

Preview

Bugs R Us: Restoring sociability with microbiota in autism

Camilla Bellone^{1,*} and Christian Lüscher^{1,*}¹Department of Basic Neuroscience, University of Geneva, Geneva, Switzerland*Correspondence: camilla.bellone@unige.ch (C.B.), christian.luscher@unige.ch (C.L.)<https://doi.org/10.1016/j.xcrm.2021.100256>

In a recent publication in *Cell*, Buffington et al. provide a fascinating example of hologenomic behavioral regulation in an autism mouse model.¹ The authors report that gut bacteria from wild-type mice rescue the social deficit of *Cntnap2* knockout mice.

The hologenome theory of evolution, first formulated in the 1980s,² posits that the genetic information of the host is complemented by the genetic information of all symbiotic microorganisms. Based on this definition, the host and the symbiotic microbes act as a single biological entity in evolution. Simple examples of symbiotic interactions with an evolutionary success include termites and *Cryptocercus* cockroaches that are strongly distinguished from other insects by a cellulose-based diet. Indeed, the insect symbionts provide these insects the enzymatic capability to synthesize nutrients from the plant polymer.³ Emerging research investigates the role of microbial symbionts on behavior across the animal kingdom with particular attention on the complex relationship between symbiotic bacteria and host sociability.⁴ Here, the authors went a big step further and explored the effect of gut microbiota on social behavior in a disease model (Figure 1).

Mice that lack *Cntnap2* (a gene coding for a neurexin-like adhesion molecule) loosely associated to autism, when bred in homozygous isolation, show behavioral abnormalities that range from enhanced spontaneous locomotion to a lack of interest for conspecifics along with a gut microbiome that is distinct from wild type (WT). Surprisingly, the deficit in social interaction was not observed when *Cntnap2* knockout (KO) mice were bred from heterozygous parents. At this stage, many factors including better parental care by the heterozygous mother and pheromonal or semiochemical signals could possibly ameliorate social deficits observed in isolated KO mice. The

authors, however, favor another explanation. What if infection between siblings could homogenize the microbiota between WT and KO, and then rescue the deficit in social interaction? To make their case, authors housed WT and KO mice together *after* weaning, which indeed led to the disappearance of the difference in gut microbiota and restored sociability. While many bacterial species differed between isolated WT and KO, the authors found that one bacterial species, *Lactobacillus reuteri*, was sufficient to restore interest in conspecifics when fed to isolated KO mice. Exploring the underlying mechanisms, the authors implicate synaptic plasticity at excitatory inputs onto dopamine neurons of the ventral tegmental area (VTA). Indeed, social interactions normally potentiate excitatory afferents,⁵ a plasticity absent in isolated KO mice, but again rescued by *Lactobacillus reuteri*. Finally, the authors performed a metabolic analysis of the gut and found that tetrahydrobiopterin, a cofactor of aromatic amino acid hydroxylase enzymes, used in the biosynthesis dopamine, was deficient in isolated KO mice but restored by *L. reuteri*.

While the study is a breathtaking technological tour de force, many questions arise. Why is the microbiome of *Cntnap2*^{-/-} mice altered in the first place? Is the social deficit observed in germ-free mice⁶ explained by the same underlying mechanism? In fact, distinct mechanisms have been previously described in other autism-related mouse models. For example, in the inbred mouse strain BTBR T+ tf/J taurin and 5AV have been linked to altered social behavior.⁷ Because of the complexity of social

behavior indeed, we can hypothesize that different elements of conspecific interaction are mediated by distinct neural mechanisms and therefore differently influenced by microbiome. While some microorganisms may influence the communication between conspecifics via the production of volatile semiochemicals, others could influence the rewarding properties of the behavior. Future studies matching high-density behavioral analysis with neuronal activity and genetic and metabolomic profiling will need to parse the specific modules of social interaction that are modulated by gut microbiota.

The present study provides additional evidence for a link between gut microbiota and social behavior in rodents, adding to the examples described in invertebrates and vertebrates where interaction between conspecific often provides a channel for microorganism transmission. In honeybees, the transfer of microbiota promoted by social interaction confers resistance against pathogens,⁴ while intimate interactions in humans facilitate the transfer of oral microbiota, which may diversify microbiota within a social network.⁸ The data presented here reinforces the idea that the microbiome should be considered as an important unit of analysis within a social network.

Studies probing the link between gut microbiome in human disease reported that autistic children who suffer from gastrointestinal disorders⁹ have low levels of some bacterial species, such as Prevotella, Coprococcus, and Veillonellaceae along with an altered permeability of the blood-brain barrier and intestinal-epithelial barrier.¹⁰ The face validity of rodent



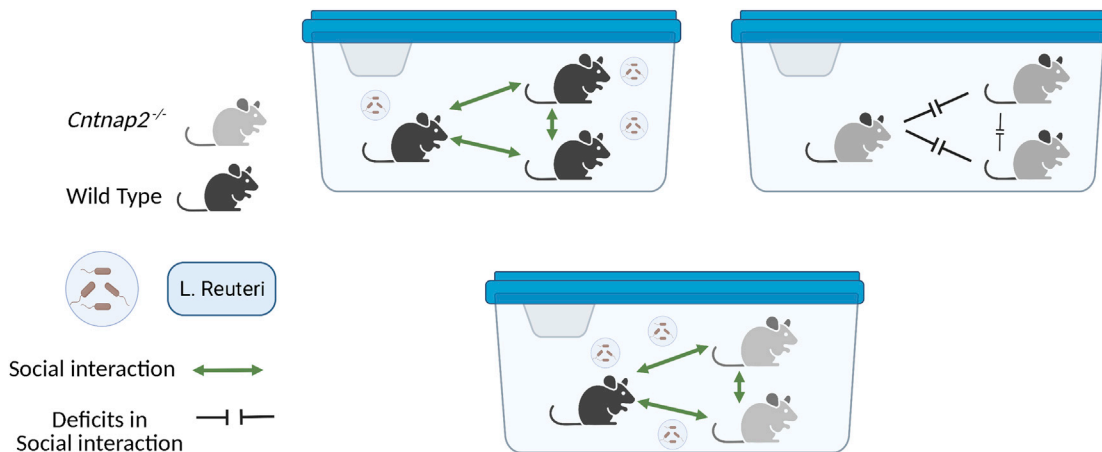


Figure 1. Role of *L. Reuteri* in social behavior

Social impairments in *Cntnap 2* KO mice are rescued when co-housed with WT mice. The authors identified *L. reuteri* as the commensal bacterial species lacking in *Cntnap2* KO mice and passed by WT co-housing.

models is further supported by experiments where transfer to gut microbiota from human donors with autism into mice was sufficient to reveal behavioral alterations that are reminiscent of core symptoms of the disease.⁷

Development of microbiota-based therapeutic intervention is still in the future, but since *Lactobacillus reuteri* can also improve anxiety and stereotyped behavior in mice, probiotic intervention may benefit patients suffering from a wider range of symptoms across mental health diseases. Microbiome-based stratification of patients should be considered for future medical trials who may greatly benefit from mechanistic investigations such as the one by Buffington published here.

Taken together the study provides fuel for thoughts and brings us a step closer to understanding how microbiomes shape the behavior of vertebrates including humans.

REFERENCES

1. Buffington, S.A., Dooling, S.W., Sgritta, M., Noecker, C., Murillo, O.D., Felice, D.F., Turnbaugh, P.J., and Costa-Mattioli, M. (2021). Dissecting the contribution of host genetics and the microbiome in complex behaviors. *Cell* 184, S0092-8674(21)00159-8.
2. Rosenberg, E., Koren, O., Reshef, L., Efrony, R., and Zilber-Rosenberg, I. (2007). The role of microorganisms in coral health, disease and evolution. *Nat. Rev. Microbiol.* 5, 355–362.
3. Berlanga, M., and Guerrero, R. (2016). The holobiont concept: the case of xylophagous termites and cockroaches. *Symbiosis* 68, 49–60.
4. Sherwin, E., Bordenstein, S.R., Quinn, J.L., Dinan, T.G., and Cryan, J.F. (2019). Microbiota and the social brain. *Science* 366, eaar2016.
5. Bariselli, S., Hörnberg, H., Prévost-Solié, C., Musardo, S., Hatstatt-Burklé, L., Scheiffele, P., and Bellone, C. (2018). Role of VTA dopamine neurons and neuroligin 3 in sociability traits related to nonfamiliar conspecific interaction. *Nat. Commun.* 9, 3173.
6. Desbonnet, L., Clarke, G., Shanahan, F., Dinan, T.G., and Cryan, J.F. (2014). Microbiota is essential for social development in the mouse. *Mol. Psychiatry* 19, 146–148.
7. Sharon, G., Cruz, N.J., Kang, D.-W., Gandal, M.J., Wang, B., Kim, Y.-M., Zink, E.M., Casey, C.P., Taylor, B.C., Lane, C.J., et al. (2019). Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell* 177, 1600–1618.
8. Brito, I.L., Gurry, T., Zhao, S., Huang, K., Young, S.K., Shea, T.P., Naisilisili, W., Jenkins, A.P., Jupiter, S.D., Gevers, D., and Alm, E.J. (2019). Transmission of human-associated microbiota along family and social networks. *Nat. Microbiol.* 4, 964–971.
9. Kang, D.-W., Park, J.G., Ilhan, Z.E., Wallstrom, G., Labaer, J., Adams, J.B., and Krajmalnik-Brown, R. (2013). Reduced incidence of *Prevotella* and other fermenters in intestinal microflora of autistic children. *PLoS ONE* 8, e68322.
10. Fiorentino, M., Sapone, A., Senger, S., Camhi, S.S., Kadzielski, S.M., Buie, T.M., Kelly, D.L., Cascella, N., and Fasano, A. (2016). Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol. Autism* 7, 49.