<Further Development 25_04>

Microbes, social behaviors, and autism

Remarkably, the gut microbiota were shown to be critical for normal *social behavior* in mice. Germ-free mice have aberrant behaviors, including excessive time spent in repetitive self-grooming, social avoidance, and very little time spent in social investigation. Desbonnet and colleagues (2013) remarked that these traits appeared to be similar to those of autistic children. Moreover, many of these behavioral traits were made normal by providing the mice with gut bacteria early in life. The same year, Hsaio and colleagues (2013) showed that the symbiotic bacterium *Bacteroides fragilis* ameliorated the aberrant communicative, anxiety-like, and stereotypic behaviors seen in a mouse model of autism (Figure 1A-C). Moreover, it did so as it altered the composition of gut microbiota, improved the integrity of the gut epithelium, and reduced the leakage of particular gut metabolites into the blood. Several investigators had seen that a subset of autistic children had altered gut bacteria, and the germ-free mice had a similarly skewed pattern of microbial species. Once the integrity of the gut epithelium had been restored and the population of bacteria changed, different metabolites were seen in the blood. Levels of indolepyruvate and ethylphenylsulfate (a chemical that induces anxiety-like behaviors) plummeted (Figure 1D).

Moreover, gut microbes are responsible for controlling the permeability of the blood-brain barrier, the tight lining of the capillaries feeding the brain. This barrier shields the brain from blood-borne infections and toxins, since most large molecules cannot flow through it. However, the blood-brain barrier of germ-free mice is not impermeable to proteins, both as pups and adults. This defect could be cured by adding normal gut bacteria back to the gut of the pups (Braniste et al 2014). It appears, then, that material from the mother's symbiotic gut bacteria are regulating the permeability of the blood brain barrier while it is being formed in the fetal mice.

It is likely that neither our brain nor our behaviors develop properly without the appropriate symbionts.

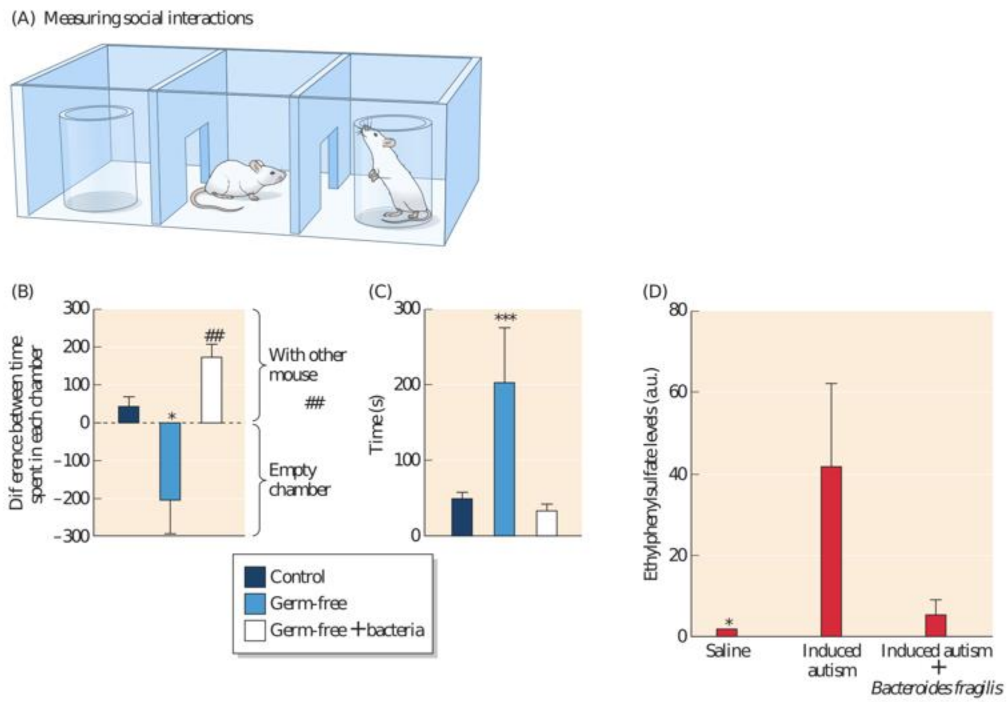
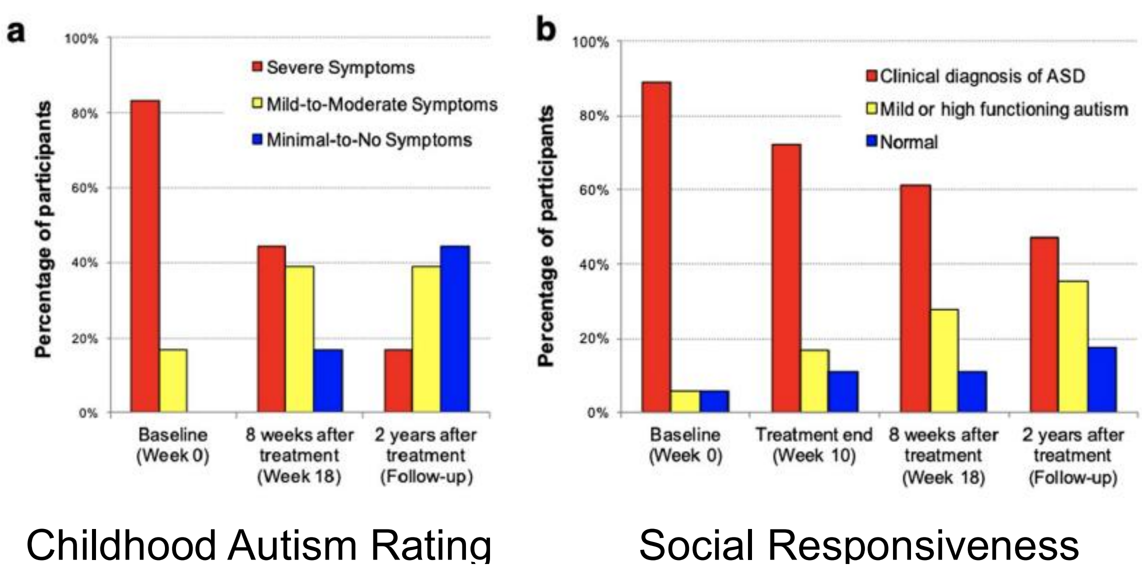


Figure 1. Effects of germ-free rearing and germ-free bacterial consortium on social behaviors in male mice. (A) Measuring social interaction by the difference between ties spent in chambers with and without other mice. (B and C) Germ-free mice had social avoidance. *, p < 0.05 versus controls; ##, p < 0.001 versus germ-free mice. Time spent in repetitive self-grooming. Both autistic-like behaviors could be relieved by adding microbes later in life. (D) Ethylphenylsulfate levels are extremely high in germ0free mice and can also be removed when epithelial integrity is restored by the additions of Bacteroides fragilis. *, p < 0.05 ***, p < 0.001. (A, B, C after Desbonnet et al. 2013; D after Hsaio et al. 2013.)

Microbial (probiotic) treatment has been beneficial in treating psychological distress and chronic fatigue symptoms in humans (Messaoudi et al., 2011; Rao et al., 2009). In 2020, the absence of other bacteria involved in tyrosine metabolism was associated with depression (Valles-Colomer et al 2020). So it is possible that several of the diseases that we have come to classify as psychological have a root in bacterial metabolism.

There is even the possibility that certain forms of autism may be caused by microbial imbalances. Obviously, controlled experiments are difficult to do. Still, epidemiological studies and clinical experiments point to roles of bacteria in human brain development and behavior. Pilot studies show that replacing the gut bacteria of severely autistic children with those of normal children can dramatically improve their sociability (Figure 2; Kang et al 2019). The butyrate-producing bacteria *Bifidobacterium* and *Prevotella* appear to play a role in this amelioration. Conversely, the microbiota from the guts of human autistic patients did not reverse the autism-like behaviors when transplanted into germ free mice. However, gut bacteria from normally developing people did reverse some of the symptoms (Sharon et al 2019). So it is likely that even the thinking "neurological self" may be a holobiont property. Indeed, if bacteria make us social, perhaps we are their way for making more environments for their descendants (Gilbert 2018; 2021). In helping make us social, both humans and microbes benefit.

Figure 2. **Pilot study of the ability of replacing the microbiota of autistic children with microbes from healthy children. At the start of this experiment, 83% of patients were ranked as severely autistic. After two years, only 17% of the same patients ranked as severe. Their ability to function socially improved with treatment. (From Kang et al 2019.)**



References:

Braniste, V. and 17 others. 2014. The gut microbiota influences blood-brain barrier permeability in mice. *Science Transl. Med*. 6: 263ra158.

Desbonnet, L., G. Clarke, F. Shanahan, T. G. Dinan and J. F. Cryan. 2014. Microbiota is essential for social development in the mouse. Mol. Psychiatry 19: 146–148.

Gilbert, S. F. 2018. "Perspective: Rethinking parts and wholes" In *Landscapes of Collectivity In The Life Sciences*, edited by Gissis, S., Lamm, E., and Shavit, A., Cambridge (Massachusetts): MIT Press. Pp. 123-132.

Gilbert, S. F. 2021. Como era en umpricipio, ahotra y siempre, por los siglos de los siglos. (As it was in the beginning, is now, and ever shall be.) *Microhabitable*, edited by Pietroiusti, L. and Garcia Dory, F.) Madrid: Matedero. pp. 34-45.

Hsiao, E. Y. and 11 others. 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 155: 1451–1463.

Kang, D.W., Adams, J.B., Coleman, D.M., Pollard, E.L., Maldonado, J., McDonough-Means, S., Caporaso, J.G., Krajmalnik-Brown, R.2019. Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. *Scientific Reports* 9: 5821. doi: 10.1038/s41598-019-42183-0.

Messaoudi, M. and 10 others. 2011. Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br. J. Nutr*. 105: 755–764.

Rao, A. V., A. C. Bested, T. M. Beaulne, M. A. Katzman, C. Iorio, J. M. Berardi and A. C. Logan. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog*. 1: 6.

Sharon, G., Cruz. N. J.,, Kang, D. W., Gandal, M. J., Wang, B., Kim, Y. M., et al. 2019. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell* 177: 1600-1618.e17. doi: 10.1016/j.cell.2019.05.004.

Valles-Colomer, M., Falony ,G., Darzi, Y., Tigchelaar, E. F, Wang, J., Tito, R. Y., Schiweck, C., et al. 2019. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nature Microbiology* 4: 623-632. doi: 10.1038/s41564-018-0337-x.