

Gut Microbiome Composition in Relation to Gastrointestinal and Neurobehavioral Symptoms in Autism Spectrum Disorder

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Introduction

ASD is defined by the American Psychiatric Association as a life-long, complex neurodevelopmental condition marked by restricted interests, repetitive behaviors, and persistent challenges with social communication (American Psychiatric Association, 2021). Over the past decade, research has begun to investigate the possible connection between unstable microbe community contents in those with the neurobehavioral condition, Autism Spectrum Disorder (ASD), and how it may contribute to the progression of certain gastrointestinal and neurological symptoms (Parracho et al., 2005; Rose et al., 2018; Sharon et al., 2017). The gut microbiome consists of trillions of widely variegated species of bacteria, archaea, viruses as well as other eukaryotic microbes that mediate essential functions such as dictating immune responses, modulating digestion through breaking down postdigestion by-products, and aiding the body in the absorption of nutrients (Lozupone et al., 2012). Furthermore, dysbiosis, or the significant reduction or adjustment to the beneficial phyla community, results in a rise of cytotoxic and pathogenic species that inhibit intestinal mucosal barrier function as well as promote the creation of inflammatory cytokines and additional harmful digestive byproducts (Furguson et al., 2016, Ming et al., 2012, Stan et al., 2020). The most popular hypothesized theory explaining how alterations of microbial health can influence the brain is through a path termed the "gut-brain axis", or GBA, which connects the lumen of the gut to the enteric nervous system, which leads to the brain (Carabotti et al., 2015). Furthermore, that proposed interrelationship between the vitality of the microbiota and the brain via the GBA is such an interest in ASD research because of the clinical findings relating to not only improvements in gastric symptoms, but neurobehavioral symptoms as well when patients received microbiome-targeted treatments, illustrating the potential of this avenue for others with the disorder who are struggling (Carabotti et. al, 2015; Sandler et al; 2000; Sharon et al; 2019).

Objective

In this review, I investigate the potential causative relationship between dysbiosis in the gut microbiome of those with Autism Spectrum Disorder and its influence on the co-morbid presentation severity of gastrointestinal and neurobehavioral symptoms attributable to their theorized connection via the gut-brain axis.

Microbiome Impact on ASD Neurobehavioral Symptoms

Propionic acid (PPA), causes increased levels of immunoreactivity in the white matter around, and in hippocampal areas; including heightened occurrences of ASD core neurobehavioral symptoms (MacFabe, 2011).

Fig. 3: Group means (±SEM) of mmunohistochemical quantification of immunoreactivity (A) and CD68 cell counts (B) in hippocampal areas CA1/CA2 and adjacent external capsule white matter (MacFabe,

Statistically significant deviation of blood-brain barrier forming units in those with ASD (Fiorentino et al., 2016).

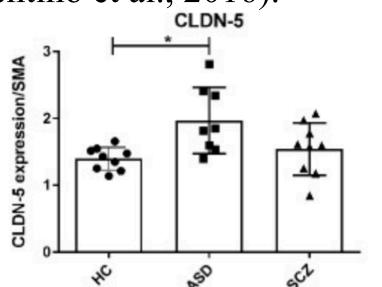
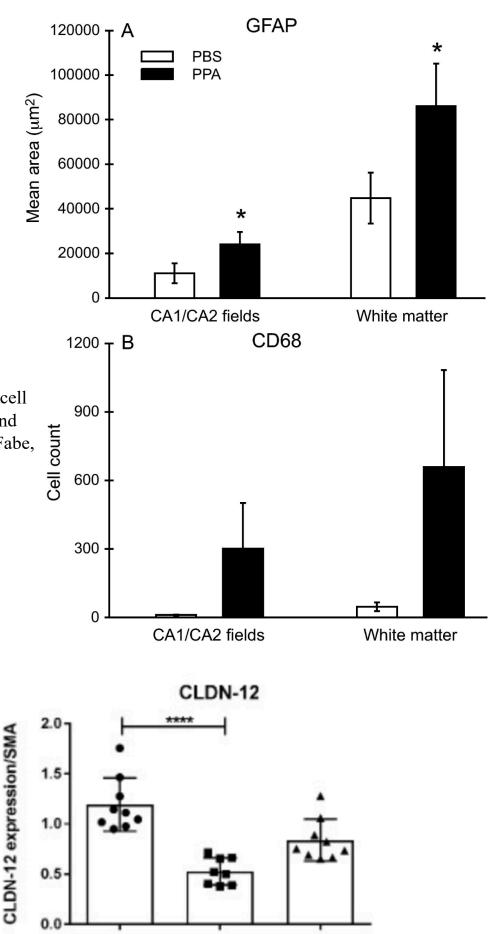


Fig. 4: Increased CLDN-5 and decreased CLDN-12 expression in the cortex of ASD subjects (Fiorentino et al., 2016).



Microbiome in those with Autism Spectrum Disorder

Lowered presence of beneficial bacteria involved in digestion, biomarking and immunity (Kang et al., 2013).

		Mann-W	hitney .	Median (25%/75%)	
Family. Genus	AUC	P	P adj.	Neurotypical	Autistic
Veillonellaceae.unknown_genus	0.829	0.000	0.039	0.04(0.01/0.21)	0(0/0.01)
Prevotellaceae.Prevotella	0.809	0.001	0.039	0.06(0.01/0.67)	0(0/<0.01)
Lachnospiraceae.Coprococcus	0.800	0.001	0.062	0.03(0.02/0.05)	0.01(0/0.01)
Lactobacillaceae.Lactobacillus	0.771	0.003	0.096	<0.01(0/<0.01)	0.01(<0.01/0.04)
Prevotellaceae.unknown_genus	0.754	0.002	0.062	< 0.01(0/0.02)	0(0/0)
Alcaligenaceae.Sutterella	0.746	0.004	0.096	0.06(0/0.18)	0(0/0)
Lachnospiraceae.Roseburia	0.746	0.009	0.139	0.06(0.03/0.18)	0.02(0.01/0.05)
Porphyromonadaceae.Butyricimonas	0.712	0.007	0.139	0.01(0/0.09)	0(0/0)
Eubacteriaceae,Eubacterium	0.709	0.026	0.277	0.03(0.02/0.10)	0.13(0.05/0.25)
Prevotellaceae.Paraprevotella	0.703	0.009	0.139	< 0.01(0/0.35)	0(0/0)

Table 1: Top 10 genera generating the highest area under curves in a receiver operating characteristics curve. (Kang et al.,

Elevated concentrations of pathogenic bacteria and their cytotoxic byproducts (Fiorentino et al., 2016).

Specimens	CFU/g	3				Numbe	r of po	sitive s	pecim	ens
	Total	C. perfringens isolated	Clostridium	C. perfringens	Beta2-Toxin gene- positive C. perfringens	Beta2- Toxin	CPE	Alpha	Beta	El
Autism	33	30	9.20×10^{7}	2.12×10^5	6.55×10^4	26/33 (79%)	3/33 (9%)	30	0	0
Control	13	10	4.73×10^7	1.70×10^4	1.48×10^3	5/13 (38%)	1/13 (8%)	10	0	0
p-value			0.17	0.031	0.015	0.014				

Microbiome Effect on ASD-related Gastrointestinal

Symptoms

• "Leaky gut hypothesis" inhibited function of mucosal barrier tight junctions promotes increased levels of intestinal permeability (IPT) (Magistris, 2010).

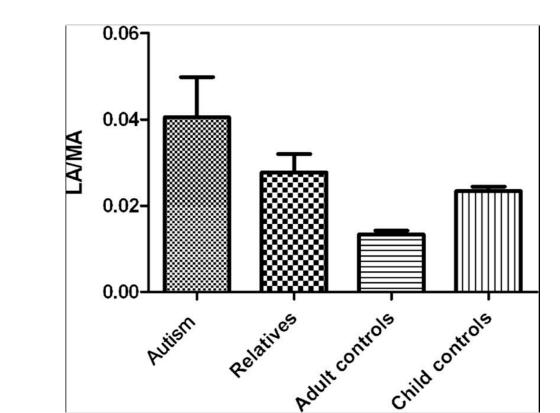


Fig. 1: IPT is measured in the 4 investigated subgroups and expressed as LA/MA values (mean \pm SD): patients with autism spectrum disorders (N = 90), relatives (N = 146), adult controls (N = 146), child controls (N = 64) (Magistris, 2010).

• Metabolites, products of the gut bacteria's metabolism, show statistically significant profile discrepancies in those with ASD and GI disturbances vs other groups (Ming et al., 2012).

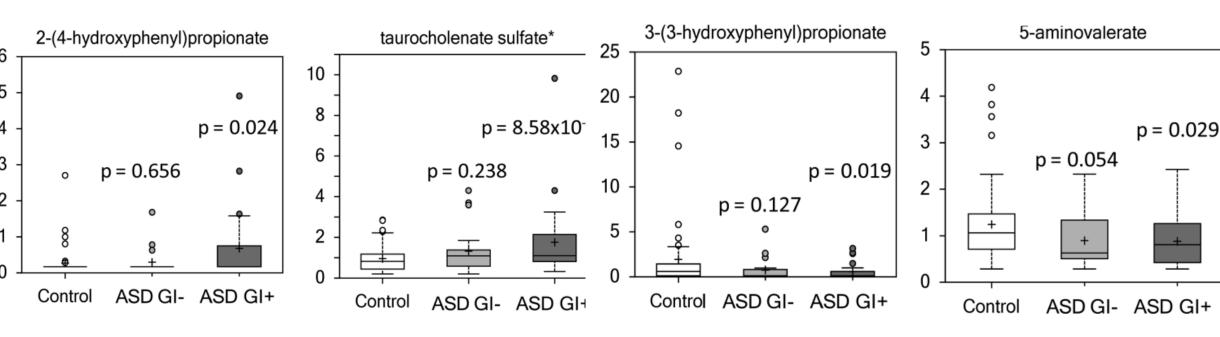


Fig. 2: Alteration in gut bacterial metabolites in ASD subjects (Ming et al., 2012).

Microbiome-centered ASD Treatments

	Placebo (32)			Probiotics (3	1)		p ANOVA Pla/Pro	p ANOVA Pla/Pro
Characteristics	Т0	T2	Change T0- T2	Т0	T2	Change T0- T2	Т0	T0-T2
Age, mean (SD), y	4.09 (0.97)	4.62 (0.98)	0.52	4.29 (1.22)	4.82 (1.23)	0.53	ns	ns
Boys, No. (%)	27 (84.4)	27 (84.4)	n. a.	24 (77.4)	24 (77.4)	n. a.	ns	ns
BMI m (DS)	16.06 (1.73)	15.91 (1.76)	-0.15	15.95 (1.93)	16.01 (2.18)	0.06	ns	ns
Melatonin supplementation n (%)			2 (6.25)			3 (9.7)		ns
Vitamin supplementation			3 (9.4)			7 (22.6)		ns
ADOS CSS ^a								
Total	6.97 (1.91)	7.00 (1.80)	0.03	6.84 (1.39)	6.19 (1.56)	-0.65	ns	ns
Social Affect	6.41(2.21)	6.09 (1.82)	-0.31	6.26 (1.79)	5.35 (1.56)	-0.90	ns	ns
Restricted and repetitive behavior	8.22(1.31)	8.53 (1.34)	0.31	7.94 (1.57)	8.23 (1.45)	0.29	ns	ns
GI Severity Index h								
Total 6-GSI	1.38 (1.45)	1.29 (1.19)	-0.08	2.06 (2.14)	1.23 (1.48)	-0.83	ns	ns
Total GSI	2.91 (2.19)	2.16 (1.57)	-0.74	3.61 (2.92)	2.53 (2.19)	-1.08	ns	ns
Linguistic Level ⁱ		Pla T0-T2 (%	5)		Pro T0-T2 (%)		
	\downarrow	=	↑	\downarrow	=	↑		
	0	87.50	12.50	9.68	70.97	19.35	ns	ns

Table 3: Efficacy Measures at Baseline and 6 months in the two treatment groups (Santocchi et al., 2020).

Statistically significant improvements in GI and behavioral symptoms, even two years posttreatment (Kang et al., 2017).

control children (Fiorentino et al., 2016

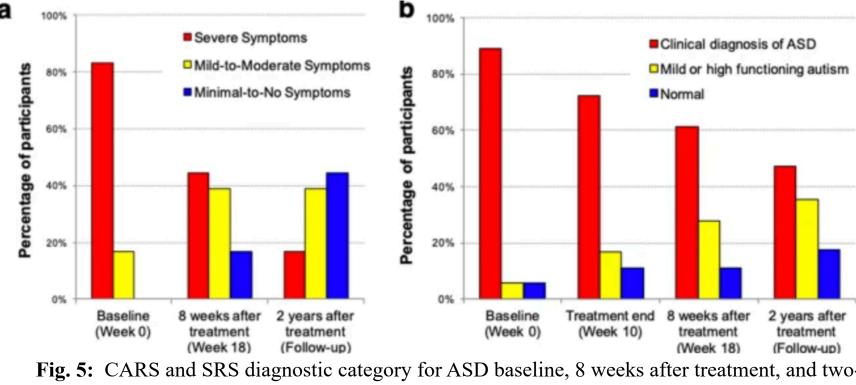


Fig. 5: CARS and SRS diagnostic category for ASD baseline, 8 weeks after treatment, and two-year follow-up after treatment stopped (Kang et al., 2017).

Synthesis and Future Direction

Conclusion

- Studies support the theory of the potential two-way connection between the gastrointestinal system and the brain.
- Lowered levels of beneficial bacteria are replaced by pathogenic bacteria, dysregulating digestion and the intestinal mucosal barrier (Ming et al., 2012, Magistris et al., 2012).
- Toxic species permeate across the mucosal barrier and into the enteric nervous system promoting neuroinflammation and immunoreactivity within the brain (Fiorentino et al., 2016, MacFabe et al., 2011).

Future Direction

- More wide-scale research needs to be conducted on the potential mechanisms of the GBA pathways, as current knowledge is limited, and focused studies are scarce.
- Additional long-term microbiome-directed therapy research, especially on probiotics and fecal transplants as past findings have been very promising in improving GI disturbances and behavioral symptoms.

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