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Full Length Article

Beyond the neuro-immune interplay in depression: Could gut microbes be the missing link?

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ABSTRACT

Accumulating evidence have positioned inflammatory signaling pathways as crucial routes by which microbes inhabiting the gastrointestinal tract (the gut microbiota) communicate with the host brain to influence behavior, with impacts on mental illnesses. In this short review, an overview of inflammatory and gut microbiota status in human depression and in rodent models of the illness are provided. Next, potential inflammatory pathways mediating the communications between the gut and the brain under stressful conditions are described. Finally, dietary interventions targeting the gut microbiota-immune-brain axis in the context of depression are briefly discussed.

1. Introduction

Inflammatory molecules are now recognized as key contributors to the pathogenesis of major depression, likely owing to their actions on brain processes involved in stress responsiveness and resilience (Enache et al., 2019; Hodes et al., 2015; Osimo et al., 2020). Appreciable evidence suggest that inflammatory disturbances seen in depression could stem from pro-inflammatory shifts in microbial communities inhabiting the gastrointestinal tract, referred to as the gut microbiota (Audet, 2019; Dinan and Cryan, 2017; Forsythe et al., 2016; Foster et al., 2017). The observation that microbiota colonization of the gastrointestinal tract, maturation of the immune system, and development of the brain overlap at crucial stages of development further points to the possibility that these processes may start to influence each other early during development (Jašarević et al., 2016), leading to the establishment of a dysfunctional gut microbiota-immune-brain axis and of abnormal behavioral patterns in the face of environmental insults (e.g., stressors). In this review, an up-to-date overview of inflammatory and gut microbiota status in human depression and in rodent models of the illness will first be provided. Next, potential inflammatory pathways mediating the gut-brain crosstalk as well as their establishment and maintenance in stressful conditions will be described. Finally, the use of dietary interventions targeting the gut microbiota-immune-brain axis for depression will be briefly discussed.

2. The gut microbiota-immune-brain axis and depressive illnesses

A growing body of evidence suggest that perturbations to the signaling of key inflammatory molecules between gut microbes and the host brain (the gut microbiota-immune-brain axis), either caused by psychological stressors or by other immunogenic insults, could promote the development and maintenance of depressive phenotypes (Dinan and Cryan, 2017; Foster et al., 2017; Kelly et al., 2015). The contribution of inflammatory factors to depression has been consistently confirmed by several meta-analyses showing that non-medicated individuals with major depression had higher circulating concentrations of pro-inflammatory cytokines (signaling molecules between immune cells), particularly of interleukin (IL)-6 and tumor necrosis factor (TNF)-α (Dowlati et al., 2010; Köhler et al., 2017; Liu et al., 2012; Osimo et al., 2020). The capacity of interferon (IFN)-α to elicit a syndrome similar to that of major depression in patients with hepatitis C or some types of cancer also supports a role, more causal in this instance, for pro-inflammatory factors in depression (Capuron and Miller, 2004; Musselman et al., 2001). More recently, the use of chimeric antigen receptor T-cell therapy in the treatment of hematological malignancies was similarly reported to promote depressive symptoms, potentially because of the cytokine release syndrome these patients experienced post-therapy (Dai et al., 2021). Although fewer studies exist in this regard, markers of

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brain inflammatory activation have been reported in individuals with major depression. Higher cerebrospinal fluid levels of IL-6 and up-regulated post-mortem brain expression of TNF-α and of other cytokine transcripts were detected in individuals with major depression (Dean et al., 2010; Sasayama et al., 2013; Shelton et al., 2011), along with an elevated density of the translocator protein (a marker of increased activity of microglia, the brain immune cells) in different regions of the brain (Holmes et al., 2018; Richards et al., 2018; Setiawan et al., 2015). Notably, some of the peripheral and central inflammatory markers in depressed individuals were linked with symptom severity (Calarge et al., 2019; Setiawan et al., 2015), suggesting that higher inflammatory activation in depression could reflect more severe states of the illness.

One research avenue that we and others have been pursuing is the possibility that the increased inflammatory activation in circulation and in the brain of individuals with depression could originate from impairments at the intestinal barrier that would allow bacterial fragments to translocate into the bloodstream, leading to an extra-intestinal inflammatory cascade (Kelly et al., 2015; Maes et al., 2008). A clear picture of the microbiota components altered in depression has yet to be established (Dinan and Cryan, 2017), but available reports suggest that compositional differences in gut bacterial communities in individuals with depression may be reflective of a pro-inflammatory intestinal environment (Chen et al., 2018; Jiang et al., 2015; Kelly et al., 2016; Valles-Colomer et al., 2019; Zheng et al., 2016). In line with this view, individuals with major depression had higher levels of Proteobacteria and of *Enterobacteriaceae*, which are mainly composed of Gram-negative bacteria capable of producing the endotoxin lipopolysaccharide (LPS) (Jiang et al., 2015). They also had lower levels of *Faecalibacterium* (Chen et al., 2018; Jiang et al., 2015; Zheng et al., 2016), and levels of this anti-inflammatory genus were negatively correlated with depression severity (Jiang et al., 2015) and positively correlated with quality of life indicators (Valles-Colomer et al., 2019). Markers of intestinal permeability (e.g., urinary lactulose to mannitol ratio, plasma levels of intestinal fatty acid binding protein) and of bacterial translocation (e.g., plasma levels of the 16S rDNA subunit of gut microbiota) were also higher in non-medicated individuals with depression and/or correlated to symptom severity (Calarge et al., 2019; Kéri et al., 2014; Ohlsson et al., 2019), adding support to the view that fragments from a pro-inflammatory microbiota could cross an impaired intestinal barrier and initiate extra-intestinal inflammation in the context of depression. Curiously, however, it appears that higher levels of inflammatory markers in the brain were not strongly correlated with those in circulation (Enache et al., 2019). Whether brain inflammatory activation in depression results from higher circulating cytokines is still not entirely clear, although a decreased expression of the tight junction protein claudin-5 (Menard et al., 2017) and of astrocyte and oligodendrocyte density (Enache et al., 2019) have been found in the post-mortem brain of depressed individuals, potentially reflecting damages to the blood-brain barrier in this population.

The possibility that the inflammatory activation seen in depression could stem from a pro-inflammatory intestinal environment, facilitated by a compromised intestinal barrier, has also been supported by animal studies. Rodent models of depression are using naturalistic stressors of psychosocial nature (e.g., chronic social defeat) or regimens of variable stressors administered according to a chronic and/or unpredictable sequence (e.g., chronic mild stress) (Golden et al., 2011; Willner, 2005). These stressor procedures mimic human stressors that are potent risk factors for depression (Marin et al., 2011) and have demonstrated immunogenic properties (Hodes et al., 2014; Krishnan et al., 2008). Our work and that of others showed that chronic social stressors in adult male mice disturbed gut microbiota communities (Bailey et al., 2011; Bharwani et al., 2016; McGaughey et al., 2019; Szyszkowicz et al., 2017; Yang et al., 2017) and increased pro-inflammatory cytokines, particularly IL-6, peripherally and in brain regions involved in stress-related disorders (Audet et al, 2010, 2011; Hodes et al., 2014; Menard et al., 2017). Using chronic social defeat in male mice, we showed that some of the long-lasting bacterial changes in cecum contents were linked to severity of social avoidance (a behavioral feature reflective of susceptibility to the depressive-like effects of the stressor) and to brain pro-inflammatory cytokines (Szyszkowicz et al., 2017). Although these observations were correlational, considering that the genera affected by the social stressor and correlated to behavioral and brain cytokine phenotypes (*Oscillospira* and *Parabacteroides*) have anti-inflammatory properties (Koh et al., 2018; Yang et al., 2019), they suggest that severity of social avoidance in chronically defeated mice could be linked to an increased inflammatory tone along the gut microbiota-immune-brain axis. We confirmed this possibility by showing that male mice exposed to chronic social defeat had long-lasting elevations of the pro-inflammatory cytokines IL-1β and TNF-α in the middle section of the small intestine (jejunum), which were accompanied by abnormal expression of tight junction proteins (reflective of increased membrane permeability) (Santos et al., 2021). These findings further support the possibility that stress-induced pro-inflammatory shifts in the intestinal environment, combined with a breach in the intestinal barrier, could promote extra-intestinal inflammatory activation, potentially ramifying to the brain. Considering that these outcomes have been observed in a mouse model of depression, it is possible to think that they could relate, at least in part, to the inflammatory pathways underlying some forms of the illness, as it has been suggested by others (Doney et al., 2021).

3. Inflammatory pathways mediating the gut-brain crosstalk and their development in stressful conditions

The mechanistic pathways by which gut bacteria and the brain talk to each other are only starting to be uncovered. Although it is acknowledged that inflammatory molecules transit between the gut and the brain to relay key messages, how these routes are being established, and how their trajectories may change under adverse conditions, has yet to be defined. Beyond promoting changes in gut microbiota communities and in inflammation (Audet et al, 2010, 2011; Bailey et al., 2011; Bharwani et al., 2016; Hodes et al., 2014; Menard et al., 2017; Szyszkowicz et al., 2017), stressors induced damages to the intestinal barrier and allowed the passage of bacterial fragments from the intestinal lumen to the bloodstream in male rodents and in humans (Bailey et al., 2006; Karl et al., 2017; Söderholm et al., 2002). These fragments, referred to as microbial-associated molecular patterns (MAMPs), are recognized by pattern recognition receptors (PRRs) on immune cells, which once activated, promote pro-inflammatory cytokine synthesis and release (Takeuchi and Akira, 2010). The endotoxin LPS is recognized mainly by Toll-like receptor 4 (TLR4), but also by TLR2, whereas peptidoglycan (PGN; cell wall component of Gram-positive and to a lesser extent Gram-negative bacteria) is recognized principally by Nod-like receptor 1 (NOD1), as well as by NOD2, TLR2, and peptidoglycan recognition proteins (PGRPs), particularly PGLYRP2 (Takeuchi and Akira, 2010) (Fig. 1). The pro-inflammatory cytokines produced in response to LPS-TLR4 or PGN-NOD1 binding are identical to the cytokines elevated in individuals with major depression (IL-6, TNF-α, and to a lesser extent IL-1β) or, in some instances, found to promote depressive-like states when administered exogenously (IFN-α) (Richez et al., 2009; Takeuchi and Akira, 2010), supporting a role for these inflammatory signaling pathways in depression.

Increases of LPS in the bloodstream and of TLR4 in the brain have been reported in male rats after exposure to acute and chronic stressors (Gárate et al, 2011, 2014) and TLR-4 was up-regulated in post-mortem prefrontal cortex of individuals with major depression (Pandey et al., 2019). A role for LPS derived from the gut microbiota and its downstream signaling upon stressor exposure has been confirmed by the observation that a LPS-inhibiting antibiotic prevented plasma IL-1β and IL-18 (Maslanik et al., 2012) and prefrontal TLR4 (Gárate et al, 2011, 2014) elevations ordinarily induced by a stressor in male rats. In support of the view that LPS-TLR4 signaling is involved in abnormal behavioral patterns

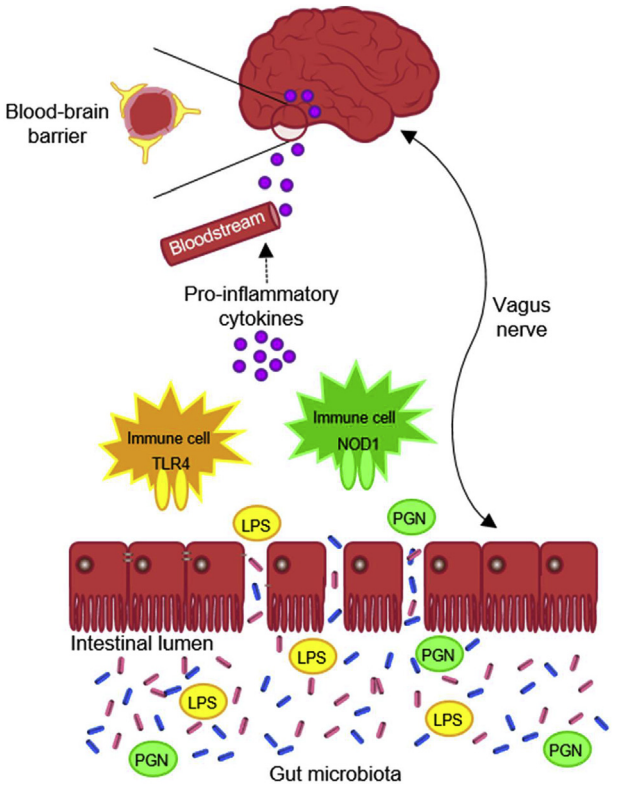

Fig. 1. Schematic representation of the gut microbiota-immune-brain axis under stressful conditions, where an increase in pro-inflammatory bacterial fragments modulates immune signaling routes mediating the crosstalk between the gut environment and the brain. It is suggested that stress-induced pro-inflammatory shifts within the intestinal environment, combined with damages to the intestinal barrier, promote the translocation of lipopolysaccharide (LPS) and of peptidoglycan (PGN) fragments from the intestinal lumen to the bloodstream, where they activate their respective sensors Toll-like receptor 4 (TLR4) and NOD-like receptor 1 (NOD1) on immune cells, leading to pro-inflammatory cytokine synthesis and release. Pro-inflammatory bacterial fragments could also be recognized by receptors located within the enteric nervous system, the dorsal root ganglia, and the vagus nerve, leading to the activation of gut-brain neural inflammatory signals. An impaired blood-brain barrier under stress could promote the transition of inflammatory molecules to the brain, contributing to brain inflammatory activation.

upon stressor exposure, TLR4 blockade in male mice prevented depressive-like behaviors elicited by chronic social defeat (K. Zhang et al., 2020). Likewise, microbiota-derived PGN has been reported to translocate to the bloodstream under basal conditions (Clarke et al., 2010) as well as in socially stressed male mice (Allen et al., 2012), and to cross the blood-brain barrier to reach the developing brain in male mice (Arentsen et al., 2017). Importantly, the deletion of NOD1 on intestinal cells specifically enhanced anxiety-like behaviors following stressor exposure in a pooled sample of male and female mice (Pusceddu et al., 2019), suggesting that PGN-NOD1 signaling could also be a contributor to the communicating routes between gut bacteria and the brain under stress, with impact on stressor-related behaviors.

It has been reported that chronic social stressors in adult male mice (Menard et al., 2017) as well as the absence of gut microbes in germ-free male mice (Braniste et al., 2014) decreased tight junction proteins in specific regions of the brain, thus increasing blood-brain barrier permeability. It is thus possible that under chronic stress, pro-inflammatory changes in the gut microbiota, combined with compromised gut and blood-brain barriers, ultimately promote brain inflammatory activation, by allowing the transition of inflammatory molecules from the gut environment to circulation and to the brain (Doney et al., 2021). Further supporting a role for gut microbes in brain inflammatory activity and behaviors, germ-free rodents had impairments in microglia activity and barrier integrity as well as reduced anxiety- and depressive-like behaviors (Braniste et al., 2014; Diaz Heijtz et al., 2011; Erny et al., 2015; Neufeld et al., 2011; Thion et al., 2018).

Beyond the passage of inflammatory molecules in the bloodstream, the modulation of neural innervation of the vagus nerve or the spinal cord may also contribute to the inflammatory crosstalk between the gastrointestinal tract and the brain (see Cryan et al., 2019 for a detailed review). Gut microbiota-derived neuroactive molecules (e.g., hormones, neurotransmitters) as well as bacterial fragments such as LPS may be detected by receptors located within the enteric nervous system, the dorsal root ganglia, and the vagus nerve (Barajon et al., 2009; Egerod et al., 2018; Hyland and Cryan, 2016). In support of a role for gut-brain neural inflammatory signaling in host brain function and behavior, vagotomy reduced microglia activation in the rat hippocampus (Ronchi et al., 2012) and limited the depressive-like phenotype, plasma cytokine elevations, and gut microbiota alterations promoted by LPS in male mice (J. Zhang et al., 2020).

4. Microbiota-targeted interventions for mental health improvements

The effects of dietary patterns on the gut microbiota are now well recognized (David et al., 2014; Sandhu et al., 2017). Although the exact mechanisms by which diet modulates brain function and influences mental health are not entirely elucidated, they point to the involvement of pathways related to inflammation, oxidative stress, mitochondrial dysfunction, tryptophan-kynurenine metabolism, and neurogenesis, to name a few (Marx et al., 2021). A study in male mice has also shown that a diet enriched in prebiotics decreased microglial activation and reduced anxiety-like behaviors (Boehme et al., 2019), suggesting that targeting the gut microbiota using dietary interventions may possibly influence brain inflammatory activity, with potential impact on behavior.

The emerging field of Nutritional Psychiatry has seen a rapidly growing number of observational and experimental studies in the past decade, supporting a role for healthy dietary patterns and dietary interventions in improving mental health (Berding et al., 2021; Marx et al., 2021). Although targeting gut microbes using dietary supplementation has shown mitigated efficacy in improving depressive symptoms (Firth et al., 2019; Goh et al., 2019; Schefft et al., 2017), the use of whole-diet approaches appears promising in reducing symptoms of mental illnesses (Berding et al., 2021). Adherence to dietary patterns based on the Mediterranean diet, characterized by high intakes of fruits, vegetables, whole grains, legumes, fish, nuts, and extra virgin olive oil, has consistently been associated with low risk for depression, anxiety, and psychological distress (Akbaraly et al., 2009; Li et al., 2017; Sadeghi et al., 2019). Notably, the efficacy of Mediterranean-based diet interventions in improving symptoms in patients with depression has been confirmed in a few studies, highlighting the therapeutic prospects of the diet for this illness (Jacka et al., 2017). The mechanisms behind the mood-improving effects of the Mediterranean diet have yet to be entirely defined, although it has been shown to increase levels of the beneficial bacteria *Faecalibacterium prausnitzii* and Bacteroidetes as well as those of the short-chain fatty acids propionate and butyrate (Gutiérrez-Díaz et al., 2016; Meslier et al., 2020).

5. Conclusion and future directions

Major depression is the leading cause of disabilities worldwide and only 30 % of individuals with the illness completely remit after their first treatment (Trivedi et al., 2006), suggesting that first-line antidepressants may not be targeting all the biological systems at play in this heterogeneous illness and that alternative and/or complementary therapeutic approaches could alleviate symptoms. Although there is no unanimity on what a “mentally healthy” or a “mentally ill” gut microbiota is (Dinan and Cryan, 2017), appreciable evidence points to the presence of

pro-inflammatory shifts in gut microbiota communities in individuals with depression (Chen et al., 2018; Jiang et al., 2015; Kelly et al., 2016; Valles-Colomer et al., 2019; Zheng et al., 2016). As suggested here and by others (Doney et al., 2021), the possibility exists that pro-inflammatory changes in the gut microbiota, as seen under chronic stress, could play a role in promoting brain inflammatory activation in depression, by transitioning from the gut environment to circulation and to the brain through impaired gut and blood-brain barriers. Although data in this regard are still limited, consistent findings are supporting whole-diet interventions focusing on the intake of plant-based foods with a high content of grains/fibers, fermented foods, polyphenols or poly-unsaturated fatty acids in the context of depression (Dinan et al., 2019). The development of such approaches, focused on targeting beneficial intestinal microbes, may have the potential to help dampening the inflammatory effects of stressors on the gut microbiota-immune-brain axis in vulnerable populations and improve mental health when used as alternative and/or complementary approaches to prevent and/or alleviate symptoms. Finally, as it has been previously emphasized (Audet, 2019; Eid et al., 2019), there is a pressing need for animal- and human-based research to be conducted in males and females to better characterize sex differences in relation to inflammatory-related depression and thus better inform the development of evidence-based interventions for this illness.

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Declarations of competing interest

None.

References

Akbaraly, T.N., Brunner, E.J., Ferrie, J.E., Marmot, M.G., Kivimaki, M., Singh-Manoux, A., 2009. Dietary pattern and depressive symptoms in middle age. Br.. J. Psychiatry J. Ment. Sci. 195, 408–413. https://doi.org/10.1192/bjp.bp.108.058925.

Allen, R.G., Lafuse, W.P., Powell, N.D., Webster Marketon, J.I., Stiner-Jones, L.M., Sheridan, J.F., Bailey, M.T., 2012. Stressor-induced increase in microbicidal activity of splenic macrophages is dependent upon peroxynitrite production. Infect. Immun. 80, 3429–3437. https://doi.org/10.1128/IAI.00714-12.

Arentsen, T., Qian, Y., Gkotzis, S., Femenia, T., Wang, T., Udekwu, K., Forssberg, H., Diaz Heijtz, R., 2017. The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. Mol. Psychiatr. 22, 257–266. https://doi.org/10.1038/mp.2016.182.

Audet, M.-C., 2019. Stress-induced disturbances along the gut microbiota-immune-brain axis and implications for mental health: does sex matter? Front. Neuroendocrinol. 54 (100772). https://doi.org/10.1016/j.yfrne.2019.100772.

Audet, M.-C., Jacobson-Pick, S., Wann, B.P., Anisman, H., 2011. Social defeat promotes specific cytokine variations within the prefrontal cortex upon subsequent aggressive or endotoxin challenges. Brain Behav. Immun. 25, 1197–1205. https://doi.org/10.1016/j.bbi.2011.03.010.

Audet, M.-C., Mangano, E.N., Anisman, H., 2010. Behavior and pro-inflammatory cytokine variations among submissive and dominant mice engaged in aggressive encounters: moderation by corticosterone reactivity. Front. Behav. Neurosci. 4. https://doi.org/10.3389/fnbeh.2010.00156.

Bailey, M.T., Dowd, S.E., Galley, J.D., Hufnagle, A.R., Allen, R.G., Lyte, M., 2011. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. Brain Behav. Immun. 25, 397–407. https://doi.org/10.1016/j.bbi.2010.10.023.

Bailey, M.T., Engler, H., Sheridan, J.F., 2006. Stress induces the translocation of cutaneous and gastrointestinal microflora to secondary lymphoid organs of C57BL/6 mice. J. Neuroimmunol. 171, 29–37. https://doi.org/10.1016/j.jneuroim.2005.09.008.

Barajon, I., Serrao, G., Arnaboldi, F., Opizzi, E., Ripamonti, G., Balsari, A., Rumio, C., 2009. Toll-like receptors 3, 4, and 7 are expressed in the enteric nervous system and dorsal root ganglia. J. Histochem. Cytochem. Off. J. Histochem. Soc. 57, 1013–1023. https://doi.org/10.1369/jhc.2009.953539.

Berding, K., Vlckova, K., Marx, W., Schellekens, H., Stanton, C., Clarke, G., Jacka, F., Dinan, T.G., Cryan, J.F., 2021. Diet and the microbiota–gut–brain Axis: sowing the seeds of good mental health. Adv. Nutr. https://doi.org/10.1093/advances/nmaa181.

Bharwani, A., Mian, M.F., Foster, J.A., Surette, M.G., Bienenstock, J., Forsythe, P., 2016. Structural & functional consequences of chronic psychosocial stress on the microbiome & host. Psychoneuroendocrinology 63, 217–227. https://doi.org/10.1016/j.psyneuen.2015.10.001.

Boehme, M., van de Wouw, M., Bastiaanssen, T.F.S., Olavarría-Ramírez, L., Lyons, K., Fouhy, F., Golubeva, A.V., Moloney, G.M., Minuto, C., Sandhu, K.V., Scott, K.A., Clarke, G., Stanton, C., Dinan, T.G., Schellekens, H., Cryan, J.F., 2019. Mid-life microbiota crises: middle age is associated with pervasive neuroimmune alterations that are reversed by targeting the gut microbiome. Mol. Psychiatr. https://doi.org/10.1038/s41380-019-0425-1.

Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Tóth, M., Korecka, A., Bakocevic, N., Ng, L.G., Guan, N.L., Kundu, P., Gulyás, B., Halldin, C., Hultenby, K., Nilsson, H., Hebert, H., Volpe, B.T., Diamond, B., Pettersson, S., 2014. The gut microbiota influences blood-brain barrier permeability in mice. Sci. Transl. Med. 6. https://doi.org/10.1126/scitranslmed.3009759, 263ra158.

Calarge, C.A., Devaraj, S., Shulman, R.J., 2019. Gut permeability and depressive symptom severity in unmedicated adolescents. J. Affect. Disord. 246, 586–594. https://doi.org/10.1016/j.jad.2018.12.077.

Capuron, L., Miller, A.H., 2004. Cytokines and psychopathology: lessons from interferon-alpha. Biol. Psychiatr. 56, 819–824. https://doi.org/10.1016/j.biopsych.2004.02.009.

Chen, Z., Li, J., Gui, S., Zhou, C., Chen, J., Yang, C., Hu, Z., Wang, H., Zhong, X., Zeng, L., Chen, K., Li, P., Xie, P., 2018. Comparative metaproteomics analysis shows altered fecal microbiota signatures in patients with major depressive disorder. Neuroreport 29, 417–425. https://doi.org/10.1097/WNR.0000000000000985.

Clarke, T.B., Davis, K.M., Lysenko, E.S., Zhou, A.Y., Yu, Y., Weiser, J.N., 2010. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat. Med. 16, 228–231. https://doi.org/10.1038/nm.2087.

Cryan, J.F., O'Riordan, K.J., Cowan, C.S.M., Sandhu, K.V., Bastiaanssen, T.F.S., Boehme, M., Codagnone, M.G., Cussotto, S., Fulling, C., Golubeva, A.V., Guzzetta, K.E., Jaggar, M., Long-Smith, C.M., Lyte, J.M., Martin, J.A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., O'Connor, R., Cruz-Pereira, J.S., Peterson, V.L., Rea, K., Ritz, N.L., Sherwin, E., Spichak, S., Teichman, E.M., van de Wouw, M., Ventura-Silva, A.P., Wallace-Fitzsimons, S.E., Hyland, N., Clarke, G., Dinan, T.G., 2019. The microbiota-gut-brain Axis. Physiol. Rev. 99, 1877–2013. https://doi.org/10.1152/physrev.00018.2018.

Dai, H., Xu, S., Han, J., Li, Z., Cao, J., Hu, T., Li, H., Wei, J., Dou, X., Zhou, F., Zheng, J., 2021. Prevalence and factors associated with anxiety and depressive symptoms among patients hospitalized with hematological malignancies after chimeric antigen receptor T-cell (CAR-T) therapy: a cross-sectional study. J. Affect. Disord. 286, 33–39. https://doi.org/10.1016/j.jad.2021.02.041.

David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A., Biddinger, S.B., Dutton, R.J., Turnbaugh, P.J., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563. https://doi.org/10.1038/nature12820.

Dean, B., Tawadros, N., Scarr, E., Gibbons, A.S., 2010. Regionally-specific changes in levels of tumour necrosis factor in the dorsolateral prefrontal cortex obtained postmortem from subjects with major depressive disorder. J. Affect. Disord. 120, 245–248. https://doi.org/10.1016/j.jad.2009.04.027.

Diaz Heijtz, R., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., Hibberd, M.L., Forssberg, H., Pettersson, S., 2011. Normal gut microbiota modulates brain development and behavior. Proc. Natl. Acad. Sci. U. S. A 108, 3047–3052. https://doi.org/10.1073/pnas.1010529108.

Dinan, T.G., Cryan, J.F., 2017. Brain-gut-microbiota Axis and mental health. Psychosom. Med. Times 79, 920–926. https://doi.org/10.1097/PSY.0000000000000519.

Dinan, T.G., Stanton, C., Long-Smith, C., Kennedy, P., Cryan, J.F., Cowan, C.S.M., Cenit, M.C., van der Kamp, J.-W., Sanz, Y., 2019. Feeding melancholic microbes: MyNewGut recommendations on diet and mood. Clin. Nutr. Edinb. Scotl 38, 1995–2001. https://doi.org/10.1016/j.clnu.2018.11.010.

Doney, E., Cadoret, A., Dion-Albert, L., Lebel, M., Menard, C., 2021. Inflammation-driven brain and gut barrier dysfunction in stress and mood disorders. Eur. J. Neuroscience. https://doi.org/10.1111/ejn.15239.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatr. 67, 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033.

Egerod, K.L., Petersen, N., Timshel, P.N., Rekling, J.C., Wang, Y., Liu, Q., Schwartz, T.W., Gautron, L., 2018. Profiling of G protein-coupled receptors in vagal afferents reveals novel gut-to-brain sensing mechanisms. Mol. Metab 12, 62–75. https://doi.org/10.1016/j.molmet.2018.03.016.

Eid, R.S., Gobinath, A.R., Galea, L.A.M., 2019. Sex differences in depression: insights from clinical and preclinical studies. Prog. Neurobiol. Sex and gender differences in the brain 176, 86–102. https://doi.org/10.1016/j.pneurobio.2019.01.006.

Enache, D., Pariante, C.M., Mondelli, V., 2019. Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain. Behav. Immunity 81, 24–40. https://doi.org/10.1016/j.bbi.2019.06.015.

Erny, D., Hrabě de Angelis, A.L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W.S., McCoy, K.D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I., Prinz, M., 2015. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18, 965–977. https://doi.org/10.1038/nn.4030.

Firth, J., Marx, W., Dash, S., Carney, R., Teasdale, S.B., Solmi, M., Stubbs, B., Schuch, F.B., Carvalho, A.F., Jacka, F., Sarris, J., 2019. The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials. Psychosom. Med. Times 81, 265–280. https://doi.org/10.1097/PSY.0000000000000673.

Forsythe, P., Kunze, W., Bienenstock, J., 2016. Moody microbes or fecal phrenology: what do we know about the microbiota-gut-brain axis? BMC Med. 14 (58). https://doi.org/10.1186/s12916-016-0604-8.

Foster, J.A., Rinaman, L., Cryan, J.F., 2017. Stress & the gut-brain axis: regulation by the microbiome. Neurobiol. Stress 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001.

Gárate, I., García-Bueno, B., Madrigal, J.L.M., Bravo, L., Berrocoso, E., Caso, J.R., Micó, J.A., Leza, J.C., 2011. Origin and consequences of brain Toll-like receptor 4 pathway stimulation in an experimental model of depression. J. Neuroinflammation 8 (151). https://doi.org/10.1186/1742-2094-8-151.

Gárate, I., García-Bueno, B., Madrigal, J.L.M., Caso, J.R., Alou, L., Gómez-Lus, M.L., Leza, J.C., 2014. Toll-like 4 receptor inhibitor TAK-242 decreases neuroinflammation in rat brain frontal cortex after stress. J. Neuroinflammation 11 (8). https://doi.org/10.1186/1742-2094-11-8.

Goh, K.K., Liu, Y.-W., Kuo, P.-H., Chung, Y.-C.E., Lu, M.-L., Chen, C.-H., 2019. Effect of probiotics on depressive symptoms: a meta-analysis of human studies. Psychiatr. Res. 282 (112568). https://doi.org/10.1016/j.psychres.2019.112568.

Golden, S.A., Covington, H.E., Berton, O., Russo, S.J., 2011. A standardized protocol for repeated social defeat stress in mice. Nat. Protoc 6, 1183–1191. https://doi.org/10.1038/nprot.2011.361.

Gutiérrez-Díaz, I., Fernández-Navarro, T., Sánchez, B., Margolles, A., González, S., 2016. Mediterranean diet and faecal microbiota: a transversal study. Food Funct 7, 2347–2356. https://doi.org/10.1039/C6FO00105J.

Hodes, G.E., Kana, V., Menard, C., Merad, M., Russo, S.J., 2015. Neuroimmune mechanisms of depression. Nat. Neurosci. 18, 1386–1393. https://doi.org/10.1038/nn.4113.

Hodes, G.E., Pfau, M.L., Leboeuf, M., Golden, S.A., Christoffel, D.J., Bregman, D., Rebusi, N., Heshmati, M., Aleyasin, H., Warren, B.L., Labonté, B., Horn, S., Lapidus, K.A., Stelzhammer, V., Wong, E.H.F., Bahn, S., Krishnan, V., Bolaños-Guzman, C.A., Murrough, J.W., Merad, M., Russo, S.J., 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc. Natl. Acad. Sci. U. S. A 111, 16136–16141. https://doi.org/10.1073/pnas.1415191111.

Holmes, S.E., Hinz, R., Conen, S., Gregory, C.J., Matthews, J.C., Anton-Rodriguez, J.M., Gerhard, A., Talbot, P.S., 2018. Elevated Translocator Protein in Anterior Cingulate in Major Depression and a Role for Inflammation in Suicidal Thinking: A Positron Emission Tomography Study. Biol. Psychiatry 83, 61–69. https://doi.org/10.1016/j.biopsych.2017.08.005.

Hyland, N.P., Cryan, J.F., 2016. Microbe-host interactions: influence of the gut microbiota on the enteric nervous system. Dev. Biol. 417, 182–187. https://doi.org/10.1016/j.ydbio.2016.06.027. Enteric Nervous System.

Jacka, F.N., O'Neil, A., Opie, R., Itsiopoulos, C., Cotton, S., Mohebbi, M., Castle, D., Dash, S., Mihalopoulos, C., Chatterton, M.L., Brazionis, L., Dean, O.M., Hodge, A.M., Berk, M., 2017. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). BMC Med. 15 (23). https://doi.org/10.1186/s12916-017-0791-y.

Jašarević, E., Morrison, K.E., Bale, T.L., 2016. Sex differences in the gut microbiome–brain axis across the lifespan. Philos. Trans. R. Soc. B Biol. Sci. 371 (20150122). https://doi.org/10.1098/rstb.2015.0122.

Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., Wang, W., Tang, W., Tan, Z., Shi, J., Li, L., Ruan, B., 2015. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav. Immun. 48, 186–194. https://doi.org/10.1016/j.bbi.2015.03.016.

Karl, J.P., Margolis, L.M., Madslien, E.H., Murphy, N.E., Castellani, J.W., Gundersen, Y., Hoke, A.V., Levangie, M.W., Kumar, R., Chakraborty, N., Gautam, A., Hammamieh, R., Martini, S., Montain, S.J., Pasiakos, S.M., 2017. Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress. Am. J. Physiol. Gastrointest. Liver Physiol 312, G559–G571. https://doi.org/10.1152/ajpgi.00066.2017.

Kelly, J.R., Borre, Y., O' Brien, C., Patterson, E., El Aidy, S., Deane, J., Kennedy, P.J., Beers, S., Scott, K., Moloney, G., Hoban, A.E., Scott, L., Fitzgerald, P., Ross, P., Stanton, C., Clarke, G., Cryan, J.F., Dinan, T.G., 2016. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J. Psychiatr. Res. 82, 109–118. https://doi.org/10.1016/j.jpsychires.2016.07.019.

Kelly, J.R., Kennedy, P.J., Cryan, J.F., Dinan, T.G., Clarke, G., Hyland, N.P., 2015. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front. Cell. Neurosci. 9 (392). https://doi.org/10.3389/fncel.2015.00392.

Kéri, S., Szabó, C., Kelemen, O., 2014. Expression of Toll-Like Receptors in peripheral blood mononuclear cells and response to cognitive-behavioral therapy in major depressive disorder. Brain Behav. Immun. 40, 235–243. https://doi.org/10.1016/j.bbi.2014.03.020.

Koh, G.Y., Kane, A., Lee, K., Xu, Q., Wu, X., Roper, J., Mason, J.B., Crott, J.W., 2018. Parabacteroides distasonis attenuates toll-like receptor 4 signaling and Akt activation and blocks colon tumor formation in high-fat diet-fed azoxymethane-treated mice. Int. J. Canc. 143, 1797–1805. https://doi.org/10.1002/ijc.31559.

Köhler, C.A., Freitas, T.H., Maes, M., de Andrade, N.Q., Liu, C.S., Fernandes, B.S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C.L., Miller, B.J., Lanctôt, K.L., Carvalho, A.F., 2017. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr. Scand 135, 373–387. https://doi.org/10.1111/acps.12698.

Krishnan, V., Berton, O., Nestler, E., 2008. The use of animal models in psychiatric research and treatment. Am. J. Psychiatry 165 (1109). https://doi.org/10.1176/appi.ajp.2008.08071076.

Li, Y., Lv, M.-R., Wei, Y.-J., Sun, L., Zhang, J.-X., Zhang, H.-G., Li, B., 2017. Dietary patterns and depression risk: a meta-analysis. Psychiatr. Res. 253, 373–382. https://doi.org/10.1016/j.psychres.2017.04.020.

Liu, Y., Ho, R.C.-M., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J. Affect. Disord. 139, 230–239. https://doi.org/10.1016/j.jad.2011.08.003.

Maes, M., Kubera, M., Leunis, J.-C., 2008. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuroendocrinol. Lett. 29, 117–124.

Marin, M.-F., Lord, C., Andrews, J., Juster, R.-P., Sindi, S., Arsenault-Lapierre, G., Fiocco, A.J., Lupien, S.J., 2011. Chronic stress, cognitive functioning and mental health. Neurobiol. Learn. Mem. 96, 583–595. https://doi.org/10.1016/j.nlm.2011.02.016.

Marx, W., Lane, M., Hockey, M., Aslam, H., Berk, M., Walder, K., Borsini, A., Firth, J., Pariante, C.M., Berding, K., Cryan, J.F., Clarke, G., Craig, J.M., Su, K.-P., Mischoulon, D., Gomez-Pinilla, F., Foster, J.A., Cani, P.D., Thuret, S., Staudacher, H.M., Sánchez-Villegas, A., Arshad, H., Akbaraly, T., O'Neil, A., Segasby, T., Jacka, F.N., 2021. Diet and depression: exploring the biological mechanisms of action. Mol. Psychiatr. 26, 134–150. https://doi.org/10.1038/s41380-020-00925-x.

Maslanik, T., Tannura, K., Mahaffey, L., Loughridge, A.B., Beninson, L., Benninson, L., Ursell, L., Greenwood, B.N., Knight, R., Fleshner, M., 2012. Commensal bacteria and MAMPs are necessary for stress-induced increases in IL-1β and IL-18 but not IL-6, IL-10 or MCP-1. PloS One 7, e50636. https://doi.org/10.1371/journal.pone.0050636.

McGaughey, K.D., Yilmaz-Swenson, T., Elsayed, N.M., Cruz, D.A., Rodriguiz, R.M., Kritzer, M.D., Peterchev, A.V., Roach, J., Wetsel, W.C., Williamson, D.E., 2019. Relative abundance of Akkermansia spp. and other bacterial phylotypes correlates with anxiety- and depressive-like behavior following social defeat in mice. Sci. Rep. 9 (3281). https://doi.org/10.1038/s41598-019-40140-5.

Menard, C., Pfau, M.L., Hodes, G.E., Kana, V., Wang, V.X., Bouchard, S., Takahashi, A., Flanigan, M.E., Aleyasin, H., LeClair, K.B., Janssen, W.G., Labonté, B., Parise, E.M., Lorsch, Z.S., Golden, S.A., Heshmati, M., Tamminga, C., Turecki, G., Campbell, M., Fayad, Z.A., Tang, C.Y., Merad, M., Russo, S.J., 2017. Social stress induces neurovascular pathology promoting depression. Nat. Neurosci. 20, 1752–1760. https://doi.org/10.1038/s41593-017-0010-3.

Meslier, V., Laiola, M., Roager, H.M., Filippis, F.D., Roume, H., Quinquis, B., Giacco, R., Mennella, I., Ferracane, R., Pons, N., Pasolli, E., Rivellese, A., Dragsted, L.O., Vitaglione, P., Ehrlich, S.D., Ercolini, D., 2020. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut 69, 1258–1268. https://doi.org/10.1136/gutjnl-2019-320438.

Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., Miller, A.H., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N. Engl. J. Med. 344, 961–966. https://doi.org/10.1056/NEJM200103293441303.

Neufeld, K.M., Kang, N., Bienenstock, J., Foster, J.A., 2011. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. 23, 255–264. https://doi.org/10.1111/j.1365-2982.2010.01620.x e119.

Ohlsson, L., Gustafsson, A., Lavant, E., Suneson, K., Brundin, L., Westrin, Å., Ljunggren, L., Lindqvist, D., 2019. Leaky gut biomarkers in depression and suicidal behavior. Acta Psychiatr. Scand 139, 185–193. https://doi.org/10.1111/acps.12978.

Osimo, E.F., Pillinger, T., Rodriguez, I.M., Khandaker, G.M., Pariante, C.M., Howes, O.D., 2020. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain. Behav. Immunity 87, 901–909. https://doi.org/10.1016/j.bbi.2020.02.010.

Pandey, G.N., Rizavi, H.S., Bhaumik, R., Ren, X., 2019. Innate immunity in the postmortem brain of depressed and suicide subjects: role of Toll-like receptors. Brain Behav. Immun. 75, 101–111. https://doi.org/10.1016/j.bbi.2018.09.024.

Pusceddu, M.M., Barboza, M., Keogh, C.E., Schneider, M., Stokes, P., Sladek, J.A., Kim, H.J.D., Torres-Fuentes, C., Goldfild, L.R., Gillis, S.E., Brust-Mascher, I., Rabasa, G., Wong, K.A., Lebrilla, C., Byndloss, M.X., Maisonneuve, C., Bäumler, A.J., Philpott, D.J., Ferrero, R.L., Barrett, K.E., Reardon, C., Gareau, M.G., 2019. Nod-like receptors are critical for gut-brain axis signalling in mice. J. Physiol. 597, 5777–5797. https://doi.org/10.1113/JP278640.

Richards, E.M., Zanotti-Fregonara, P., Fujita, M., Newman, L., Farmer, C., Ballard, E.D., Machado-Vieira, R., Yuan, P., Niciu, M.J., Lyoo, C.H., Henter, I.D., Salvadore, G., Drevets, W.C., Kolb, H., Innis, R.B., Zarate, C.A., 2018. PET radioligand binding to translocator protein (TSPO) is increased in unmedicated depressed subjects. EJNMMI Res. 8 (57). https://doi.org/10.1186/s13550-018-0401-9.

Richez, C., Yasuda, K., Watkins, A.A., Akira, S., Lafyatis, R., Van Seventer, J., Rifkin, I.R., 2009. Toll-like receptor 4 ligands induce IFN-α production by mouse conventional dendritic cells and human monocytes after IFN-β priming. J. Immunol. Baltim. Md 1950 (182), 820–828.

Ronchi, G., Ryu, V., Fornaro, M., Czaja, K., 2012. Hippocampal plasticity after a vagus nerve injury in the rat. Neural Regen. Res. 7, 1055–1063. https://doi.org/10.3969/j.issn.1673-5374.2012.14.003.

Sadeghi, O., Keshteli, A.H., Afshar, H., Esmaillzadeh, A., Adibi, P., 2019. Adherence to Mediterranean dietary pattern is inversely associated with depression, anxiety and psychological distress. Nutr. Neurosci. 1–12. https://doi.org/10.1080/1028415X.2019.1620425, 0.

Sandhu, K.V., Sherwin, E., Schellekens, H., Stanton, C., Dinan, T.G., Cryan, J.F., 2017. Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry.

Transl. Res. J. Lab. Clin. Med 179, 223–244. https://doi.org/10.1016/j.trsl.2016.10.002.
Sasayama, D., Hattori, K., Wakabayashi, C., Teraishi, T., Hori, H., Ota, M., Yoshida, S., Arima, K., Higuchi, T., Amano, N., Kunugi, H., 2013. Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. J. Psychiatr. Res. 47, 401–406. https://doi.org/10.1016/j.jpsychires.2012.12.001.
Schefft, C., Kilarski, L.L., Bschor, T., Köhler, S., 2017. Efficacy of adding nutritional supplements in unipolar depression: a systematic review and meta-analysis. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol 27, 1090–1109. https://doi.org/10.1016/j.euroneuro.2017.07.004.
Setiawan, E., Wilson, A.A., Mizrahi, R., Rusjan, P.M., Miler, L., Rajkowska, G., Suridjan, I., Kennedy, J.L., Rekkas, P.V., Houle, S., Meyer, J.H., 2015. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiatry 72, 268–275. https://doi.org/10.1001/jamapsychiatry.2014.2427.
Shelton, R.C., Claiborne, J., Sidoryk-Wegrzynowicz, M., Reddy, R., Aschner, M., Lewis, D.A., Mirnics, K., 2011. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. Mol. Psychiatr. 16, 751–762. https://doi.org/10.1038/mp.2010.52.
Söderholm, J.D., Yates, D.A., Gareau, M.G., Yang, P.-C., MacQueen, G., Perdue, M.H., 2002. Neonatal maternal separation predisposes adult rats to colonic barrier dysfunction in response to mild stress. Am. J. Physiol. Gastrointest. Liver Physiol 283, G1257–G1263. https://doi.org/10.1152/ajpgi.00314.2002.
Szyszkowicz, J.K., Wong, A., Anisman, H., Merali, Z., Audet, M.-C., 2017. Implications of the gut microbiota in vulnerability to the social avoidance effects of chronic social defeat in male mice. Brain Behav. Immun. 66, 45–55. https://doi.org/10.1016/j.bbi.2017.06.009.
Takeuchi, O., Akira, S., 2010. Pattern recognition receptors and inflammation. Cell 140, 805–820. https://doi.org/10.1016/j.cell.2010.01.022.
Thion, M.S., Low, D., Silvin, A., Chen, J., Grisel, P., Schulte-Schrepping, J., Blecher, R., Ulas, T., Squarzoni, P., Hoeffel, G., Coulpier, F., Siopi, E., David, F.S., Scholz, C., Shihui, F., Lum, J., Amoyo, A.A., Larbi, A., Poidinger, M., Buttgereit, A., Lledo, P.-M., Greter, M., Chan, J.K.Y., Amit, I., Beyer, M., Schultze, J.L., Schlitzer, A., Pettersson, S., Ginhoux, F., Garel, S., 2018. Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell 172, 500–516. https://doi.org/10.1016/j.cell.2017.11.042 e16.
Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., STAR*D Study Team, 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163, 28–40. https://doi.org/10.1176/appi.ajp.163.1.28.
Valles-Colomer, M., Falony, G., Darzi, Y., Tigchelaar, E.F., Wang, J., Tito, R.Y., Schiweck, C., Kurilshikov, A., Joossens, M., Wijmenga, C., Claes, S., Van Oudenhove, L., Zhernakova, A., Vieira-Silva, S., Raes, J., 2019. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat. Microbiol. https://doi.org/10.1038/s41564-018-0337-x.
Willner, P., 2005. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology 52, 90–110. https://doi.org/10.1159/000087097.
Yang, C., Fujita, Y., Ren, Q., Ma, M., Dong, C., Hashimoto, K., 2017. Bifidobacterium in the gut microbiota confer resilience to chronic social defeat stress in mice. Sci. Rep. 7 (45942). https://doi.org/10.1038/srep45942.
Yang, Y., Zhang, Y., Xu, Y., Luo, T., Ge, Y., Jiang, Y., Shi, Y., Sun, J., Le, G., 2019. Dietary methionine restriction improves the gut microbiota and reduces intestinal permeability and inflammation in high-fat-fed mice. Food Funct 10, 5952–5968. https://doi.org/10.1039/c9fo00766k.
Zhang, J., Ma, L., Chang, L., Pu, Y., Qu, Y., Hashimoto, K., 2020. A key role of the subdiaphragmatic vagus nerve in the depression-like phenotype and abnormal composition of gut microbiota in mice after lipopolysaccharide administration. Transl. Psychiatry 10 (186). https://doi.org/10.1038/s41398-020-00878-3.
Zhang, K., Lin, W., Zhang, J., Zhao, Y., Wang, X., Zhao, M., 2020. Effect of Toll-like receptor 4 on depressive-like behaviors induced by chronic social defeat stress. Brain Behav. https://doi.org/10.1002/brb3.1525 e01525.
Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., Zeng, L., Chen, J., Fan, S., Du, X., Zhang, X., Yang, D., Yang, Y., Meng, H., Li, W., Melgiri, N.D., Licinio, J., Wei, H., Xie, P., 2016. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol. Psychiatr. 21, 786–796. https://doi.org/10.1038/mp.2016.44.
Santos, A., Osborne, N., Audet, M.C., 2021. Chronic social defeat in male mice elicits long-lasting changes to intestinal inflammatory status and barrier permeability. Manuscript submitted for publication.

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