among families of autistic subjects.

TREATMENT WITH B. FRAGILIS



……..Taken together, these findings support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms in human neurodevelopmental disorders.



A new hope for effective prevention and treatment ?

MICROBIAL ECOLOGY in Health and Disease

THE MICROBIOME IN AUTISM SPECTRUM DISORDER

Approaches to studying and manipulating the enteric microbiome to improve autism symptoms

Richard E. Frye[1,2*], John Slattery[1,2], Derrick F. MacFabe[3], Emma Allen-Vercoe[4], William Parker[5], John Rodakis[6], James B. Adams[7], Rosa Krajmalnik-Brown[8], Ellen Bolte[6], Stephen Kahler[1,2], Jana Jennings[9], Jill James[10], Carl E. Cerniglia[11] and Tore Midtvedt[12]

All new avenues start from case reports

N. of 1 trial on probiotics at Villa Santa Maria Institute

Case Report

SAGE Open Medical Case Reports

Unexpected improvement in core autism spectrum disorder symptoms after long-term treatment with probiotics

SAGE Open Medical Case Reports
Volume 4: 1–5
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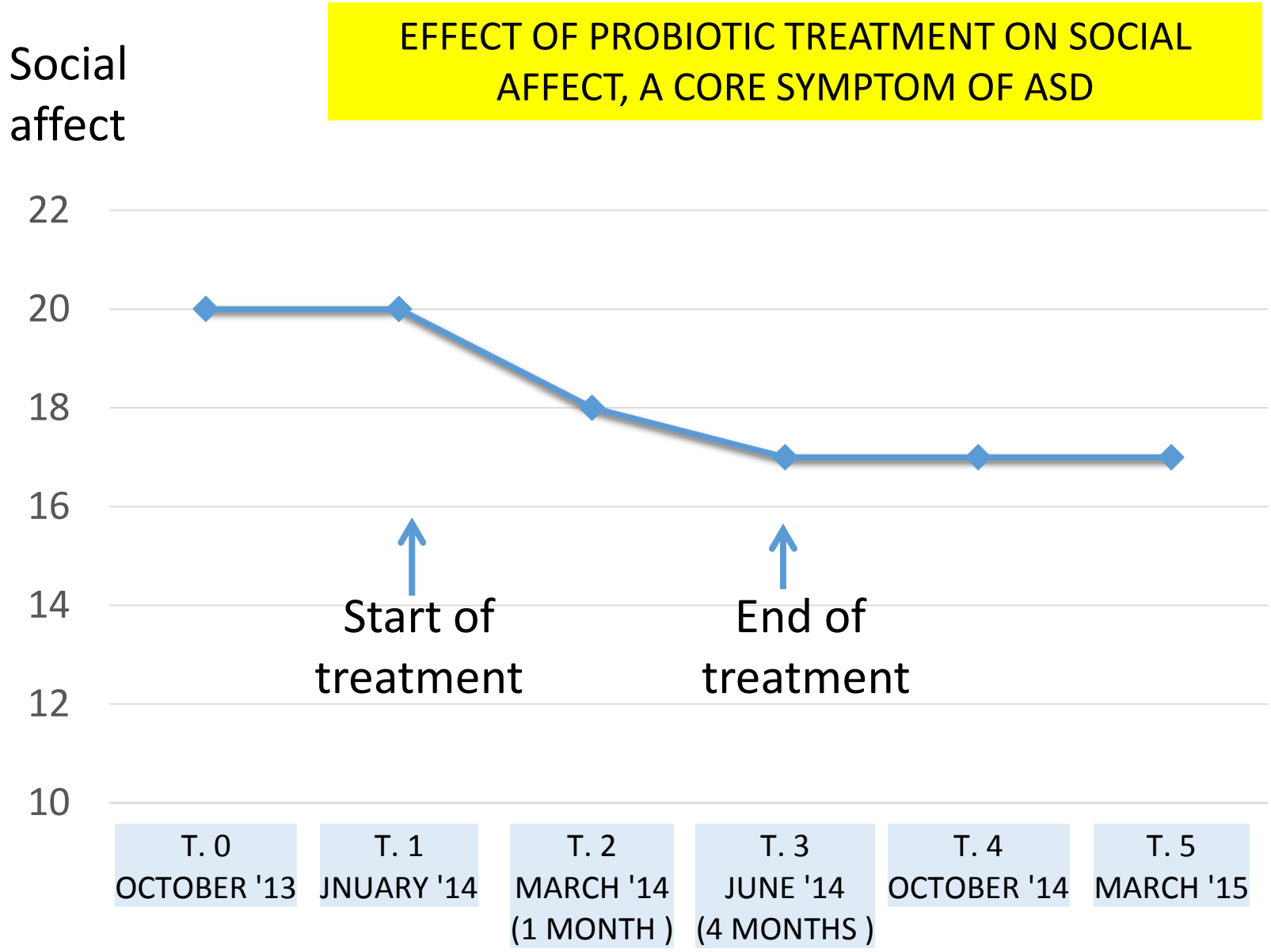
DOI: 10.1177/2050313X16666231
sco.sagepub.com
SAGE

Enzo Grossi, Sara Melli, Delia Dunca and Vittorio Terruzzi

CASE REPORT PRESENTATION

- 12 years old boy with ASD and severe cognitive disability
- He has been attending Villa Santa Maria Institute as resident care since 2009.
- Diagnosis of ASD according to DSM-V criteria was confirmed by ADOS-2 assessment (Autism Diagnostic Observation Schedule) in October 2013.
- For 4 months (February- May 2014) the patient has been treated with the probiotic VSL–3 due to gastrointestinal disturbances .


EFFECT OF PROBIOTIC TREATMENT ON SOCIAL AFFECT, A CORE SYMPTOM OF ASD
Social affect
22
20
18
16
14
12
10
Start of treatment
End of treatment
T. 0 OCTOBER '13
T. 1 JNUARY '14
T. 2 MARCH '14 (1 MONTH)
T. 3 JUNE '14 (4 MONTHS)
T. 4 OCTOBER '14
T. 5 MARCH '15

The role of probiotics in children with autism spectrum disorder: A prospective, open-label study

Sanaa Y. Shaaban[1], Yasmin G. El Gendy[1], Nayra S. Mehanna[2], Waled M. El-Senousy[3], Howaida S. A. El-Feki[1], Khaled Saad[4], Osama M. El-Asheer[4]

30 ASD children received 3 months of supplementation of probiotics nutritional supplement formula (each gram contains 100×10^6 colony forming units of three probiotic strains; Lactobacillus acidophilus, Lactobacillus rhamnosus and Bifidobacteria longum).

After probiotic supplementation, the stool PCR of autistic children showed increases in the colonycounts of Bifidobacteria and Lactobacilli levels, with a significant reduction in their body weight as well a significant improvements in the severity of autism (assessed by the ATEC), and gastrointestinal symptoms(assessed by the 6-GSI) compared to the baseline evaluated at the start of the study.

Table 1 Anthropometric data, ATEC subscales and 6-GSI score of autistic children

	Autistic group before probiotic supplementation	Autistic group after probiotic supplementation	*P* value
Anthropometric data			
Weight (kg)	25.91 ± 5.32	25.79 ± 5.16	0.014
Weight z-scores	0.67 ± 0.50	0.66 ± 0.45	0.181
Height (cm)	122.48 ± 8.27	122.52 ± 8.26	0.025
Height z-scores	0.16 ± 0.28	0.16 ± 0.27	0.025
BMI (kg/m^2)	17.043 ± 1.36	16.960 ± 1.24	0.010
BMI z-score	0.80 ± 0.56	0.77 ± 0.52	0.104
ATEC subscales mean ± SD			
Speech/language/communication	18.60 ± 4.61	18.30 ± 4.59	0.017
Sociability	17.50 ± 4.75	15.73 ± 4.28	0.001
Sensory/cognitive awareness	20.47 ± 4.26	19.67 ± 4.17	0.026
Health/physical/behavior	36.83 ± 8.32	27.10 ± 5.83	0.0001
Total ATEC score	93.40 ± 12.80	80.80 ± 10.54	0.0001
6-GSI score items			
Constipation	1.27 ± 0.45	0.73 ± 0.83	0.01
Diarrhea	0.83 ± 0.83	0.5 ± 0.78	0.076
Stool consistency	1.2 ± 0.71	0.87 ± 0.73	0.023
Stool smell	1.2 ± 0.61	0.97 ± 0.61	0.07
Flatulence	1.17 ± 0.53	0.87 ± 0.51	0.037
Abdominal pain	1.17 ± 0.65	0.73 ± 0.64	0.002
Total 6-GSI score	7.23 ± 1.61	3.57 ± 0.97	0.0001
Lactobacilli	$1.98 \times 10^7 \pm 1.24 \times 10^7$	$2.53 \times 10^7 \pm 1.52 \times 10^7$	0.0001
Bifidobacteria	$0.73 \times 10^7 \pm 0.40 \times 10^7$	$1.62 \times 10^7 \pm 1.06 \times 10^7$	0.0001

Kang *et al. Microbiome* (2017) 5:10
DOI 10.1186/s40168-016-0225-7

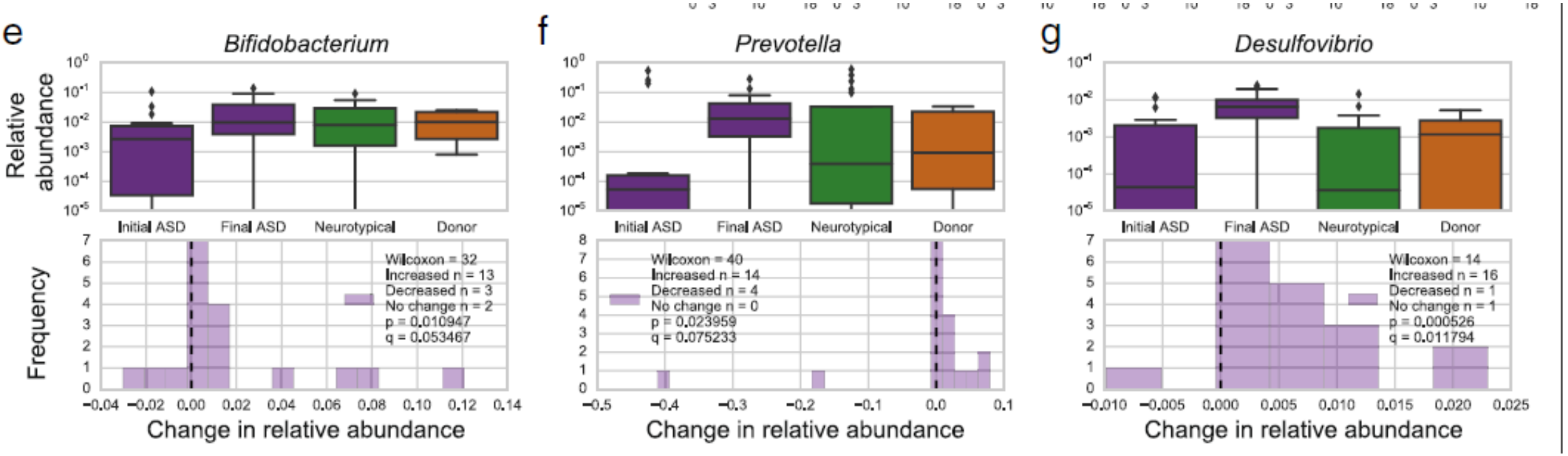
Microbiome

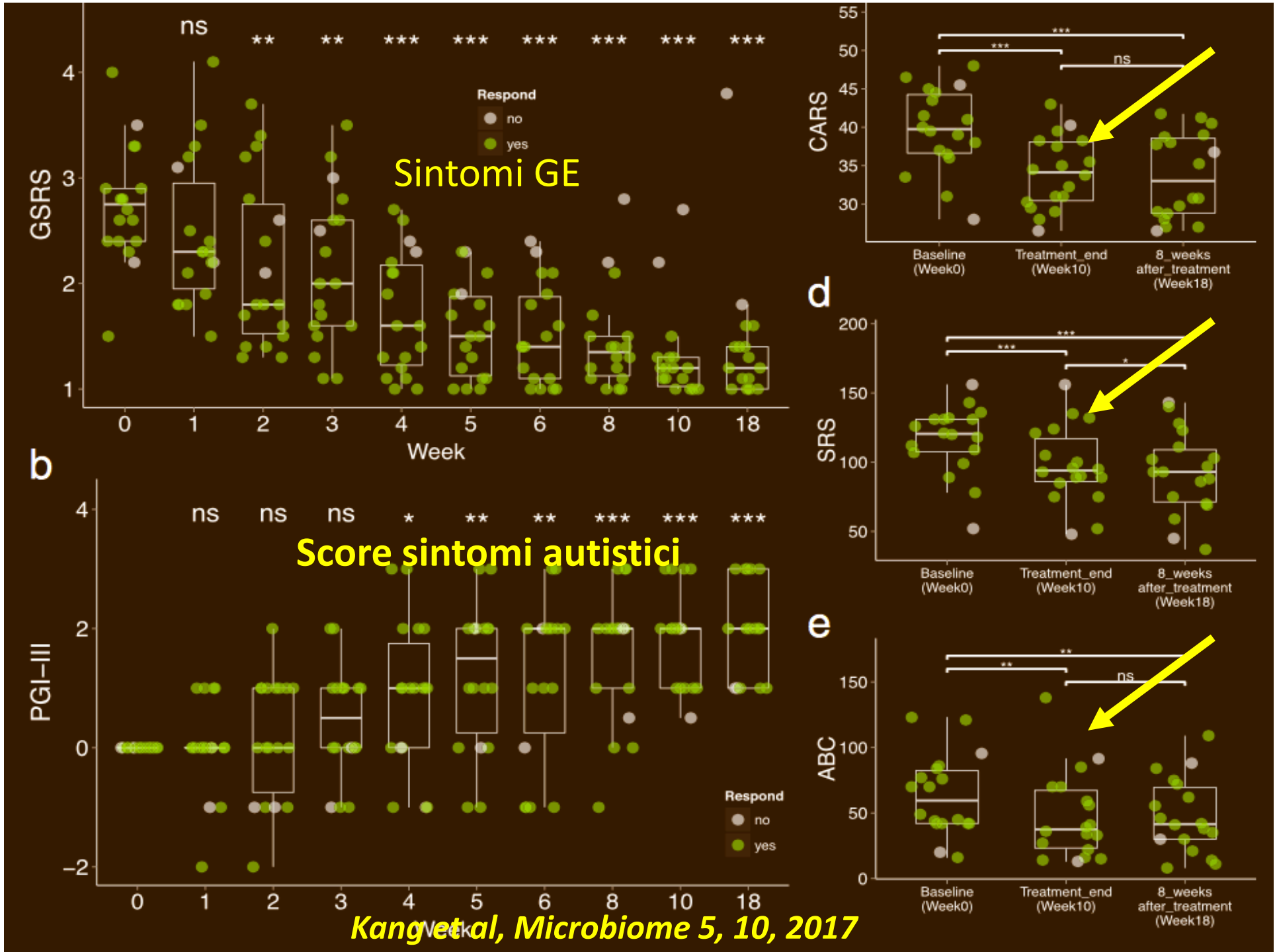
RESEARCH Open Access

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang[1†], James B. Adams[2†], Ann C. Gregory[3,15†], Thomas Borody[4], Lauren Chittick[5,15], Alessio Fasano[6], Alexander Khoruts[7,8,9], Elizabeth Geis[2], Juan Maldonado[1], Sharon McDonough-Means[10], Elena L. Pollard[2], Simon Roux[5,15], Michael J. Sadowsky[8,11], Karen Schwarzberg Lipson[12], Matthew B. Sullivan[3,5,15,16*], J. Gregory Caporaso[12,13*] and Rosa Krajmalnik-Brown[1,14*]

Effetti sulla composizione del microbiota





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BMC Psychiatry

STUDY PROTOCOL Open Access

Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters

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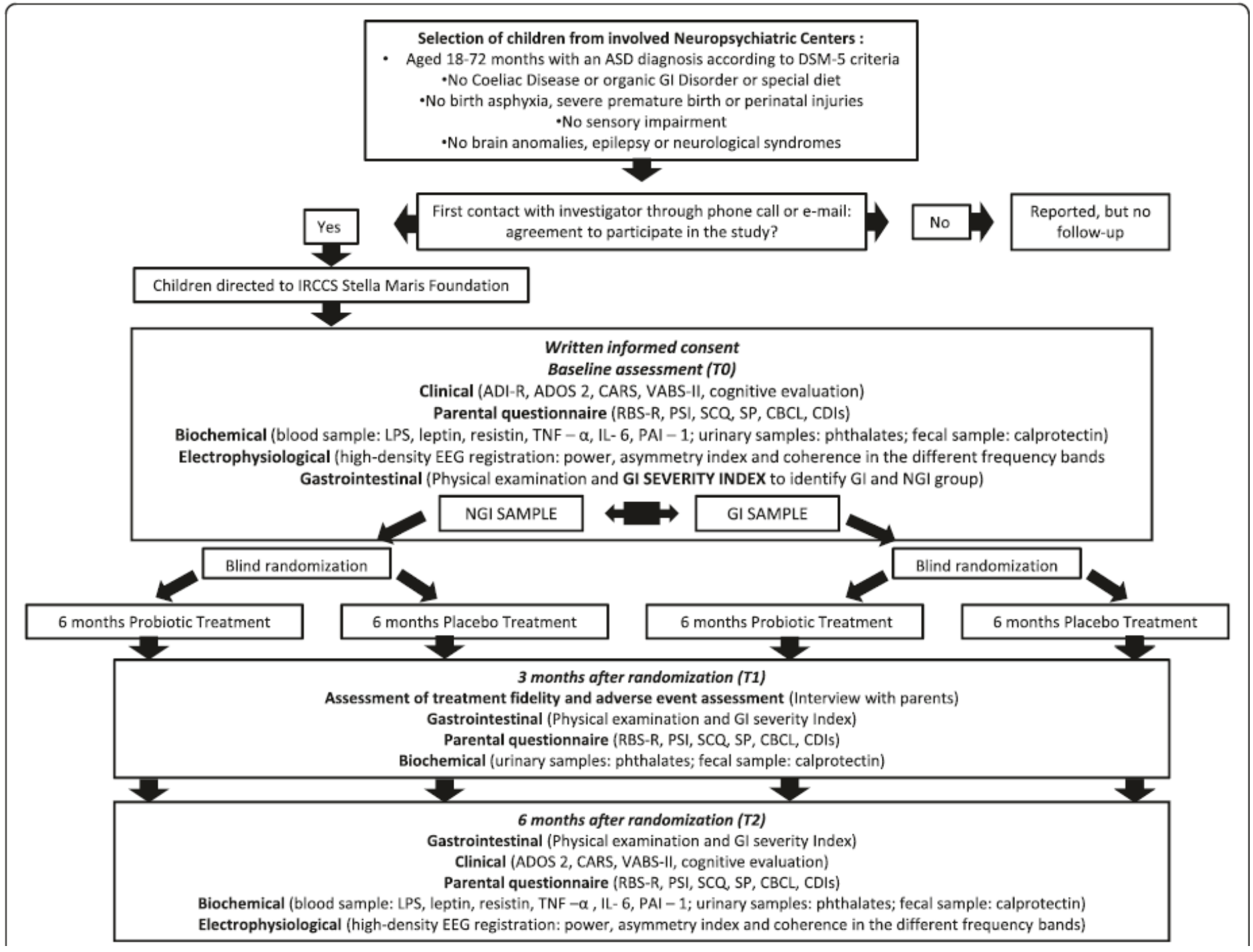
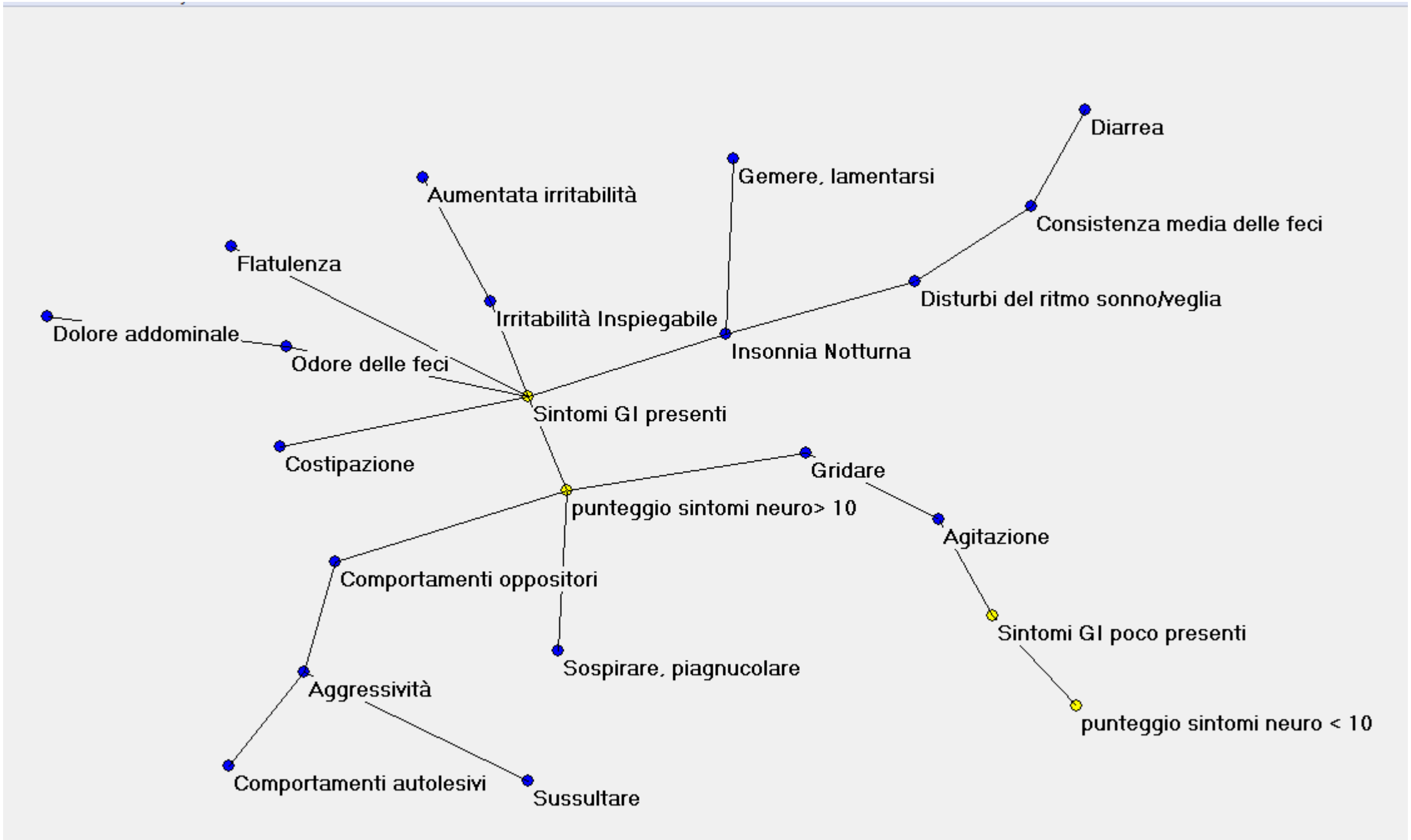

Selection of children from involved Neuropsychiatric Centers :
• Aged 18-72 months with an ASD diagnosis according to DSM-5 criteria
•No Coeliac Disease or organic GI Disorder or special diet
•No birth asphyxia, severe premature birth or perinatal injuries
•No sensory impairment
•No brain anomalies, epilepsy or neurological syndromes
First contact with investigator through phone call or e-mail: agreement to participate in the study?
Yes
No
Reported, but no follow-up
Children directed to IRCCS Stella Maris Foundation
Written informed consent
Baseline assessment (T0)
Clinical (ADI-R, ADOS 2, CARS, VABS-II, cognitive evaluation)
Parental questionnaire (RBS-R, PSI, SCQ, SP, CBCL, CDIs)
Biochemical (blood sample: LPS, leptin, resistin, TNF – α, IL- 6, PAI – 1; urinary samples: phthalates; fecal sample: calprotectin)
Electrophysiological (high-density EEG registration: power, asymmetry index and coherence in the different frequency bands
Gastrointestinal (Physical examination and GI SEVERITY INDEX to identify GI and NGI group)
NGI SAMPLE
GI SAMPLE
Blind randomization
Blind randomization
6 months Probiotic Treatment
6 months Placebo Treatment
6 months Probiotic Treatment
6 months Placebo Treatment
3 months after randomization (T1)
Assessment of treatment fidelity and adverse event assessment (Interview with parents)
Gastrointestinal (Physical examination and GI severity Index)
Parental questionnaire (RBS-R, PSI, SCQ, SP, CBCL, CDIs)
Biochemical (urinary samples: phthalates; fecal sample: calprotectin)
6 months after randomization (T2)
Gastrointestinal (Physical examination and GI severity Index)
Clinical (ADOS 2, CARS, VABS-II, cognitive evaluation)
Parental questionnaire (RBS-R, PSI, SCQ, SP, CBCL, CDIs)
Biochemical (blood sample: LPS, leptin, resistin, TNF –α , IL- 6, PAI – 1; urinary samples: phthalates; fecal sample: calprotectin)
Electrophysiological (high-density EEG registration: power, asymmetry index and coherence in the different frequency bands)


Diarrea
Gemere, lamentarsi
Aumentata irritabilità
Consistenza media delle feci
Flatulenza
Disturbi del ritmo sonno/veglia
Irritabilità Inspiegabile
Dolore addominale
Insonnia Notturna
Odore delle feci
Sintomi GI presenti
Costipazione
Gridare
punteggio sintomi neuro> 10
Agitazione
Comportamenti oppositori
Sintomi GI poco presenti
Sospirare, piagnucolare
Aggressività
punteggio sintomi neuro < 10
Comportamenti autolesivi
Sussultare

CONCLUSIONS

- Gut Microbiota profile in ASD exhibits a number of abnormalities and can explain the high frequency of GI symptoms in autism
- Animal models of autism point out the causative role of abnormal microbiota lacking important commensals and give a strong rational for interventions on microbiota.
- Open studies on probiotics in autism, still anedoctal, are promising
- The imminent end of the first formal RCT on probiotics in autism could definitely change the therapy scenario representing a giant step for Autism Spectrum Disorder.

Apertura codice randomizzazione: 3 Ottobre