

Gut microbiome at the crossroad of genetic variants and behavior disorders

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ABSTRACT

Genetic variants are traditionally known to shape the susceptibility to neuropsychiatric disorders. An increasing number of studies indicate that remodeling of the gut microbiome by genetic variance serves as a versatile regulator of gut-brain crosstalk and behavior. Evidence also emerges that certain behavioral symptoms are specifically attributed to gut microbial remodeling and gut-to-brain signals, which necessitates rethinking of neuropsychiatric disease etiology and treatment from a systems perspective of reciprocal gene-microbe interactions. Here, we present an emerging picture of how gut microbes and host genetics interactively shape complex psychiatric phenotypes. We illustrate the growing understanding of how the gut microbiome is shaped by genetic changes and its connection to behavioral outcome. We also discuss working strategies and open questions in translating associative gene-microbiome-behavior findings into causal links and novel targets for neurobehavioral disorders. Dual targeting of the genetic and microbial factors may expand the space of drug discovery for neuropsychiatric diseases.

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Introduction

The incidence of neuropsychiatric diseases is ever on the increase in modern society. Cumulative genome-wide association study (GWAS) findings have highlighted association of common genetics variants with neuropsychiatric disorders typically including autism spectrum disorder (ASD)¹, major depressive disorder (MDD)², bipolar disorder (BD), and schizophrenia³ (Table 1). Although the contribution of heritability varies, deciphering their links to behavioral symptoms provides a promising route to therapeutic innovation and clinical care. A traditional view is that, by directly impacting brain development and function, genetic variants are the primary drivers of the behavioral symptoms. Indeed, the genetic-risk loci are increasingly linked to parameters of neuroinflammation, neurogenesis, synaptic, or neurocircuit function, which are commonly viewed as fundamental to disease phenotypes^{17,18}. However, given the inherent complex etiology of neuropsychiatric diseases, a major unanswered question is how the genetic variance may interact with other environmental factors underlying the complex behavioral phenotypes.

The gut microbiome can modulate host behaviors in a very powerful manner via the gut-brain axis^{19,20}. Interestingly, gut dysbiosis has been observed as a common trait for neuropsychiatric disorders, and emerging data are suggesting that host genetics and the gut microbiome interdependently regulate different complex behaviors in genetic neurological disorders²¹. Therefore, it is reasonable to propose that dissecting the mechanisms through which host and microbial factors regulate complex behaviors will not only expand our understanding of neurobehavioral disorders but may also broaden the way of novel therapies. Here, we present a growing picture from animal studies that gut microbe interaction with host genetics to interactively shape complex psychiatric phenotypes. We discuss the challenges and potential strategies in gaining mechanistic insights into the genetic-microbe interplay in behavior control, with a major focus on microbial metabolites as signaling molecules for drug discovery. We also envision how advances in this frontier may potentially change the way we view and treat these complex mental illnesses in the clinic.

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Table 1. Representative risk genes of neurobehavioral disorders and gut microbial changes reported in these patients.

Neurobehavioral Disorders	Candidate risk genes	Gut microbial changes			Refs
		Positive association/Higher abundance in patients	Negative association/Lower abundance in patients		
Autism spectrum disorder	<i>Negr1</i> ; <i>Ptbp2</i> ; <i>Cadps</i> ; <i>Fzef2</i> ; <i>Tmem33</i> ; <i>Dcaf11</i> ; <i>Slc30a9</i> ; <i>Bend4</i> ; <i>Nudt12</i> ; <i>Kcnn2</i> ; <i>Mims22</i> ; <i>Pou3f2</i> ; <i>Xmt2e</i> ; <i>Chd8</i> ; <i>Srpk2</i> ; <i>C8orf74</i> ; <i>Sox7</i> ; <i>Shank3</i> ; <i>Pinx1</i> ; <i>Mroh5</i> ; <i>Mark3</i> ; <i>Ckb</i> ; <i>Trmi61a</i> ; <i>Bag5</i> ; <i>Apoop1</i> ; <i>Klcl1</i> ; <i>Cntnap2</i> ; <i>Xrcc3</i> ; <i>Macrod2</i> ; <i>Xin2</i> ; <i>Kiz</i> ; <i>Nkx2-4</i> ; <i>Nkx2-2</i>	family <i>Prevotellaceae</i> ; genus <i>Bacteroides</i> ; genus <i>Clostridium</i> ; genus <i>Faecalibacterium</i> ; genus <i>Phascolarctobacterium</i> ; genus <i>Collinsella</i> ; genus <i>Corynebacterium</i> ; genus <i>Dorea</i> ; genus <i>Lactobacillus</i>	phylum <i>Bacteroidetes</i> ; family <i>Acidaminococcaceae</i> ; genus <i>Lachnoclostridium</i> , genus <i>Tyzerella</i> subgroup 4; genus <i>Flavonifractor</i> ; genus <i>Coproccoccus</i> ; genus <i>Bifidobacterium</i> ; genus <i>Alistipes</i> ; genus <i>Bilophila</i> ; genus <i>Dialister</i> ; genus <i>Veillonella</i> phylum <i>Bacteroidetes</i> ; family <i>Prevotellaceae</i> ; genus <i>Dialister</i> ; genus <i>Coproccoccus</i> ; genus <i>Sutterella</i> ; genus <i>Faecalibacterium</i> ; genus <i>Clostridium</i> cluster <i>XIVa</i> ; genus <i>Coproccoccus</i>		4-7
Major depressive disorder	<i>Ccdc71</i> ; <i>Acb1l1</i> ; <i>Rp11-3b7.1</i> ; <i>Tlr4</i> ; <i>Celf4</i> ; <i>Fcfl1</i> ; <i>Fads1</i> ; <i>Arel1</i> ; <i>Fads2</i> ; <i>Ephx2</i> ; <i>Chrna7</i> ; <i>Ylpm1</i> ; <i>Spp13</i> ; <i>Tiaf1</i> ; <i>Traf3</i> ; <i>Ccdc36</i> ; <i>Sorcs3</i> ; <i>Klhdc8b</i> ; <i>Tmem258</i> ; <i>Lamb2</i> ; <i>Nlrp3</i>	phylum <i>Actinobacteria</i> ; class <i>Bacilli</i> ; order <i>Enterobacteriales</i> ; family <i>Enterobacteriaceae</i> ; family <i>Bifidobacteriaceae</i> ; family <i>Coriobacteriaceae</i> ; family <i>Lachnospiraceae</i> ; family <i>Streptococcaceae</i> ; genus <i>Eggertella</i> ; genus <i>Olsenella</i> ; genus <i>Collinsella</i> ; genus <i>Lactobacillus</i> ; genus <i>Oscillibacter</i> ; genus <i>Blautia</i> ; genus <i>Erysipelotrichaceae</i> <i>incertae sedis</i> ; genus <i>Holdemanella</i> ; genus <i>Streptococcus</i> ; genus <i>Desulfovibrio</i> ; genus <i>Paraprevotella</i> Class <i>Betaproteobacteria</i> genus <i>Bifidobacterium</i> ; genus <i>Oscillibacter</i> ; genus <i>Megasphaera</i> ; genus <i>Enterococcus</i> ; genus <i>Flavonifractor</i> ; genus <i>Streptococcus</i>			8-10
Bipolar disorder	<i>Tmem108</i> ; <i>Rhebl1</i> ; <i>Nek4</i> ; <i>Glt8b1</i> ; <i>Mcm3ap</i> ; <i>Cacna1</i> ; <i>Ank3</i> ; <i>Ncan</i> ; <i>Scn2a</i> ; <i>Pou3f2</i> ; <i>Stk4</i> ; <i>Add3</i> ; <i>Furin</i> ; <i>Haplh4</i> ; <i>Ac092661.1</i> ; <i>Dclk3</i> ; <i>Tmem258</i> ; <i>Rp5-882c2.2</i> ; <i>Gnl3</i> ; <i>Lman2l</i> ; <i>Pacs1</i> ; <i>Lrrc57</i> ; <i>Pacsin2</i> ; <i>Htr6</i> ; <i>Mchr1</i>		genus <i>Faecalibacterium</i> ; genus <i>Roseburia</i> ; genus <i>Ruminococcus</i>		5,11-13

(Continued)

Table 1. (Continued).

	Candidate risk genes	Gut microbial changes		Refs
		Positive association/Higher abundance in patients	Negative association/Lower abundance in patients	
Neurobehavioral Disorders				
Schizophrenia	<i>Grin2a</i> ; <i>Sp4</i> ; <i>Stag1</i> ; <i>Fam120a</i> ; <i>Bcl11b</i> ; <i>Cacna1c</i> ; <i>Rere</i> ; <i>Foxp1</i> ; <i>Myt1l</i> ; <i>Slc39a8</i>	phylum <i>Firmicutes</i> ; class <i>Actinobacteria</i> ; order <i>Enterobacteriales</i> ; family <i>Enterobacteriaceae</i> ; genus <i>Haemophilus</i> ; genus <i>Lachnospirillum</i> ; genus <i>Prevotella</i> ; genus <i>Escherichia</i> ; genus <i>Shigella</i> ; genus <i>Veillonella</i> ; genus <i>Megasphaera</i> family <i>Bacteroidaceae</i> ; family <i>Erysipelotrichaceae</i> ; genus <i>Escherichia</i> ; genus <i>Clostridium</i> ; genus <i>Sutterella</i>	genus <i>Bifidobacterium</i> ; genus <i>Coprococcus</i> ; genus <i>Ruminococcaceae</i> ; genus <i>Bacteroides</i> ; genus <i>Haemophilus</i> ; genus <i>Streptococcus</i> ; genus <i>Roseburia</i>	5,10,13,14
Rett syndrome	<i>Mecp2</i>		family <i>Ruminococcaceae</i>	15,16

Gut dysfunction and dysbiosis in neuropsychiatric diseases

In addition to brain-centric symptoms, somatic complications have emerged as a common clinical problem for neuropsychiatric diseases. Gut dysfunction, among others, seems to be the most common comorbidity with the behavioral changes²². For example, a spectrum of gastrointestinal disorders, such as constipation, diarrhea, abdominal pain, vomiting, and poor nutritional absorption, have been reported in up to 90% of children with ASD²³. Likely, MDD patients largely exhibit abnormality in gut motility, dyspepsia, and increased susceptibility to colitis. Also, patients with BD exhibit an increased frequency of gastrointestinal illnesses, such as inflammatory bowel disease, which has been mechanistically connected to microbial community function²⁴. Gut dysfunction and associated metabolic and immune changes could in turn aggravate the behavioral symptoms, such as anxiety and social disruption²⁵, thus forming a vicious cycle that calls for multi-dimensional intervention.

Changes in gut physiology are well known to affect the colonization and fitness of the commensal microbial community. In addition, altered feeding behavior and nutritional status, commonly observed in neuropsychiatric diseases, are powerful in shaping the gut microbial configuration²⁶. Not surprisingly, gut microbial remodeling has now been extensively observed in patients with neuropsychiatric disorders (Table 1). For example, there is early metagenomic and metabolic evidence suggesting that ASD is accompanied by gut dysbiosis²⁷, and a recent large-cohort study confirmed progressive deviation in the development of gut microbiota in children with ASD²⁸. Intriguingly, ASD risk genes are directly involved in regulating gut nutrition processing. For example, human patients with *Shank3* mutation-associated autism show lower expression of zinc transporter in enterocytes²⁹. *Chd8* mutation, a validated risk factor for ASD, is associated with slower intestinal motility and discomfort in humans, which is also proved in mouse and zebrafish models³⁰. Rett syndrome (RTT), a progressive neurological disorder characterized by autism-like behaviors, is thought to be caused by mutations in the *Mecp2* gene³¹. Recent study has moved the field one

step further by showing that RTT patients harbored a gut microbiome featuring reduced microbial richness and a dominance of *Bifidobacterium*, *Actinomyces*, *Lactobacillus* and *Enterococcus*³². In addition, ample clinical findings show that the gut microbiome is altered in MDD patients^{8,33}.

Consistently, genetic manipulations in animals induce both behavioral changes and gut microbiome remodeling (Table 2). For example, a study in *Chd8* ± mice revealed changes in gut microbial structure and amino acid transporters, which were linked to an increased glutamate/γ-aminobutyric acid (GABA) ratio in the brain³⁴. Similarly, a previous study in *Shank3*^{KO} mice reported a significantly different gastrointestinal morphology and altered microbial composition⁴¹. A recent study in RTT mice also reported alteration of gut microbiome across postnatal development as behavioral symptoms appear and progress⁴². Together, the extensive observation of gut microbial remodeling in clinical patients and preclinical models sheds an additional layer of insights into neuropsychiatric diseases and genetic underpinnings (Figure 1).

Gut microbiome contributes to genetic variance associated behavioral changes

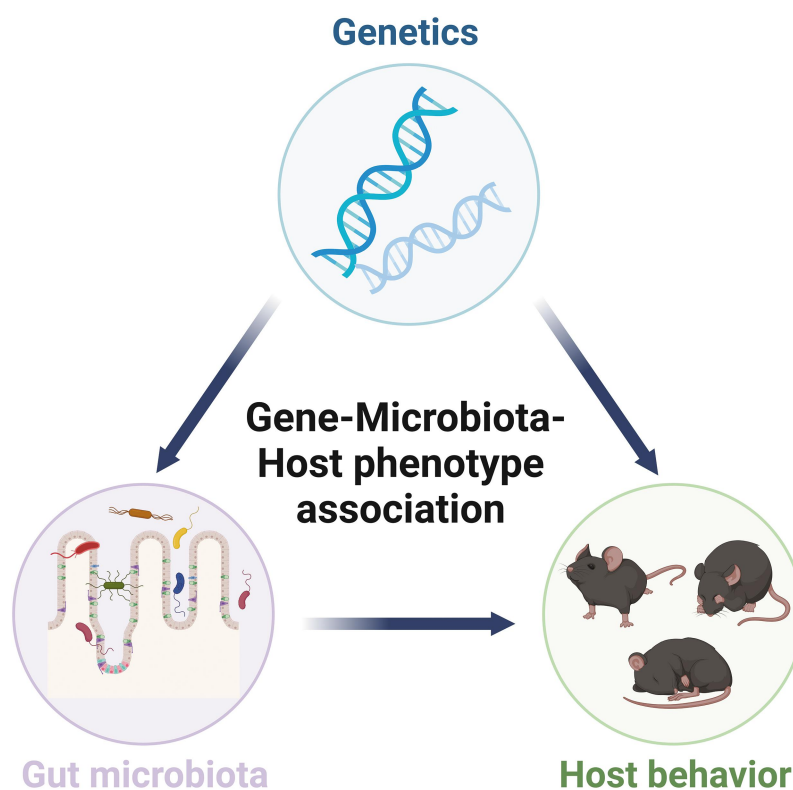
A link between the brain and gut microbiome has long been surmised⁴³. In 2009, pioneering studies implied that the altered gut microbiota may be correlated with social or learning behavior changes in rodents^{44,45}. In the following several years, causal evidence for the role of gut microbiome in host nervous system development and behavior continued to accumulate^{46–48}. To date, the gut microbiome has been firmly established as a critical regulator of gut-brain communication and behavior⁴⁹. In line with the notion that neuropsychiatric disorders involve a complex interaction of gene-environmental factors, here we provide recent evidence from animal studies showing that gut microbial remodeling is causally linked to behavioral changes induced by genetic variance.

ASD

ASD is traditionally thought to be a neurological disease with a high heritability. Studies in 2013

Table 2. Preclinical studies exploring gut microbial alteration and its role in genetic-associated behavioral changes.

Genetic variant	Behavioral phenotype	Microbial changes	Functional validation method	Role of microbial remodeling	Refs
<i>Chd8</i> ^{+/-}	ASD-like anxiety, impaired social interaction, learning and memory deficits	<i>Bacteroides uniformis</i> ↓	Co-housing, mono-colonization	Increased excitory/Inhibitory (E/I) ratio	34
<i>Shank3B</i> ^{-/-}	ASD-like social deficits	<i>Lactobacillus reuteri</i> ↓	Mono-colonization	Increased level of oxytocin	35
<i>Shank3</i> ^{-/-}	ASD-like social deficits, repetitive behaviors	<i>Lactobacillus reuteri</i> ↓	Mono-colonization	GABA receptor subunits, oxytocin signaling	36
<i>Cntnap2</i> ^{-/-}	ASD-like social deficits	<i>Lactobacillus reuteri</i> ↓	Co-housing, fecal microbiota transplantation, mono-colonization	Increased tetrahydrobiopterin (BH4) metabolism pathway	21
<i>EphB6</i> ^{-/-}	Stereotyped behavior and social deficits, accompanied by anxiety-like behavior	<i>Mucispirillum</i> ↓	Fecal microbiota transplantation	Vitamin B6 homeostasis, decrease in dopamine	37
<i>Nlrp3</i> ^{-/-}	Depression and anxiety-like behavior	uncharacterized	Fecal microbiota transplantation	Astrocyte dysfunction, expression of circHIPK2	38
<i>Ephx2</i> ^{-/-}	Depressive-resilient phenotypes	<i>Faecalibaculum rodentium</i> ↓	Fecal microbiota transplantation, mono-colonization	Systemic inflammation, and synaptic proteins in the prefrontal cortex	39
<i>Chrna7</i> ^{-/-}	Depression-like behavior	uncharacterized	Fecal microbiota transplantation	synaptic proteins in the prefrontal cortex	40

**Figure 1.** A triangular connection exists among host genetic variants, gut microbiome and neurobehavioral phenotype.

have shown direct evidence that gut microbiota could modulate autism-related behavior⁴⁷. A more recent study transplanting gut microbiota from human donors with ASD to germ-free (GF) mice showed that ASD microbiota was sufficient to induce hallmark autistic behaviors, accompanied by discrete metabolome profiles⁵⁰. Intriguingly, treatment of the BTBR ASD mouse model with

key differential microbial metabolites improved behavioral abnormalities and modulated neuronal excitability–inhibition balance in the brain, providing further causal evidence for microbial factors. Interestingly, treatment with *Lactobacillus reuteri* (*L. reuteri*) was shown to generally rescue social deficits in *Shank3b*^{KO} and other environmental and idiopathic ASD models³⁵. Also, of interest is the

finding that *L. reuteri*⁶⁴⁷⁵ intervention selectively rescued the social deficits but not the hyperactivity phenotype in *Cntnap2*^{KO} mice by bolstering the oxytocinergic system²¹. Together, these studies provide strong evidence that the gut ecosystem plays an important regulatory role in many aspects of ASD symptomatology.

MDD

MDD is a polygenic disease, and a most recent GWAS covering over 1.2 million participants identified 178 genetic risk loci and 223 independently significant single-nucleotide polymorphisms (SNPs) that were associated with the disorder at genome-wide significance². However, the heritability estimates for MDD (40%) are lower than those for other neuropsychiatric illnesses (between 75% and 80%), implying that additional factors are involved. Several preclinical studies have shown that genetic manipulation can effectively modulate depression-like behavior, with the mechanism being partially attributed to the gut microbiota. For example, a recent study showed that the relative abundance of *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* in the gut microbiota of *Nlrp3*^{KO} and WT mice was substantially different³⁸. Notably, fecal microbiome transplantation (FMT) from the *Nlrp3*^{KO} mice alleviated stress-induced depressive-like behaviors in recipient mice. *Chrna7*^{KO} mice, which have a deficiency in $\alpha 7$ subtype of nicotinic acetylcholine receptors ($\alpha 7$ nAChR), exhibited depression-like behavior and gut microbial changes (increased *Lactobacillus animalis*, *Helicobacter ganmani*, and decreased *Muribaculum intestinale*). In a following study, FMT proved successful to transmit the depressive behavior to recipient mice via vagal nerve signaling⁴⁰.

BD and schizophrenia

GWAS reveals a genetic connection between schizophrenia and BD, and many of the risk genes have been linked to immunological response and inflammation⁵¹. Ample data point to poor diversity and dysbiosis with respect to the abundance of *Faecalibacterium* and *Bacteroides* as possible traits and state-dependent characteristics of BD. Reduced butyrate production and richness also drives inflammation, which may be a previously unappreciated component of the pathophysiology

driving BD⁵². Association also exists between gut microbial dysbiosis and the hypothalamic-pituitary-adrenal (HPA) axis dysregulation in BD, as a significant negative correlation between the count of *Bifidobacterium* and cortisol levels was recently found⁵³. Notably, HPA axis dysfunction in BD may worsen intestinal permeability and gut microbial dysbiosis in turn. Supporting the role of gut dysbiosis in schizophrenia patients, colonization of *Streptococcus vestibularis*, a bacterium enriched in treatment naïve schizophrenia patients, causes social behavior abnormalities, and alters neurotransmitter levels in peripheral tissues in antibiotics-treated recipient mice⁵⁴.

Fragile X syndrome (FXS)

FXS is an inheritable neurodevelopmental disease characterized by autistic traits, such as mental retardation and impaired social communication or interaction. Recently, there is accumulating evidence that FXS caused by *Fmr1* deficiency is likely to be caused by alterations in gut microbiota. More recently, gut microbiome changes involving *Akkermansia*, *Allobaculum*, *Bifidobacterium*, *Odoribacter*, *Flexispira*, *Bacteroides*, and *Oscillospira* have been profiled in *Fmr1*^{KO} mice, and, of note, FMT from normal mice proved effective to mitigate autistic-like behaviors^{55,56}.

Amyotrophic lateral sclerosis (ALS)

ALS is a fatal neurodegenerative disease that causes progressive motor neuron loss. ALS patients often show behavioral symptoms such as depression and anxiety⁵⁷. ALS is thought to have a substantial genetic component with a high heritability, and many of the gene variations (e.g., *Sod1*, *Tardbp*, *Fus*, *C9orf72*) that cause or predispose an individual to ALS have been identified⁵⁸. In 2017, gut dysbiosis with a reduced population of butyrate-producing bacteria was reported in *Sod1* (G93A) mice, which was rescued by butyrate treatment⁵⁹. Indeed, novel evidence indicating a disease-modifying role for the gut microbiome has recently emerged, with certain gut microbial strains being causally linked to the behavioral symptoms in *Sod1* and *C9orf72* model mice^{60,61}. Therefore, it is reasonable to dissect neuropsychiatric disorders from the perspective of reciprocal host gene-microbiome interactions.

Strategies for identifying psychoactive microbes

Microbe-wide association analysis, including 16S rRNA/18S rRNA/ITS and metagenomic sequencing, produce long lists of differential microbes. Due to the inherent complexity, diversity, and flexibility of the microbiome, standard correlative microbiome study is largely insufficient to elucidate the causal microbes. In further consideration of the complex routes of gut-brain communication²⁰, unbiased identification of causal microbes in shaping neuropsychological diseases due to genetic variation is undoubtedly challenging. Here, we describe ongoing efforts and strategies

seeking to answer this basic open question in microbiome study (Figure 2), which may serve as a framework for further mechanistic studies in neuropsychiatric disease.

Microbe-phenotype triangulation

Early pioneering studies by Gordon *et al.* describe the transplantation of combinatorial bacterial communities from human donors to gnotobiotic mice followed by mono-colonization validation⁶². This strategy features random fractionation of bacterial communities into subsets that are gavaged to recipient mice to identify the strains whose presence or absence best explain the observed phenotypic

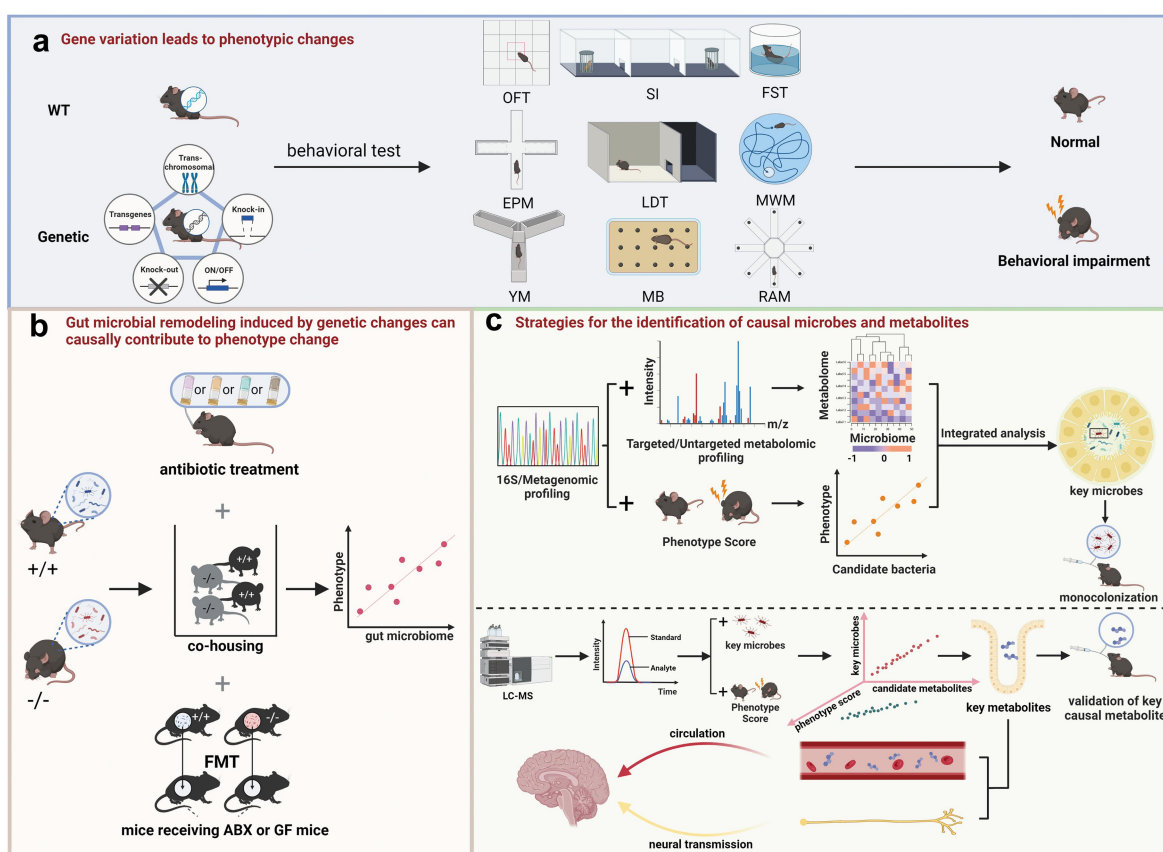


Figure 2. A tentative framework to disentangle gene-microbiome-phenotype interaction in complex neurobehavioral disease network. (a) Assessment of behavioral phenotypic changes after genetic manipulations. The commonly used behavioral tests used were open field test (OFT), social interaction (SI), forced swimming test (FST), elevated plus maze (EPM), light/dark test (LDT), Morris water maze (MWM), Y-maze (YM), marble-burying test (MB) and radial arm maze (RAM). (b) Causal role validation of gut microbial remodeling induced by genetic changes. The causal link between microbiome and behavioral phenotypes can be verified by antibiotics (ABX) treatment, co-housing, fecal microbiota transplantation (FMT) experiment with germ free (GF) mice. (c) Integrative strategies for the identification of causal microbes and metabolites. Combined analysis of microbiome and metabolomics, and a microbe-phenotype strategy to refine the catalog of differentially abundant microbes to most probably causal members followed by mono-colonization validation. Candidate metabolites identified by metabolomics are then assayed for the impacts on behavioral changes.

variation in metabolic and immune responses. Notably, by showing metabolite-microbe interactions under complex logics, this approach offers initial clues for deciphering the single and collective impact of different strains on the host metabolic phenotype. Therefore, this approach should facilitate mechanistic studies of how bacterial strains influence host behavioral phenotypes through metabolic and immune signals. A seminal work in recent years is the proposal of a microbe-phenotype triangulation strategy by Surana *et al.*, which nicely refines the catalog of differentially abundant microbes to most probably causal members⁶³. This strategy is based on the premise that co-housing mice with different microbial background can allow their flora to be recombined to form the ‘intermediate microbiome’ that blends the characteristics of the original flora. If the microbial effect on disease was dominant, mapping of microbe-phenotype relationships in parental and hybrid-microbiota mice would efficiently narrow down of the inherent noise in sequencing data and sort out key candidates. Of interest, this microbe-phenotype triangulation strategy is observed in the study of Regen *et al.*, which proved useful to elucidate the microbial basis of the central nervous system autoimmunity shaped by *interleukin17 (Il17)* genetic variant⁶⁴. When healthy control and patients are carefully selected, such a microbe-phenotype triangulation strategy can be more generally applicable to human microbiome studies. However, this strategy has several caveats that may compromise the scalability. As a major concern, co-housing does not always result in intermediate phenotypes, and, instead, mono-directional transmission of one dominant phenotype could be observed⁶⁵. Also, for rare species that may mediate a host phenotype, causal bacteria may be masked due to their relative low abundance⁶⁶.

In essence, the microbe-phenotype triangulation strategy relies on the spatial transmission of causal microbes to enable comprehensive microbial analyses from microbially related mice⁶³. For studies where co-housing is impractical, an alternative strategy would be dirty cage sharing, as recently shown by Guo *et al.*⁶⁷. Specifically, in the search for key protective microbe in elite-survivors which were old male mice, a traditional cohousing approach

with young male recipients might lead to fighting and injury to the older mice. By analyzing bacterial 16S rRNA genes in feces from donors and recipients after sharing dirty cages, it was shown that dirty cage sharing was effective in exchanging gut microbiota from donors to recipients.

Select antibiotic disentanglement

Antibiotic cocktail comprising ampicillin, vancomycin, neomycin, and metronidazole is commonly used for assessing the role of gut microbiota in the host phenotype, although each antibiotic modulated the microbiota composition in a distinct way. Recent studies have also shown that the use of single antibiotics could also provide useful clues for identifying causal microbes. As an illustrative example, Miyauchi *et al.* showed that both depletion of the gut microbiota by antibiotic cocktail and oral treatment with ampicillin alone limited the development of experimental allergy encephalomyelitis (EAE)⁶⁸. In consistence, ampicillin-treated mice showed a unique microbiota structure in the small intestine, and a novel strain named operational taxonomic unit (OTU)0002 was the sole sequence that was almost completely depleted only from the small intestine of ampicillin-treated mice. Notably, mono-colonization with OTU0002 resulted in an increased severity of EAE symptoms and frequency of T helper 17 (Th17) cells, both in the small-intestinal lamina propria and spleen. In another study seeking to identify gut bacterial species that affect social activity⁶⁹, mice were treated with different combinations of antibiotics, which showed that a microorganism exclusively sensitive to neomycin appeared to be responsible for modulating social activity and corticosterone levels after social stress. Further study identified *Enterococcus faecalis* (ATCC 19,433) that promoted social activity and reduced activation of the HPA axis.

Spatiotemporal microbial mapping

Gut microbial structure shows inherent plasticity and dynamics. To strengthen the confidence of causal microbe identification, temporal patterns of the gut microbiota could be mapped for integration with spatial profiling. In the study by Blacher

et al., for example, several important time points were selected for bacterial sequencing along with the disease progression, and then the results were further integrated with spatial transmission features⁶⁰. Eleven distinct commensal bacteria that would increase or decrease within the disease process were subsequently identified, and the role of each strain was verified by single bacterial colonization into antibiotic pre-treated model group. This strategy is of special value for causal microbe identification from human microbiome samples, which is complicated with high interindividual variance⁷⁰. For example, in the search for irritable bowel syndrome (IBS) subtype-specific microbial composition and metabolites, longitudinal sampling effectively limited heterogeneity seen in cross-sectional microbiome studies⁷¹. The results showed that stool microbiota composition exhibited greater variability over time in patients with constipation-type IBS (IBS-C) compared to diarrhea-type (IBS-D) cohorts. In another clinical study involving hematopoietic cell transplantation patients, daily changes in circulating neutrophil, lymphocyte, and monocyte counts and more than 10,000 longitudinal microbiota samples were profiled to reveal consistent associations between gut bacteria and immune cell dynamics overtime⁷². These strategies are readily applicable to screen causal microbes underlying behavioral disorders.

Computational algorithm and machine learning

Computational algorithm is also finding a wide application on identifying causal microbes or biomarkers from clinical large-scale databases of microbial community. Batch inconsistency of multi-population metagenomic data presents a challenge in identifying robust microbial markers. Addressing this issue, recently an algorithm called Network Module Structure Shift (NetMoss) has been devised, which proved useful to identify shared and unique microbial biomarkers from a network perspective⁷³. This method is expected to enable reliable meta-analysis of metagenomic dataset from neuropsychiatry disease cohorts. Also, of note is the recent report of a machine learning-based framework that could jointly analyze paired host transcriptomic and gut microbiome data for deciphering host gene and gut

microbiome interactions in disease⁷⁴. This computational method can be applied to neuropsychiatric diseases for the identification of host gene-microbiome associations and key microbes that may influence behavioral outcomes.

It should be noted that current microbial mapping techniques have limitations in providing high-resolution and functional information, especially given the difficulties associated with assigning gene-based labels and gene-function correlation. The commonly used 16S rRNA sequencing technique reveals the bacterial genes they carry and the compounds they produce or consume. Thus, a better approach might be identifying not just the taxonomy, but the metagenomic signature, a matrix describing which genes are stored in which bacteria, and what is their abundance. This fact suggests that the screening and validation of potential causal microbes should consider strain and host origin differences and the sequencing depth. Moreover, even in the same model, intestinal site, and mucosal region-dependent changes of gut microbial composition should receive due attention in sampling and data interpretation⁷⁵.

Deciphering gut microbial signals in behavioral control

Current research in neurogenetics mostly seeks to answer how genetic variants regulate neuronal activity and circuit function in key brain regions using sophisticated cell-specific imaging, electrophysiology, and genetic manipulation techniques. Understanding how gut microbes communicate with the brain therefore holds another key to therapeutic target discovery. The past decade has witnessed huge advances in decoding the signaling mechanisms along the microbiota-gut-brain axis, which provide snapshots into the network connecting microbiome, brain and behavior including anxiety, cognition, nociception, and social interaction^{20,76}. Concerning the neural transmission pathway, the message could be transmitted via the vagal or the sympathetic nervous system^{77,78}. The effects of *L. reuteri* on social behavior were no longer present in vagotomized animals in a *Shank3B*^{KO} mouse model of autism³⁵. Also, via direct synapsing with vagal nodose neurons, enteroendocrine cells (EEC) have emerged as

a new sensory mechanism for rapid transmission of gut signals⁷⁹. More recently, in zebrafish, microbial, pharmacological, or optogenetic activation of Trpa1+ EECs proved successful to directly stimulate vagal sensory ganglia and activate cholinergic enteric neurons by secreting the neurotransmitter 5-hydroxytryptamine (5-HT)⁸⁰. Microbial signals can also transmit through the sympathetic nerve. A gut-brain-gut neural circuit, which regulates efferent sympathetic tone and gastrointestinal transit has been recently identified⁷⁸. This effect was mainly attributed to microbial metabolites, such as short-chain fatty acids and bile acids, as well as microorganism-modulated GLP-1 release.

Bidirectional gut-brain signaling can also occur via circulating hormones, metabolites, cytokines, and other neuromodulatory molecules^{69,75}, which appear to affect the brain in a direct or indirect manner. Elevated level of a microbial metabolite 4-ethylphenyl sulfate was previously reported in mice with social impairment⁴⁷. A follow-up study showed that this gut-derived metabolite can enter the brain to affect oligodendrocyte function and neuronal myelin sheath pattern and promotes anxiety-like behavior in mice⁸¹. More recently, it is also reported that direct sensing of bacterial cell wall components (peptidoglycan) by hypothalamic Nod2+ neurons regulate appetite and body temperature in mice⁸². However, for those messengers that could not directly enter the brain, much more work is needed to fully address the exact mechanisms by which gut microbiota could distally impact on the brain and behavior. One common route is the sensing and transmission by neural pathway. For example, *Lactobacillus brevis* Bb14 (ATCC14869)-derived trehalose from sugar metabolism by the bacterial enzyme xylose isomerase activates peripheral octopaminergic neurons to regulate locomotor behavior in the fruit fly *Drosophila melanogaster*, while germ-free status or antibiotic treatment results in hyperactive locomotor behavior⁸³. Recently, an inter-organ neural circuit for appetite suppression has been mapped, which conveys gut local GLP-1 signal to induce satiety⁸⁴. Since gut microbes are intimately involved in the regulation of GLP-1 release, and GLP-1 has behavioral effects more than appetite control⁸⁵, it would be of interest to further explore the involvement of this pathway in gut microbial regulation of behavior.

The involvement of immunologic signal pathways in microbiota-brain interaction has also been reported. For example, gut microbiome members such as *segmented filamentous bacteria* (SFB), *Bifidobacterium adolescentis*, and *Odoribacter splanchnicus* are well known to induce IL-17 production. Notably, SFB-induced susceptibility to stress-induced depressive-like behaviors in mice were causally linked to the expansion of Th17 cells, which accumulated in the hippocampus⁸⁶. Context-dependent (during embryonic brain development or in the adult brain) effects of IL-17 in social behavior has been previously reported⁸⁷⁻⁸⁹, and, more recently, mucosa-associated fungi was shown to promote social behavior in mice via sensory neuron IL-17 receptor⁸⁶.

Generally, the integration of 'omics' datasets, such as transcriptomics, metagenomics, proteomics, and metabolomics can be useful to pinpoint the regulatory microbes and signaling molecules underpinning host behavioral phenotype. This strategy is nicely depicted by the study of Sharon *et al.*, which transplanted gut microbiota from human ASD donors into GF mice for mechanistic interrogation⁵⁰. Through the inter-correlative analysis of species, metabolites, and behaviors of mice harboring human microbiota, candidate microbes, and metabolite that may mediate ASD behaviors were picked out for further validation. This strategy is also observed in profiling microbiota-host interaction in a *Chd8±* mouse model with ASD-like behavior, in which increased expression of amino acid transporters in the intestines of ASD mouse and high level of serum glutamine offer clues to understand the increased excitation/inhibition ratio in the brain³⁴.

Given the inherent noise in the omics data, 'trial and error' screening is necessary, and several more criteria are worthy of consideration. This is elegantly demonstrated by the study of Blacher *et al.* to identify causal microbial metabolites in ALS from nicotineamide (NAM) and phenol sulfate, which had the highest metagenomic probability. By showing that phenol sulfate administration to mice did not relieve the symptoms of ALS mice, they focused on NAM for the following reasons: the marked differences in the metagenomic NAM biosynthetic pathway; the enrichment of NAM biosynthetic intermediates in serum upon supplementation with *Akkermansia*

muciniphila (ATCC BAA-835); reduced abundance of genes from the gut-microbiome-derived tryptophan metabolizing pathway, which may be involved in NAM production; and the alteration of metabolites in the tryptophan pathway upon treatment with antibiotics or upon *Akkermansia muciniphila* supplementation⁶⁰. Functional validation with NAM supplementation finally identified NAM as a key protective metabolite in ALS.

Mechanisms underlying host genetics-induced gut microbial remodeling

Although host genetic variation is known to shape the gut microbial ecology^{90,91}, there is still limited insights into how the composition and function of gut microbial community are altered. In essence, this reflects the interaction between the host's mutated genes and microbial genes that shape their fitness and survival in the gut, as shown by recent studies in mice. A balanced gut microbial configuration is characterized by the dominance of obligate anaerobic members of the phyla *Firmicutes* and *Bacteroidetes*, which prevents dysbiotic expansion of facultative anaerobic microbes, such as *Enterobacteriaceae* in part by limiting the generation of host-derived nitrate and oxygen. Epithelial mitochondrial bioenergetics and metabolism has therefore proven to be a canonical pathway by which host genetic signals remodel the gut microbial configuration. A typical sensor/mediator is epithelial peroxisome proliferator-activated receptor γ (PPAR- γ), which drives the energy metabolism of colonic epithelial cells toward β -oxidation and limits both the luminal bioavailability of oxygen and nitrate to prevent a dysbiotic expansion of potentially pathogenic *Escherichia* and *Salmonella*⁹². Mice lacking epithelial PPAR- γ signaling exhibited significantly elevated nitrate availability in the lumen and dysbiotic expansion of *Escherichia coli* that carries the genetic machinery for nitrate respiration⁹³. Moreover, treatment with 5-amino salicylic acid, a PPAR- γ agonist, restored mitochondrial bioenergetics in the colonic epithelium, which alleviated dysbiosis triggered by high-fat diet and antibiotics⁹². A recent study has also established that intestinal hypoxia-inducible factor-2 α (*Hif2 α*) deficiency altered the balance of intestinal *Bacteroides vulgatus* to *Ruminococcus torques* to

affect bile acid signaling and obesity-related insulin resistance⁹⁴. Mechanistically, ablation of intestinal *Hif2 α* reduced the level of epithelial-derived lactate, which enriched the polysaccharide utilization genes to promote the growth of *Bacteroides vulgatus*.

Host genetics can also shape the commensal microorganisms by regulating the secretion of defense signals, such as antimicrobial peptides and immunoglobulin A (IgA)⁹⁵. Typically, secretory IgA directed against bacterial antigens has been proposed to shape intestinal microbial composition by multiple mechanisms, including inhibition of bacterial motility and reduction in bacterial fitness. As has been recently reported, activation of mechanistic target of rapamycin complex 1 (mTORC1) signal in CD11c cells alters IgA secretion at the mucosal site⁹⁶. Reduced IgA production results in decreased gastrointestinal colonization of *Lactobacillus johnsonii* Q1-7, which in turn leads to lower food intake and body mass. In addition, another investigation has shown that mice with T cell-specific ablation of *Myd88*, an innate adaptor molecule, have defective development of T follicular helper cells in the gut, contributing to inappropriate IgA targeting of *Clostridia* and altered microbial balance⁹⁷. This results in imbalanced expansion of *Desulfovibrio* at the expense of the loss of *Clostridia*, which contributes to increased lipid absorption and obesity susceptibility.

Goblet cell secretion of mucin represents another way by which host genetics influence the symbiotic microbes⁹⁸. A recent study shows that loss of forkhead box O 1 (*Foxo1*) in intestinal epithelial cells results in defects in goblet cell autophagy and mucus secretion, which induces gut dysbiosis, disruption of gut barrier integrity, and increased susceptibility to intestinal inflammation⁹⁹. Deficiency G protein-coupled receptor 35 (*Gpr35*), previously known to regulate the activity of Na/K-ATPase and mitochondrial oxidative phosphorylation (OXPHOS) of epithelial cells¹⁰⁰, was recently shown to induce goblet cell depletion and dysbiosis^{101,102}. Interestingly, ablation of Calcitonin gene-related peptide (*Cgrp*) in nociceptor neurons or epithelial *Ramp1* is also shown to reduce goblet cell mucus secretion, which induces dysbiosis and susceptibility to colitis¹⁰³.

Practical considerations in gene-microbe-behavior study

The interwoven gene-microbiota connection in neurobehavioral changes, as well as the limitations in current techniques, suggests some practical issues deserving attention in the effort to better understand the etiology and treatment strategy for neuropsychiatric disease. Firstly, given the strong impact of environmental factors on microbial composition, diet composition, and housing condition variance should be carefully considered in screening differential bacteria¹⁰⁴. Conclusive evidence that a genomic mutation is responsible for a specific behavioral phenotype can be obtained when littermate controls are used²¹. If wild-type control mice were provided from other animal facility, the influence of environment factors on gut flora was difficult to exclude. Of note, the fact that mice from different suppliers showed markedly variance in microbial background and biologic responses provides excellent clues for identifying key causal microbe, as demonstrated previously^{61,105}.

Secondly, in mono-colonization studies, it would be necessary to profile whether the global microbial community would be affected to understand whether the host impact may derive from microbe interactions. Indeed, studies have shown that colonization of a single strain may elicit microbiome-wide changes³⁵. It is reasonable that host impacts of gut microbial change could be attributed to the interactions among different microbes. Indeed, in the study of Miyauchi *et al.*, mice mono-colonized with OTU0002 exhibited EAE symptoms that were less severe than those of specific-pathogen-free (SPF) mice, which indicated that other bacterial members of the microbiota could also be participating in the pathogenesis of EAE. In the search for potential microbial interactions, they further showed that two distinct signals from OTU0002 and a *L. reuteri* strain (H4 and LMG 18,238) coordinately activate autoreactive T cells in the small intestine to drive autoimmune responses. In practice, to better mimic microbial interaction network in host regulation, a simplified microbial community consisting of representative high-abundance bacterial species would provide more physiologically similar, while structurally defined microbial models for the validation of key

causal microbes. This strategy is readily found in the study of Lobel *et al.*¹⁰⁶ and Kasahara *et al.*¹⁰⁷, which support that the colonization of the structurally defined consortium of bacteria could provide physiologically relevant and therefore more strong insights into microbe-host interactions.

Thirdly, although we largely focus on data from mice models, non-mouse model organisms, such as zebrafish, *Drosophila melanogaster*, and *Caenorhabditis elegans* are useful for gut-brain-microbiota studies related to neuropsychiatric diseases¹⁰⁸. The accumulated expertise in genetic and microbial manipulation and human-relevant neurobehavioral parameters could become advantages for gaining holistic insights into gene-microbiota-behavior interplay and the signaling basis. Some elegant studies are available in relation to the dissection of microbial connection to sensory and locomotive behavior^{83,109}.

Lastly, in the clinical setting, age, sex, dietary habits, co-morbid diseases, and drug exposure are common confounding factors for identifying causal links. Addressing these inter-individual variability factors is crucial to elucidating the genetic and microbial factors that causally shape human neuropsychiatry diseases. A recent prospective large-population study dissecting the influence of the gut microbiome, diet, and genetics on plasma metabolome variation presents a useful workflow to tackle this issue¹¹⁰. In particular, through Mendelian randomization and mediation analyses, this study uncovered putative causal relationships between the gut microbiome and plasma metabolites. Application to neuropsychiatric disorders would be expected to clarify robust microbial features to clinical diagnostic and preventive purposes.

Conclusions

Current therapeutic approaches for neuropsychiatric disorders aim to target the brain directly. The accumulating findings on host genetic-gut microbial interplay in neuropsychiatric diseases broaden our views on the factors shaping individual's susceptibility to mental illnesses and underscore the bidirectional gut-brain crosstalk in behavioral control. An emerging picture is that microbial and host

genetic factors may control different aspects of brain diseases, which provide the rationale for combinatorial targeting of genetic factors and microbial signaling for comprehensive intervention of complex behavioral diseases. Deciphering gene-microbiome-phenotype triologue in complex neuropsychiatric diseases may therefore inspire novel therapeutic strategies and precision intervention. However, since most of the causal data are from animal studies, the results still should be approximated to humans with caution.

The field of microbiome research is experiencing a progression from associative linking to causal and mechanistic insights, which presents new opportunities to decipher how this dynamic community is functionally implicated in the genetic predisposition to neuropsychiatric diseases in concert with other environmental factors such as diet and lifestyle. In future studies, the causal relationship between genetic variance, key microorganisms, and behavioral changes remains to be fully elucidated in the clinical setting in order to provide novel diagnostic biomarkers and therapeutic targets. Another key question is how the microbes achieve central relays of local signals to specify the behavioral changes. Research insights into the communication pathways between the gut and the brain is critical to drive this frontier forward. Meanwhile, elucidation of the key biologic synthetic pathways of microbes and the sensors for the signaling molecules could provide potential drug targets. Recently, the devise of novel techniques for genetic manipulation of gut microbes and targeted protein degradation in bacteria could enable efficient clues to answer these key questions^{111,112}. Neural circuitry allowing gut microbial control over behaviors remains to be fully unmapped, under both physiological and pathological conditions. Advances in this field increasingly benefit from the technical advances in optogenetics, chemogenetics, and virally delivered molecular tools for neural manipulation in an organ-specific and inter-organ manner^{71,113}. Progress in this field could be integrated with genetic manipulation studies to offer combinatory targets for future drug discovery. Specifically, the microbial signals or microbe-responsive pathways promoting inner homeostasis or resilience to stressful events could be strengthened as a preventive or therapeutic strategy.

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Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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