Microbiome and substances of abuse

Microbiome and substances of abuse

Salavrakos, M., Leclercq S., De Timary, P., Dom, G.

Target Journal Progress in Neuropsychopharmacology and Biological Psychiatry

Special Issue The role of gut microbiota in the pathogenesis, diagnosis and treatment of psychiatric diseases

Abstract

There is a growing amount of evidence showing a reciprocal relation between the gut microbiota and the brain. Substance use disorders (SUD), which are a major cause of preventable morbidity and mortality worldwide, have an influence on the gut microbiota and on the brain-gut axis. The communication between the microbiota and the brain exists through different pathways: (1) the immune response elicited by bacterial products, coupled with alterations of the intestinal barrier allowing these products to enter the bloodstream, (2) the direct and indirect effects of bacterial metabolites such as short chain fatty acids (SCFAs) or tryptophan on the brain, (3) and the hypothalamic-pituitary-adrenal (HPA) axis, whose peripheral afferents can be influenced by the microbiota, and can in turn activate microglia. Among substances of abuse, alcohol has been the subject of the greatest number of studies in this field. In some but not all patients suffering from alcohol-use-disorder (AUD), alcohol alters the composition of the gut microbiota and the permeability of the intestinal barrier, directly and through dysbiosis. It has also been well demonstrated that alcohol induces a peripheral inflammation; it is still unclear whether it induces a central inflammation, as there are contradictory results in human studies. In animal studies, it has been shown that neuroinflammation increases during alcohol withdrawal. Literature on opioids and stimulants is less numerous. Chronic morphine intake induces dysbiosis, increased intestinal permeability and a probable neuroinflammation, which could explain symptoms such as tolerance, hyperalgesia and deficit in reward behaviour. Cocaine induces a dysbiosis and conversely the microbiome can modulate the behavioral response to stimulant drugs. Tobacco cessation is associated with an increase in microbiota diversity.

Taken together, the findings of our literature review suggest a bidirectional influence in the pathogenesis of substance use disorders.

Keywords

Substances of abuse, alcohol-use-disorder, opioids, stimulants, gut microbiota, gut-brain axis, intestinal permeability, inflammation

1. Introduction

Substance use disorders (SUD) are increasingly recognized as one of the primary drivers of preventable morbidity and mortality. Globally in 2016, 99.2 million disability-adjusted life-years (DALYs) and 4.2% of all DALYs were attributable to alcohol use, and 31.8 million DALYs and 1.3% of all DALYs were attributable to drug use as a risk factor[1]. The attributable DALYs for tobacco smoking have been estimated to be 170.9 million in 2015[2]. In spite of this formidable impact, treatment interventions currently only have a weak to moderate effect, highlighting the need to deepen our understanding of underlying pathogenetic processes and explore new targets for treatment interventions[3].

Last decade, there has been a growing interest for the gut-brain axis and its role in a bidirectional biochemical and neural signaling between the gastrointestinal tract and the brain. Specifically the gut microbiota is able to modulate this signaling both directly and indirectly via endocrine, neural and immune pathways[4]. In disease and stress states, these pathways may become compromised, resulting in dysbiosis, changes in mood, behavior, cognition and altered inflammatory levels[4]. As such, gut microbiota have been suggested to play an important role within the pathogenic processes underlying a broad variety of psychiatric disorders[5].

Although most of the research on the relation between microbiota and mental health has been done in the fields of depression and stress-related disorders, recently there is an increase in exploring the relevance within substance use disorders [6,7,8.]

This review focuses on the relation between the microbiota and the use of substances of abuse; i.e. alcohol, heroine, stimulants (cocaine, amphetamines), and nicotine. We build and expand upon a recent review on this topic in this journal by Hillmacher and

colleagues, i.e. alcohol, microbiota and effect on psychiatric disorders, by adding the latest research on alcohol and expanding to other substances of abuse[9] (Table 1, 2,3).

2. Microbioma and brain-gut axis: general mechanisms

The human gut microbiota has recently been the subject of extended studies establishing its impact on the immune system[10–12] and metabolism[13,14] of the human host. The microbiota is the ensemble of microorganisms (bacteria, viruses, fungi and yeasts) that reside in the human gastrointestinal tract. The number of bacterial species in an individual's gut is estimated between a few hundreds[15] and a thousand[16] different identified species. The differing from the microbiota, the microbiome is defined as the total genetic material of the bacteria in this ecosystem[17]. Its composition is unique to each individual and is influenced by factors such as genetics, mode of delivery at birth[18], race, diet, living in an urban or rural environment[19] or the use of antibiotics[20,21]. It is difficult to establish what a normal and an abnormal microbiota is. The majority of the bacteria present in adults are members of the *Firmicutes* and *Bacteroidetes* phyla[22], but their relative proportions and the species present vary significantly between individuals[23]. Alterations in the composition of the gut microbiota relate to several psychiatric disorders, such as depression[24], anxiety[25], autism[26,27] and schizophrenia[28].

Several channels do exist through which the gut, in particular the gut microbiome, and the brain communicate and influence each other. The understanding of the complexity of the gut-brain axis is essential to capture how gut microbiota dysregulation could influence the development of behavioral manifestations, addictive behaviors and addictions. Among the different gut-brain axis channels that have been described, the most recognized pathways are: (1) the immune response[29–33], (2) the metabolic pathway[34–39], (3) the neuroendocrine pathway and the vagus nerve[40–45]. We will

describe these three pathways of influence and then describe the behavioral evidence supporting their existence, before moving on to the effects of different substances of abuse on the gut-brain axis.

2.1. The immune response

The first communication pathway between the microbiota and the brain is through the immune response elicited by bacterial products present in the gut lumen and passing into the systemic circulation. The intestinal wall, composed of a mucus layer, a monolayer of epithelial cells connected by junctional complexes, and mucosal immune cells acts as a physical and immune barrier, limiting the amount of gut antigens interacting with the immune system. Bacterial antigens such as lipopolysaccharides (LPS) or peptidoglycans (PGN) interact with receptors on lymphocytes and monocytes but also on other immune cells of the body to elicit an inflammatory response and induce a low grade inflammation[46]. The composition of the gut microbiota influences intestinal barrier function, with bacterias such as *E.Coli* or *Clostridium difficile* increasing intestinal permeability[29], while other species, such as *Bifidobacterium*[30] and *Butyricicoccus pullicaecorum*[31], reinforce the intestinal mucosae in animal models. Endotoxin and inflammatory mediators can then pass an intact blood-brain barrier (BBB) through an active transport[47,48] but the microbiota also affects BBB permeability, facilitating inflammatory mediators entry in the brain[32], and hence activating the microglia.

Microglial cells are the phagocytes of the brain. They are activated through direct contact with cytokines present in the interstitial environment such as colony-stimuling factors (CSF)[49] or through receptor-ligand interactions with cells in their immediate environment[50]: in vivo studies have shown that adenosine triphosphate (ATP) for

instance is released during high neuronal activity to promote surveillance by microglial processes[51,52]; a disruption of the BBB can also expose microglial cells to proteins such as fibrinogen and engage CD11b/CD18 integrin heterodimers and an intracellular activation pathway[8].

Microglia express and secrete immune-related signaling molecules that alter synaptic transmission and plasticity in the absence of inflammation; when inflammation appears, microglia modify synaptic connection and plasticity[53]. Research shows that synaptic strength and behavior can arise from immune-related signaling governed by the microglia. Application of chemokine CX_3CL1 to stimulate microglia in brain slices causes a depression in synaptic transmission, that was not observed for mice deficient in microglial receptor to CX_3CL1[54]. The cytokine TNFα released by microglial cells interacts with neurons and can modify synaptic stength[55] or induce cell death[56]. Microglia can thus eliminate entire cells or structures, especially synapses, which explains why they play a crucial role in brain development[53]. Another preclinical study shows a role of microglial brain neurotrophic factor (BDNF) in maintaining expression of postsynaptic glutamate receptor subtypes, a key player in synaptic plasticity[57]. Microglia also use cytokines and chemokines to recruit local immune cells and monocytes from the periphery to the brain[58].

In vivo studies have shown a direct correlation between microbiota composition and microglia function and maturation[33]. Type I interferon is produced in the CNS in combination with metabolites derived from dietary tryptophan, originated from the gut, to active astrocytes and regulate central inflammation[59]. Elevation of LPS serum levels, which is known to correlate with modifications of microbiota, produced a microglial activation observable on PET-CT in non-human primates[60]. Moreover, these are correlated with behavioral symptoms. In rodents, sensitization of microglia and

monocyte trafficking to the brain are regulators of recurring anxiety following exposure to prolonged stress[61]. In humans, peripheric and central inflammation have been linked to psychological symptoms[62],[63].

2.2. The metabolic pathways

Bacterial metabolites, such as short chain fatty acids (SCFAs), may also allow the communication between the gut and the brain. SCFAs are products of anaerobic fermentation in the large intestine, that activate G protein-coupled receptors, expressed in different locations, on enteroendocrine cells, adipocytes, immune cells and neurons[64]. A specific role for SCFAs, and in particular butyrate, as promoters of the intestinal barrier integrity has recently been demonstrated in preclinical models[35,65,66] : butyrate induces cell proliferation, mucin production and has an anti-inflammatory activity on intestinal immune cells. At a central level, SCFAs have an ability to diffuse across the BBB[67] and influence brain function and behavior: butyrate reduces neuroinflammation through an action on microglial receptors[36]; acetate modulates the appetite by binding to hippocampus[68]; in mice, SCFAs administration reduces symptoms of depression[69]. In keeping with these observations SCFAs depletion was observed in MDD patients[70–72].

The microbiota also plays a role in the synthesis of tryptophan, the precursor of serotonin[37,38,73], and of several neuromediators such as gamma-aminobutyric acid, norepinephrine, dopamine and serotonin[39], as demonstrated in animal models. Most of these microbiota-generated neurotransmitters do not cross the BBB but act locally on the enteric nervous system. Conversely, tryptophan crosses the BBB and is available at the brain level as a source for serotonin synthesis[74]. Under conditions of inflammation, tryptophan can also be diverted from the serotonin production into the kynurenin

pathway[75–77], thus reducing the levels of serotonin and inducing depression-like behaviour[78] through the production of neuroactive metabolites. Studies have linked modifications of the microbiota, through the use of antibiotics or probiotic supplementation, to modifications in the kynurenin/tryptophan ratio, and improvement of anxious and depressive symptoms in both animal and human models[79–81].

2.3. The neuroendocrine pathway and the vagus nerve

Mice and human studies have shown that psychological stresses such as social disruption[82], maternal separation[83] or military service[84] are associated with changes in gut microbiota and gut permeability. Germ-free (GF) mice (mice that have always lived in a sterile environment and are free of any bacteria invasion) show an exaggerated HPA reactivity, with elevated ACTH and corticosterone levels after a mild stress[40]. A recent unpublished study[85] suggests a link between microbiota composition and cortisol blood levels in both humans and animals. Microglial cells, whose maturation and activity can be influenced by bacterial products through peripheral inflammation, can activate the HPA axis[41]. Conversely, direct HPA activation, through afferents of the vagus nerve, induces glucocorticoids production, whose receptors are highly expressed on microglial cells[86], and activate brain microglia[87]. The HPA axis, the stress response and the neuroinflammatory response are largely intertwined.

The vagus nerve is also related to gut microbiota regulation[42]. Parasympathetic sensory afferents and efferents of the vagus nerve exist within the digestive tract[88]. Several works have shown an effect of microbiota on vagal gut afferents. GF mice present with emotional regulation capacities that differ from control mice and, in particular, show fewer signs of anxiety; ingestion by these mice of a strain of *Lactobacillus* induces region-dependent alterations in the expression of central GABA receptor and reduces

anxiety-like and depression-like behavior, and this effect is lost in vagotomised mice[43]. Several bacterial species may increase firing rate in vagal afferents[44-45]. Although not in direct contact with the gut lumen, as they do not cross the epithelial layer[89], vagal afferents may detect bacterial products that diffuse through the epithelial wall through an interaction possibly mediated by entero-endocrine cells[90], that express receptors which recognize bacterial products such as LPS[91] and SCFAs[92]. Furthermore, vagal sensory gut neurons are connected to brain reward neurons, inducing the release of dopamine and sustained self-stimulation[93].

Conversely, the vagus nerve may affect the composition of the gut microbiota through still poorly explored mechanisms: the vagus nerve has anti-inflammatory effects on the digestive tract; acetylcholine, the principal vagal neurotransmitter, inhibits the release of TNFα in LPS stimulated human macrophage[94], reducing local inflammation; vagal nerve stimulation also attenuates disruptions of epithelial tight junctions in endotoxemic mice[95], thus decreasing intestinal permeability. It can be hypothesized that the effects of the vagus nerve on local inflammation and gut permeability influence gut microbial composition.

2.4. Behavioral expressions of the gut-brain axis

Studies on GF mice have allowed to measure the impact of an absence of microbiome on the central nervous system, independently of the different pathways of influence. GF mice have demonstrated the importance of the microbiome in several brain developmental processes, such as myelination[96], synaptic development[97], dendritic morphology[98] and maturation of the hippocampal serotoninergic system[99]. On a behavioral level, GF mice show deficits in social cognitions[100] and increased anxiety-like behaviors[101]. A 24h-exposure to an environment outside a sterile isolator makes

GF mice less anxious[102]. Transplantation of fecal microbiota derived from patients with MDD in GF mice causes depression-like behavior, whereas transplantation from healthy subjects has no effect on their behavior[71]. The microbiota appears to also play a role in autistic behavior. A transplantation of gut microbiota from humans with suffering ASD into GF mice induces hallmark autistic behavior[103].

Insert Tables 1, 2 & 3 about here

3. Alcohol

3.1. Intestinal dysbiosis and increased gut permeability

Given the impact of diet on the gut microbiome, it is not surprising that alcohol affects the composition of our intestinal flora. However, as most studies to date that show the existence of gut dysbiosis in AUD patients are cross-sectional, it is not totally clear whether the dysbiosis is due to the alcohol consumption or whether is precedes the development of AUD and hence plays a role in its development. A seminal study dating from 1984[104] already showed an overgrowth of Gram-negative anaerobic bacteria in the jejunum of patients with AUD, and related it to the functional intestinal symptoms often observed in alcoholic patients. A more recent analysis of colonic biopsy samples revealed a higher rate of *Proteobacteria* and a lower rate of *Bacteroidetes* in alcoholic subjects compared to controls[105]. In a subset of patients, the altered microbiota composition correlated with high levels of serum endotoxin. The alterations of the microbiota in AUD patients appear to be long-lasting, as these alterations of the microbiota are also observed in AUD patients who had been sober for more than one month[105]. Another study[106] showed an increase in *Proteobacteria*, *Sutterella*, *Holdemania* and *Clostridium* families and a large decrease in *Faecalibacterium* in

patients that did not present with major liver alterations. Examining cirrhotic patients, a study[107] points an increase in potentially dangerous bacteria from the families *Prevotellaceae*, *Enterobacteriaceae*, *Veillonellaceae*, and *Streptococcaceae* in subjects with alcoholic cirrhosis, compared to subjects with hepatitis B cirrhosis and to control subjects. Species-level compositions appear to be different in AUD patients with and without cirrhosis[108]. A 2019 systematic review on microbiota composition in AUD[109] states a general increase in endotoxin-producing and decrease in autochtonous bacterial taxa. Several hypotheses have been proposed regarding the mechanism by which alcohol affects the microbiome: probably a combination of an increase of fecal pH[110], a decrease of bile secretions[111] and modifications of gastric acidity and gut motility[112]. A recent clinical study[113] shows that alcohol decreases SCFAs levels, which play a major role in the homeostasis of the gastrointestinal wall. In vitro studies[34] have shown that ethanol, at concentrations found in the body after moderate drinking, along with its metabolite acetaldehyde, disrupt intestinal tight junctions and increase intestinal permeability. In addition to altering the composition of the gut microbiota intestinal flora, alcohol appears to have direct effects on the components of the intestinal barrier. How long this increased intestinal permeability persists is unclear, as it was still present after two weeks of abstinence in one clinical study[114], and completely recovered after three weeks in another[115]. Alcohol also has a negative effect on mucus and antimicrobial peptide production[116]. Overall, AUD patients show an increased intestinal permeability to several polysaccharides such as lactulose and mannitol[117,118]. However, as proposed above, some changes in the composition of the gut microbiota may also precede the development of AUD and exposure to massive ethanol drinking. Exposure of adolescent rats to ethanol binge intoxication does induce changes in the composition

of the gut microbiota, but that are not as important as that observed in AUD populations[119].

In keeping with these observations, a study[120] focusing on dysbiosis and intestinal permeability found that only a subgroup of AUD patients with altered intestinal permeability show a dysbiosis compared to the control group, which was characterized by a general decrease in the abundance of the overall bacterial load, a decrease in the abundance of the *Ruminococcaceae* family, and an increase of *Lachnospiraceae* family. The total amount of bacteria and the amounts *Bifidobacterium* and *Fecalibacterium prausnitzii* species abundance are negatively correlated with intestinal permeability, suggesting that these bacteria reinforce the integrity of the intestinal wall[121]. The observation of a group of AUD patients that do not present with a dysbiosis also means that ethanol consumption is not sufficient to induce changes in the composition of the gut microbiota, suggesting there are other factors involved, possibly even anterior to the beginning of alcohol consumption, and that dysbiosis is not necessarily present in the disorder.

3.2. Pro-inflammatory mediators and neuroinflammation

Excessive alcohol intake induces a peripheric inflammatory response which plays an important role in the development of alcoholic liver disease[122]. It appears now that at least part of this inflammatory response is due to the gut microbiota and could also lead through the gut-brain axis to an inflammatory response in the central nervous system. Gram-negative bacteria such as *Proteobacteria* that are found in abundance in the microbiota of AUD patients account for an important source of LPS that can cross an altered intestinal wall[123]. Studies have found an elevated level of LPS in the blood of AUD patients[115] and in healthy subjects after binge drinking[124]. In rats, alcohol-induced

dysbiosis contributes to endotoxemia by favoring the growth of Gram-negative bacteria, thus increasing the production of endotoxins, and by disrupting the intestinal barrier, thus allowing endotoxins to enter the bloodstream[125]. Through activation of Toll-like (TL) 4 receptors, LPS can activate the HPA axis and an inflammatory reaction in several tissues such as the liver and the brain[126]. In the liver, Kupffer cells, the resident macrophages, are activated by LPS and produce pro-inflammatory chemokines, reactive oxygen species and leukotrienes[127], which can lead to liver injury. There is a strong correlation between endotoxin blood levels in both rats[128] and humans[129] and the severity of liver damage. Other bacterial components such as PGN can also cross the gut barrier and elicit an inflammatory reaction through activation of TL2 receptors[130]. We have described before how peripheric inflammatory mediators can then reach the brain. Animal studies have shown that alcohol intoxication induces an inflammatory response in the brain, with alterations in the expression of several cytokines in different parts of the brain[131,132]. Enhanced expression of TL receptors in brains, particularly those on microglia, were found in rats after adolescent binge drinking[133] and in AUD patients[134]. In human post-mortem brains, increased levels of MCP-1 and increased microglial markers are found in heavy drinkers[135]. It is important to note that part of this neuroinflammation could be related to a direct effect of ethanol on the brain[136–138]. Other potent sources of inflammation including the gut itself, the liver or the adipose tissue have also been suggested[139]. However, even though the importance of inflammation in animal models of alcohol addiction has been largely demonstrated, in humans, except in postmortem studies, direct evidence for the existence of a neuroinflammation in AUD patients is still lacking. Peripheral inflammation has been well described, but the few PET-CT studies that have been performed using TSPO ligand that is expected to measure the microglial activation[140–

[142], showed controversial results with lower or equal levels of neuroinflammation compared to controls. This is clearly a shadow to the neuroinflammatory theory of addiction. It is more cautious for now to talk of 'neuromodulation' of the microglial system in AUD than of 'neuroinflammation'.

Alcohol-induced neuromodulation could have many repercussions. There is a growing amount of evidence linking depressive behaviour[143–145] and anxiogenic-related behaviour[146] to a low-grade inflammatory response and an activation of cell-mediated immunity in both animal and human models. Furthermore, several animal studies show that an induced neuroinflammation could promote alcohol-seeking behaviour[147,148]. Several genes involved in immunity are overexpressed in strains of mice breeded for alcohol-preference (independently of ethanol administration)[149,150], and there is an important overlap in the brain of mice between genes activated by LPS and by ethanol[151]. Further supporting the role of inflammation, genetic deletion of inflammatory genes in mice was associated with a decrease in alcohol preference and consumption[152]. In humans, the improvement of obsessional craving scores during short-term withdrawal correlated with a decrease in the expression of IL-1b and IL-8 in peripheral blood mononuclear cells (PBMCs)[130]. Altogether, these data support that neuroinflammation plays a role in behavioral symptoms related to addiction in AUD.

3.3. Alcohol withdrawal

Alcohol withdrawal appears to be a period of time when neuroinflammation is enhanced. In rats, there is an acute expression of proinflammatory mediators, both at the mRNA and the protein level, after 48h of abstinence[153]. A study[154] shows that in mice drinking alcohol for 5 months and then being abstinent for 15 days, the activation of microglial and astroglial cells in the striatum and prefrontal cortex is maintained, and

associated with anxiety-related behaviour and cognitive impairments. Mice lacking TL4 receptors were protected against these effects. Patients undergoing alcohol withdrawal experience a number of emotional disturbances[155], which have been linked to a neuroinflammatory response in the central nucleus of the amygdala, a structure associated with the regulation of emotions[153,156]. Leclercq et al.[115] found that at the beginning of alcohol withdrawal, plasma proinflammatory cytokines of AUD patients positively correlate with scores of depression, anxiety and alcohol craving. In a later study[120] the same research group found that a subgroup of AUD subjects who develop gut leakiness and dysbiosis have higher scores of depression, anxiety and craving after three weeks of abstinence than AUD subjects with normal intestinal permeability. This suggests a circular relationship between alcohol intake, inflammation and craving in a subgroup but not in all AUD patients. It offers new perspectives on pharmacological targets for dysbiotic patients.

4. Illicit drugs: opiates and stimulants.

4.1. Opiates

In many countries, prescription opioids are used exponentially in the management of pain. However, concerns are rising concerning the substantial risks on diversion, misuse, addiction and overdose deaths, as demonstrated in the US opioid epidemic [157]. In addition, recent clinical evidence suggests that opioid use might be impairing somatic recovery as a result of their interactions with inflammatory processes[158]. However, the relationship between opioid use and immune responses seem to be complex and not consistent[159]. On the one hand, human studies indicate (peripherical) immunosuppressive effects of opioids, albeit not for all types of opioids[158,159]. In contrast, preclinical studies suggest CNS pro-inflammatory cytokine upregulation and

neuroinflammation, after acute and chronic opioid exposure, might be a contributing factor to the development of symptoms associated with chronic opioid use, i.e. tolerance, dependence and reward[158,160,161]. Interestingly, within this context, ibudilast, a glial nonselective phosphodiesterase inhibitor, attenuates subjective morphine withdrawal and motivation for low-dose oxycodone in a progressive ratio task with heroin dependent patients[158,162,163].

As opioid receptors are highly expressed within the digestive tract and opioids influence gut motility, it might be expected that systemic opioid treatment will impact the composition of the gut microbiota. Indeed, alterations in GI microbiome have been documented in human and animal opioid users. Of all opiates, morphine has been studied most with respect to the relation with the gut-brain axis[8]. Preclinical studies show that both acute and long-term treatment with morphine induces disturbances in the composition of gut microbiota, i.e. decreases in *Bacteroidetes* and *Firmicutes* and increases in *Proteobacteria*[164,165]. Interestingly, morphine induced dysbiosis is antagonized by naltrexone, indicating the specificity of this action through the opioid receptors[8].

In animal models, chronic morphine administration induces changes in the intestinal epithelium increasing permeability and bacterial translocation mediated by Toll-like receptor (TLR)[166,167]. These mechanisms may underly a causal pathway linking chronic morphine administration associated gut dysbiosis with neuroinflammation, hyperalgesia, deficits in reward behavior and microglial activation[168,169]. Of interest, pre-treatment with a probiotic Lactobacillus acidophilus in a rat model was associated with increased pain threshold, improved hypersensitivity and expression of MOR[170].

Taken together findings from preclinical studies suggest an association between chronic (and acute) opioid intake, gut dysbiosis and subsequentially development of tolerance,

hyperalgesia and changes in reward behavior, all of which may play a role in developing opioid use disorders. However, up to now, very few clinical studies have been done confirming these findings within human studies, leaving this field open for future explorations.

4.2. Stimulants

Although disorders in the use of stimulants such as cocaine and amphetamines are worldwide increasing and having a major public health impact, research on the relation between stimulant use and gut microbiome is scarce. Preclinical studies show that cocaine administration depletes the *Mucispirillum*, *Ruminococcaceae*, *Lachnospiracea*, *Pseudoflavonifractor* and *Butryccicoccus* bacteria in the rodent gut[171,172]. These are all producers of short-chain fatty Acids (SCFA) and related metabolites and play a critical role in maintaining epithelial and immune homeostasis. In addition, cocaine administration has been associated with inducing inflammatory processes in the gut, i.e. increased expression of pro-inflammatory cytokines, chemokines and activation of transcription factors[172]. Taken together, very preliminary, preclinical studies suggest that (chronic) cocaine intake can induce a process of gut-barrier dysregulations, altered gut microbiota colonization and inflammation, that might contribute to behavioral (brain) changes associated with cocaine use[173,174]. Increasingly also human studies suggest that the gut microbiome can modulate the behavioral response to stimulant drugs and vice versa that (chronic) use of stimulants can change the microbiome[158]. Patients with cocaine use disorder were shown to have, compared with drug free controls, an altered gut microbiome, i.e. increased representation of the *Bacteroidetes* phylum[158,175]. However, given the paucity of studies in humans much caution is warranted in translating the preclinical findings.

5. Tobacco

Smoking changes the microbiome in several regions, i.e. periodontal, gut, and respiratory track[176], and plays a role in the mechanisms underlying changes in the mucosal immune response, fluctuation of intestinal cytokine levels, changes in gut permeability, and epigenetic modifications altering gene expression[177,178]. Consistent with these hypotheses are findings indicating that smoking is associated not only with inflammatory Bowel Disease (IBD)[177,179] but also periodontitis, asthma, chronic obstructive pulmonary disease, and cancer[177,180]. So, the effects of smoking on the microbiome and subsequent somatic disorders is consistently demonstrated. However, the effect of smoking on the gut-brain axis and its behavioral implications largely unexplored. Of interest, while smoking induces changes in the microbiome, i.e. increase of *Firmicutes* and *Actinobacteria* and decrease of *Bacteroidetes* and *Proteobacteria*, smoking cessation induces an increase in microbial diversity in patients[181,182].

6. Therapeutic implications

All this evidence suggests that the gut microbiome itself could be a therapeutic target in several substance use disorders, through the use of antibiotics, probiotics, prebiotics or fecal transplantation. In AUD, preclinical studies have shown that treatment with antibiotics reduces Gram-negative bacteria and prevents ALD[183,184]. Antibiotics such as minocyclin and rapamycin, that also present with anti-inflammatory properties, have shown positive neuroprotective effects and decreased alcohol intake in mice[185–188]. However, it is still unclear if this effect is linked to anti-inflammatory properties or changes in the composition of the gut flora, as these dimensions were not controlled for in these studies[189].

Regarding probiotics, administration of live microorganisms such as *Lactobacillus rhamnosus* and *Bifidobacterium* seem to partially prevent gut leakiness, reduce endotoxin levels and attenuate the HPA response to stress in rodents[128,190,191]. In humans, a 5-day supplementation with *Bifidobacterium bifidum* and *Lactobacillus plantarum* during alcohol detoxification shows a benefit in lowering liver enzymes compared to abstinence alone[192]. A 7-day oral supplementation with *Lactobacillus substilis* and *Streptococcus faecium* was associated with a reduction of LPS levels in patients with alcoholic hepatitis[193]. A 4-week administration of *Lactobacillus casei Shirota* restored neutrophilic phagocytic capacity in patients with alcoholic cirrhosis[194]. In a long term perspective, a 120-day treatment with probiotic VSL#3 reduced oxidative stress and cytokine production, and improved liver functiun in AUD patients[195]. A functional MRI (fMRI) clinical study shows that a 4-week intake of fermented milk containing probiotic leads to changes of activity in brain regions controlling the central processing of emotions and sensations[196]. A 4-week intake of probiotics helps reduce negative thoughts associated with sad mood[197]. A 8-week intake of *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* has a beneficial effect on depressive symptoms in patients with MDD[198].

Prebiotics are defined as non-viable dietary substrates, such as dietary fibers, selectively used by the host microorganisms and conferring a health benefit [199]. Their effect on the gut-brain axis is mediated through the production of specific metabolites such as SCFAs, modification of intestinal pH which inhibits pathogen growth, the reinforcement of the intestinal barrier and the development of anti-inflammatory properties[200]. Prebiotics have been shown to modify the abundance of more than 100 bacterial taxa in both animal and humans[201–203]. Studies on rats show that oats supplementation reduces gut leakiness and prevents alcohol-induced liver damage[204].

In mice fed with alcohol, administration of fructooligosaccharides restored the levels of antimicrobial peptide Reg3γ, reduced bacterial overgrowth and steatohepatitis[116]. Consumption of prebiotics galacto-oligosaccharide or inulin-type fructans by healthy individuals increases the proportion of *Faecalibacterium prausnitzii* and *Bifidobacteria*[203], both low in AUD patients with dysbiosis[120], suggesting that that type of intervention might be fruitful in AUD patients, or at least in the subgroup that present with a dysbiosis.

Fecal microbiota transplant is a procedure involving the transfer or intestinal microbiota from one person to another[58]. It has been used as an experimental model to determine the causal relationship between gut microbiota and host outcomes, and as a sucessfull therapeutic one in treatment of refractory *Clostridium difficile* infection[205]. In AUD, fecal microbiota transplantation was performed with feces from alcohol-resistant donor mice to alcohol-sensitive receiver mice; the result showed an intestinal microbiota very similar to that of the donor mice in the receiver mice, and a reduced liver inflammation and steatosis[206]. In humans, a trial involving 8 patients with severe alcoholic hepatitis who were administered FMT for a 7-day period found normalised levels of *Proteobacteria* and *Actinobacteria* after the transplant, and an improved survival at one year compared to historical controls[207]. A recent randomized clinical trial comparing patients with severe alcoholic hepatitis receiving FMT versus steroids showed promising results, with an improved 90-day survival in patients receiving FMT[208]. More preclinical and clinical data are needed to evaluate the benefits of FMT in acute and chronic treatment situations.

7. Discussion

Taken together, our findings fit in an already consistent body of literature revealing a complex, bidirectional role of the microbiome in the pathogenesis of different, often co-morbid, psychiatric disorders. Within these, reward, motivation and stress-related neurobiological processes are implicated. Processes that are also at the core of the pathogenesis of disorders in the use of substances. The findings from our review, provide some evidence that also within SUD, changes in microbiome might have a bi-directional causal involvement. Exposure to alcohol or illicit drugs, induces imbalances in gut microbiota[9,209]. The resulting dysbiosis correlates with altered stress and reward related processing, based upon different mechanisms, i.e. direct (vagal) or indirect via microbial metabolites (SCFAs, neurotransmitters serotonin, dopamine), or immune pathways (inflammation). Changes in reward and stress processing, in turn, can change behavioral responses to alcohol and drug rewards, initiating or continuing a vulnerability for substance use disorders. Although this line of thinking is far too simplistic and many elements are still unknown, the findings in our literature review provide some indications, most outspoken with regard to alcohol, in support of these bi-directional pathways in the pathogenesis of substance use disorders.

Different limitations need to be taken into account within the current context. First, we did not include all substances of abuse in this review, neither did we include non-chemical addictions (behavioral, e.g. gambling). We limited ourselves to those substances that account for the greatest levels of morbidity and mortality, i.e. alcohol, cigarette smoking, opiates and stimulants. The findings in this review cannot, without future research, be translated uncritically to other substances of abuse. Another major caveat within many human studies is that most patients included used more than one substance, frequently combining different drugs, smoking and alcohol use[181]. This

makes it extremely difficult to draw strict substance specific conclusions. This might be specifically true for cannabis dependence, where interreference with tobacco smoking is highly frequent. Also, studies on cannabis use and the microbiome remain extremely scarce at this moment.

Although the clinical studies included in this review suggest a relation between dysbiosis and SUD, these findings might be confounded by co-morbidity with depression and other stress-related disorders, who themselves have been associated with gut dysbiosis. Indeed, inflammation driven hypo-dopaminergia might be a common factor underlying the (frequent) co-morbidity between SUD, anhedonia and mood/stress disorders[168,210,211]. None of the included studies in this review controlled for comorbidities, warranting caution in the interpretation of these results. There are similarities with the microbiota changes induced by MDD and SUD such as an increase in *Proteobacteria*[70], that was found in MDD but also in abuse of alcohol[105,106] and morphine[164,165]. However, there are also discrepancies such as an increase in *Bacteroidetes* in MDD[196], which are found less abundantly in AUD[105] and morphine abuse[164,165], but more abundantly in cocaine abuse[158,175]. Regarding anxiety, most of the evidence is still preclinical[25]. These studies rarely control for substances of abuse which can be an important confounding factor, that should be addressed in future studies.

In summary, most data are currently available for alcohol but account for a lesser degree also for opioids and stimulants. Mostly through an alteration of gut microbiota and intestinal permeability, alcohol and substances of abuse, affect the gut-brain axis in several ways. There are still several question marks in human studies: the absence of

dysbiosis in some SUD patients, the absence of microglial activation in PET-CT studies, and the exact correlation with symptoms and behaviors of SUD.

8. Conclusion

Evidence of dysbiosis and disruption of the intestinal barrier induced by alcohol and other substances of abuse is plentiful, albeit mostly based upon preclinical studies, but the understanding of repercussions on the brain-gut axis and the symptomatology and behaviour of SUD is still incomplete. Further human-focused studies need to examine more closely the role of the vagus nerve and the role of circulating bacterial products, in order to develop a more comprehensive view of the gut-brain axis in general. The microbiota produces hundreds of metabolites that have not yet been studied but could play a role in brain function and maturation. Regarding substances of abuse, and more specifically alcohol, clinical studies using brain structural and functional imaging could shed some light on the hypothesized neuroinflammatory process and its relationship with addiction. Preclinical studies focusing on metabolites that are specific of bacteria species frequently found in AUD dysbiosis are also needed. Early stressful life events and alterations of the HPA axis have been shown to correlate with anxiety disorders[212]; it would be interesting to study microbiota and HPA alterations in AUD patients with history of childhood trauma. Translational approaches, for example using fecal matter transplant between humans and animals, can offer a more global view on the exact repercussions of an SUD dysbiosis on the individual.

Table 1. Preclinical and clinical data on microbiota alterations in substance use disorders.

Substance	Increased bacterial families	Decreased bacterial families
Alcohol	*Proteobacteria*[105,106] *Sutterella*[106] *Holdemania*[106] *Clostridium*[106] *Prevotellaceae*[107] *Enterobacteriaceae*[107] *Veillonellaceae*[107] *Streptococcaceae*[107] *Lachnospiraceae*[120]	*Bacteroidetes*[105] *Faecalibacterium*[106] *Ruminococcaceae*[120]
Morphine	*Proteobacteria*[164,165]	*Bacteroidetes*[164,165] *Firmicutes*[164,165]
Cocaine	*Bacteroidetes*[158,175]	*Mucispirillum*[171,172] *Ruminococcaceae*[171,172] *Lachnospiracea*[171,172] *Pseudoflavonifractor*[171,172] *Butryccicoccus*[171,172]
Tobacco	*Firmicutes*[181,182] *Actinobacteria*[181,182]	*Bacteroidetes*[181,182] *Proteobacteria*[181,182]

Table 2. Summary of the main studies on microbiome and susbtances of abuse reviewed.

Author	Title	Source	Sample	Main findings
Alcohol				
Mutlu (2012)	Colonic microbiome is altered in alcoholism	Am J Physiol Gastroint est Liver Physiol	48 alcoholics 18 healthy subjects	The microbiome is altered in a subset of alcoholics who present lower abundances of Bacteroidetes and higher ones of Proteobacteria. High levels of serum endotoxin are found in a subset.
Bjørkhaug (2019)	Characterization of gut microbiota composition and functiuns in patients with chronic alcohol overconsumption	Gut Microbes	Twenty-four patients with alcohol overconsumption 18 control patients	*Proteobacteria* are found in higher relative abundance, while *Faecalibacterium* are found in lower relative abundance in the group of alcohol overconsumers. The group also had higher levels of *Sutterella, Holdemania* and *Clostridium*, and lower concentration and percentage of butyric acid.
Chen (2011)	Characterization of fecal microbial communities in patients with liver cirrhosis	Hepatology	36 patients with liver cirrhosis and 24 healthy controls	Higher prevalence of potentially pathogenic bacteria, such as Enterobacteriaceae and Streptococcaceae, with a reduction of beneficial populations such as Lachnospiraceae.
Dubinkina (2017)	Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease	Microbiome	72 patients with alcohol dependance syndrome and 27 with alcoholic liver cirrhosis	Alcoholic dependence was inversely associated with the levels of butyrate-producing species from the *Clostridiales* order, while the cirrhosis—with multiple members of the *Bacteroidales* order. The opportunist pathogens linked to alcoholic dependence included pro-inflammatory *Enterobacteriaceae*, while cirrhosis included

				an increase of oral microbes in the gut.
Swanson (2020)	Disrupted diurnal oscillation of gut-derived short chain fatty acids in shift workers drinking alcohol	Transl Res .	42 subjects divided in three groups : patients with alcohol use disorder, day workers and night workers	Moderate alcohol suppresses SCFAs which was associated with increased colonic permeability
Leclercq (2014)	Intestinal permeability, gut bacterial dysbiosis, and behavioral markers of alcohol-dependance severity	PNAS	44 AUD subjects before and after a period of three-week detoxification	Some, but not all, alcohol-dependent subjects developed gut leakiness, which was associated with higher scores of depression, anxiety, and alcohol craving after 3 wk of abstinence. Moreover, subjects with increased gut permeability also had altered composition and activity of the gut microbiota.
Leclercq (2012)	Role of intestinal permability and inflammation in the biological and behavioral control of alcohol-dependant subjects	Brain Behav Immun .	40 AUD subjects hospitalised for a three-week detoxification , 16 healthy subjects	Intestinal permeability and LPS were largely increased in alcohol-dependent subjects at T1 but recovered completely at T2. A low-grade inflammation was observed at T1 that partially decreased during withdrawal. At T1, pro-inflammatory cytokines were positively correlated with craving. At T2 however, the anti-inflammatory cytokine IL-10 was negatively correlated with depression, anxiety and craving.

Bala (2014)	Acute Binge Drinking Increases Serum Endotoxin and Bacterial DNA Levels in Healthy Individuals	Plos One	25 healthy individuals who underwent acute binge drinking for experiment	A single alcohol binge results in increased serum endotoxin levels
He (2009)	Increased MCP-1 and microgla in various regions of the human alcoholic brain	Exp Neurol.	Human post-mortem brain tissue (alcoholic vs healthy controls)	Significantly increased MCP-1 levels across multiple alcoholic brain regions
Kalk (2017)	Decreased hippocampal translocator protein (18 kDa) expression in alcohol dependence: a [^{11}C]PBR28 PET study	Translational Psychiatry	Nine alcohol dependent subjects and twenty controls	No evidence for increased microglial activation in ADP, as seen pre-clinically but instead lower glial density with lower TSPO expression
Hillmer (2017)	In vivo imaging of translocator protein, a marker of activated microglia, in alcohol dependance	Mol Psychiatry .	Fifteen AUD subjects and fifteen controls	Alcohol-dependent individuals exhibited less activated microglia

Leclercq (2014)	Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependance	Biol Psychiatry .	63 actively drinking patients and 14 healthy subjects	Activated proinflammatory pathways, in particular, IL-8 and IL-1β, were positively correlated with alcohol consumption and alcohol-craving scores.
Opioids				
Kang (2017)	The effect of gut microbiome on tolerance to morphine mediated antinociception in mice	Sci Rep	Mice that underwent bacterial depletion with oral gavage of an antibiotic cocktail	The gastrointestinal microbiome is an important modulator of physiological responses induced by chronic morphine administration.
Wang (2018)	Morphine induces changes in the gut microbiome and metabolome in a morphine dependence model	Scientific Reports	Morphine murine model	Expansion of *Enterococcus faecalis* was strongly correlated with gut dysbiosis following morphine treatment, and alterations in deoxycholic acid (DCA) and phosphatidylethanolamines (PEs) were associated with opioid-induced metabolomic changes.
Meng (2013)	Morphine Induces Bacterial Translocation in Mice by Compromising Intestinal Barrier Function in a TLR-Dependent Manner	Plos One	Morphine murine model	Morphine induced gut epithelial barrier dysfunction and subsequent bacteria translocation are mediated by TLR signaling
Banerjee (2016)	Opiod-induced gut microbial disruption and bile	Mucosal Immunol	Morphine murine model	Chronic morphine treatment significantly alters the gut microbial composition and induces preferential

	dysregulation leads to gut barrier compromise and substained systemic inflammation	.		expansion of Gram-positive pathogenic and reduction in bile-deconjugating bacterial strains
Rousseaux (2007)	Lactobacillus acidophilus modulates intestinal pain and induces opiod and cannabinoid receptors	Nat Med	Mice and rats	Oral administration of specific Lactobacillus strains induced the expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells, and mediated analgesic functions in the gut-similar to the effects of morphine.
Cocaine				
Scorza (2019)	Alterations in the Gut Microbiota of Rats Chronically Exposed to Volatilized Cocaine and Its Active Adulterants Caffeine and Phenacetin	Neurotox Res .	Rats	Repeated exposure to volatilized cocaine, as well as to the adulterants caffeine and phenacetin, leads to changes in the gut microbiota
Chivero (2019)	Cocaine Induces Inflammatory Gut Milieu by Compromising the Mucosal Barrier Integrity and Altering the Gut Microbiota Colonization.	Sci Rep.	Mice	Cocaine exposure decreased colonization by *Mucispirillum*, *Ruminococcaceae*, *Lachnospiracea*, *Pseudoflavonifractor* and *Butryccicoccus* bacteria. It is also associated with inducing inflammatory processes in the gut, i.e. increased expression of pro-inflammatory cytokines, chemokines and activation of transcription factors
Volpe (2014)	Associations of cocaine use and HIV infection with the intestinal microbiota,	J Stud Alcohol Drugs	26 men and 6 women, 15 HIV infected and 17 HIV uninfected	Cocaine users had a higher relative abundance of Bacteroidetes (M ± SD = 57.0% ± 21 vs. 37.1% ± 23, p = .02) than nonusers.

	microbial translocation, and inflammation.			
Tobacco				
Biederm ann (2013)	Smoking Cessation Induces Profound Changes in the Composition of the Intestinal Microbiota in Humans	Plos One	10 healthy smoking subjects undergoing controlled smoking cessation.	An increase of *Firmicutes* and *Actinobact eria* and a lower proportion of *Bacteroidetes* and *Proteob acteria* were found after smoking a 9-week period of smoking cessation

Table 3. Summary of the main reviews on microbiome and susbtances of abuse.

Author	Title	Source
Shreiner (2015)	The gut microbiome in health and in disease	Curr Opin Gastroenterol
Rea (2016)	The microbiome: A key reulator of stress and neuroinflammation	Neurobiol Stress
Rooks (2016)	Gut, microbiota, metabolites and host immunity	Nature Reviews Immunology
Wolf (2017)	Microglia in Physiology and Disease	Annu Rev Physiol
Mittal (2017)	Neurotransmitters: The Critical Modulators Regultating Gut-Brain Axis	J Cell Physiol
De Timary (2017)	A role for the peripheral immune system in the development of alcohol use disorders?	Neuropharmacology
Hillemacher (2018)	Alcohol, microbiome, and their effect on psychiatric disorders	Prog Neuropsychopharmacol Biol Psychiatry
Cryan (2019)	The Microbiota-Gut-Brain Axis	Physiol Rev

Meroni (2019)	Alcohol or Gut Microbiota: Who is the Guilty?	Int J Mol Sci
Meckel (2019)	A potential role for the gut microbiome in substance use disorders	Psychopharmacology
Bastiaanssen (2019)	Making sense of...the Microbiome in Psychiatry	Int J Neuropsychopharmacol
Bajaj (2019)	Alcohol, liver disease and the gut microbiota	Nat Rev Gastroenterol Hepatol
Ren (2020)	The role of the gut microbiome in opiod use	Behav Pharmacol
Rueda-Ruzafa (2020)	Opiod system influences gut-brain axis: Dysbiosis and related alterations	Pharmacol Res
Hayes (2020)	Microbes and mental health: Can the microbiome help explain clinical heterogeneity in psychiatry?	Frontiers in Neuroendocrinology
Chinna Meyyappan (2020)	Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review	BMC Psychiatry

References

1. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry*. 2018;5(12):987-1012. doi:10.1016/S2215-0366(18)30337-7

2. Peacock A, Leung J, Larney S, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addict Abingdon Engl*. 2018;113(10):1905-1926. doi:10.1111/add.14234

3. Volkow ND, Boyle M. Neuroscience of Addiction: Relevance to Prevention and Treatment. *Am J Psychiatry*. 2018;175(8):729-740. doi:10.1176/appi.ajp.2018.17101174

4. Chinna Meyyappan A, Forth E, Wallace CJK, Milev R. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. *BMC Psychiatry*. 2020;20(1):299. doi:10.1186/s12888-020-02654-5

5. Hayes CL, Peters BJ, Foster JA. Microbes and mental health: Can the microbiome help explain clinical heterogeneity in psychiatry? *Front Neuroendocrinol*. Published online June 1, 2020:100849. doi:10.1016/j.yfrne.2020.100849

6. Haber PS, Kortt NC. Alcohol use disorder and the gut. *Addict Abingdon Engl*. Published online June 8, 2020. doi:10.1111/add.15147

7. Qamar N, Castano D, Patt C, Chu T, Cottrell J, Chang SL. Meta-analysis of alcohol induced gut dysbiosis and the resulting behavioral impact. *Behav Brain Res*. 2019;376:112196. doi:10.1016/j.bbr.2019.112196

8. Rueda-Ruzafa L, Cruz F, Cardona D, et al. Opioid system influences gut-brain axis: Dysbiosis and related alterations. *Pharmacol Res*. 2020;159:104928. doi:10.1016/j.phrs.2020.104928

9. Hillemacher T, Bachmann O, Kahl KG, Frieling H. Alcohol, microbiome, and their effect on psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;85:105-115. doi:10.1016/j.pnpbp.2018.04.015

10. Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. *Immunity*. 2017;46(4):562-576. doi:10.1016/j.immuni.2017.04.008

11. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016;16(6):341-352. doi:10.1038/nri.2016.42

12. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res*. 2020;30(6):492-506. doi:10.1038/s41422-020-0332-7

13. Visconti A, Le Roy CI, Rosa F, et al. Interplay between the human gut microbiome and host metabolism. *Nat Commun*. 2019;10(1):4505. doi:10.1038/s41467-019-12476-z

14. Ryan PM, Delzenne NM. Chapter 18 - Gut Microbiota and Metabolism. In: Hyland N, Stanton C, eds. *The Gut-Brain Axis*. Academic Press; 2016:391-401. doi:10.1016/B978-0-12-802304-4.00018-9

15. Davenport ER, Sanders JG, Song SJ, Amato KR, Clark AG, Knight R. The human microbiome in evolution. *BMC Biol*. 2017;15. doi:10.1186/s12915-017-0454-7

16. Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. *Curr Opin Gastroenterol*. 2015;31(1):69-75. doi:10.1097/MOG.0000000000000139

17. Bastiaanssen TFS, Cowan CSM, Claesson MJ, Dinan TG, Cryan JF. Making Sense of … the Microbiome in Psychiatry. *Int J Neuropsychopharmacol*. 2018;22(1):37-52. doi:10.1093/ijnp/pyy067

18. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A*. 2010;107(26):11971-11975. doi:10.1073/pnas.1002601107

19. Tasnim N, Abulizi N, Pither J, Hart MM, Gibson DL. Linking the Gut Microbial Ecosystem with the Environment: Does Gut Health Depend on Where We Live? *Front Microbiol*. 2017;8. doi:10.3389/fmicb.2017.01935

20. Levin AM, Sitarik AR, Havstad SL, et al. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity. *Sci Rep*. 2016;6:31775. doi:10.1038/srep31775

21. Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med*. 2016;8(343):343ra82. doi:10.1126/scitranslmed.aad7121

22. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol*. 2015;21(29):8787-8803. doi:10.3748/wjg.v21.i29.8787

23. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature*. 2012;489(7415):220-230. doi:10.1038/nature11550

24. Naseribafrouei A, Hestad K, Avershina E, et al. Correlation between the human fecal microbiota and depression. *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc*. 2014;26(8):1155-1162. doi:10.1111/nmo.12378

25. Foster JA, McVey Neufeld K-A. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci*. 2013;36(5):305-312. doi:10.1016/j.tins.2013.01.005

26. Nitschke A, Deonandan R, Konkle AT. The link between autism spectrum disorder and gut microbiota: A scoping review. *Autism Int J Res Pract*. Published online April 28, 2020:1362361320913364. doi:10.1177/1362361320913364

27. Ding HT, Taur Y, Walkup JT. Gut Microbiota and Autism: Key Concepts and Findings. *J Autism Dev Disord*. 2017;47(2):480-489. doi:10.1007/s10803-016-2960-9

28. Severance EG, Alaedini A, Yang S, et al. Gastrointestinal inflammation and associated immune activation in schizophrenia. *Schizophr Res*. 2012;138(1):48-53. doi:10.1016/j.schres.2012.02.025

29. Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability – a new target for disease prevention and therapy. *BMC Gastroenterol*. 2014;14(1):1-25. doi:10.1186/s12876-014-0189-7

30. Ling X, Linglong P, Weixia D, Hong W. Protective Effects of Bifidobacterium on Intestinal Barrier Function in LPS-Induced Enterocyte Barrier Injury of Caco-2 Monolayers and in a Rat NEC Model. *PloS One*. 2016;11(8):e0161635. doi:10.1371/journal.pone.0161635

31. Eeckhaut V, Machiels K, Perrier C, et al. Butyricicoccus pullicaecorum in inflammatory bowel disease. *Gut*. 2013;62(12):1745-1752. doi:10.1136/gutjnl-2012-303611

32. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. 2014;6(263):263ra158. doi:10.1126/scitranslmed.3009759

33. Erny D, Hrabě de Angelis AL, Jaitin D, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci*. 2015;18(7):965-977. doi:10.1038/nn.4030

34. Elamin E, Jonkers D, Juuti-Uusitalo K, et al. Effects of Ethanol and Acetaldehyde on Tight Junction Integrity: In Vitro Study in a Three Dimensional Intestinal Epithelial Cell Culture Model. *PLoS ONE*. 2012;7(4). doi:10.1371/journal.pone.0035008

35. Ratajczak W, Rył A, Mizerski A, Walczakiewicz K, Sipak O, Laszczyńska M. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). *Acta Biochim Pol*. 2019;66(1):1-12. doi:10.18388/abp.2018_2648

36. Bourassa MW, Alim I, Bultman SJ, Ratan RR. Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health? *Neurosci Lett*. 2016;625:56-63. doi:10.1016/j.neulet.2016.02.009

37. Jenkins TA, Nguyen JCD, Polglaze KE, Bertrand PP. Influence of Tryptophan and Serotonin on Mood and Cognition with a Possible Role of the Gut-Brain Axis. *Nutrients*. 2016;8(1). doi:10.3390/nu8010056

38. Yano JM, Yu K, Donaldson GP, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. 2015;161(2):264-276. doi:10.1016/j.cell.2015.02.047

39. Mittal R, Debs LH, Patel AP, et al. Neurotransmitters: The Critical Modulators Regulating Gut-Brain Axis. *J Cell Physiol*. 2017;232(9):2359-2372. doi:10.1002/jcp.25518

40. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol*. 2004;558(Pt 1):263-275. doi:10.1113/jphysiol.2004.063388

41. Rea K, Dinan TG, Cryan JF. The microbiome: A key regulator of stress and neuroinflammation. *Neurobiol Stress*. 2016;4:23-33. doi:10.1016/j.ynstr.2016.03.001

42. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. *Adv Exp Med Biol*. 2014;817:115-133. doi:10.1007/978-1-4939-0897-4_5

43. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci*. 2011;108(38):16050-16055. doi:10.1073/pnas.1102999108

44. Perez-Burgos A, Wang B, Mao Y-K, et al. Psychoactive bacteria Lactobacillus rhamnosus (JB-1) elicits rapid frequency facilitation in vagal afferents. *Am J Physiol Gastrointest Liver Physiol*. 2013;304(2):G211-220. doi:10.1152/ajpgi.00128.2012

45. Goehler LE, Gaykema RPA, Opitz N, Reddaway R, Badr N, Lyte M. Activation in vagal afferents and central autonomic pathways: Early responses to intestinal infection with Campylobacter jejuni. *Brain Behav Immun*. 2005;19(4):334-344. doi:10.1016/j.bbi.2004.09.002

46. Van Amersfoort ES, Van Berkel TJC, Kuiper J. Receptors, Mediators, and Mechanisms Involved in Bacterial Sepsis and Septic Shock. *Clin Microbiol Rev*. 2003;16(3):379-414. doi:10.1128/CMR.16.3.379-414.2003

47. Banks WA, Plotkin SR, Kastin AJ. Permeability of the blood-brain barrier to soluble cytokine receptors. *Neuroimmunomodulation*. 1995;2(3):161-165. doi:10.1159/000096887

48. Skinner RA, Gibson RM, Rothwell NJ, Pinteaux E, Penny JI. Transport of interleukin-1 across cerebromicrovascular endothelial cells. *Br J Pharmacol*. 2009;156(7):1115-1123. doi:10.1111/j.1476-5381.2008.00129.x

49. Wegiel J, Wiśniewski HM, Dziewiatkowski J, et al. Reduced number and altered morphology of microglial cells in colony stimulating factor-1-deficient osteopetrotic op/op mice. *Brain Res*. 1998;804(1):135-139. doi:10.1016/s0006-8993(98)00618-0

50. Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol*. 2009;27:119-145. doi:10.1146/annurev.immunol.021908.132528

51. Li Y, Du X-F, Liu C-S, Wen Z-L, Du J-L. Reciprocal regulation between resting microglial dynamics and neuronal activity in vivo. *Dev Cell*. 2012;23(6):1189-1202. doi:10.1016/j.devcel.2012.10.027

52. Dissing-Olesen L, LeDue JM, Rungta RL, Hefendehl JK, Choi HB, MacVicar BA. Activation of Neuronal NMDA Receptors Triggers Transient ATP-Mediated Microglial Process Outgrowth. *J Neurosci*. 2014;34(32):10511-10527. doi:10.1523/JNEUROSCI.0405-14.2014

53. Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B. Microglia: Dynamic Mediators of Synapse Development and Plasticity. *Trends Immunol*. 2015;36(10):605-613. doi:10.1016/j.it.2015.08.008

54. Ragozzino D, Di Angelantonio S, Trettel F, et al. Chemokine fractalkine/CX3CL1 negatively modulates active glutamatergic synapses in rat hippocampal neurons. *J Neurosci Off J Soc Neurosci*. 2006;26(41):10488-10498. doi:10.1523/JNEUROSCI.3192-06.2006

55. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. *Nature*. 2006;440(7087):1054-1059. doi:10.1038/nature04671

56. Wolf SA, Boddeke HWGM, Kettenmann H. Microglia in Physiology and Disease. *Annu Rev Physiol*. 2017;79:619-643. doi:10.1146/annurev-physiol-022516-034406

57. Parkhurst CN, Yang G, Ninan I, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell*. 2013;155(7):1596-1609. doi:10.1016/j.cell.2013.11.030

58. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The Microbiota-Gut-Brain Axis. *Physiol Rev*. 2019;99(4):1877-2013. doi:10.1152/physrev.00018.2018

59. Rothhammer V, Mascanfroni ID, Bunse L, et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat Med*. 2016;22(6):586-597. doi:10.1038/nm.4106

60. Hannestad J, Gallezot J-D, Schafbauer T, et al. Endotoxin-induced systemic inflammation activates microglia: [^{11}C]PBR28 positron emission tomography in nonhuman primates. *NeuroImage*. 2012;63(1):232-239. doi:10.1016/j.neuroimage.2012.06.055

61. Wohleb ES, McKim DB, Sheridan JF, Godbout JP. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. *Front Neurosci*. 2014;8:447. doi:10.3389/fnins.2014.00447

62. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457. doi:10.1016/j.biopsych.2009.09.033

63. Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. *Biol Psychiatry*. 2009;65(9):732-741. doi:10.1016/j.biopsych.2008.11.029

64. Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? *Neurochem Int*. 2016;99:110-132. doi:10.1016/j.neuint.2016.06.011

65. Elamin EE, Masclee AA, Dekker J, Pieters H-J, Jonkers DM. Short-chain fatty acids activate AMP-activated protein kinase and ameliorate ethanol-induced intestinal barrier dysfunction in Caco-2 cell monolayers. *J Nutr*. 2013;143(12):1872-1881. doi:10.3945/jn.113.179549

66. Cresci GA, Glueck B, McMullen MR, Xin W, Allende D, Nagy LE. Prophylactic tributyrin treatment mitigates chronic-binge ethanol-induced intestinal barrier and liver injury. *J Gastroenterol Hepatol*. 2017;32(9):1587-1597. doi:10.1111/jgh.13731

67. Vijay N, Morris ME. Role of monocarboxylate transporters in drug delivery to the brain. *Curr Pharm Des*. 2014;20(10):1487-1498. doi:10.2174/13816128113199990462

68. Frost G, Sleeth ML, Sahuri-Arisoylu M, et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat Commun*. 2014;5(1):3611. doi:10.1038/ncomms4611

69. van de Wouw M, Boehme M, Lyte JM, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. *J Physiol*. 2018;596(20):4923-4944. doi:10.1113/JP276431

70. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun*. 2015;48:186-194. doi:10.1016/j.bbi.2015.03.016

71. Zheng P, Zeng B, Zhou C, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol Psychiatry*. 2016;21(6):786-796. doi:10.1038/mp.2016.44

72. Skonieczna-Żydecka K, Grochans E, Maciejewska D, et al. Faecal Short Chain Fatty Acids Profile is Changed in Polish Depressive Women. *Nutrients*. 2018;10(12). doi:10.3390/nu10121939

73. O'Mahony SM, Felice VD, Nally K, et al. Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats. *Neuroscience*. 2014;277:885-901. doi:10.1016/j.neuroscience.2014.07.054

74. Ruddick JP, Evans AK, Nutt DJ, Lightman SL, Rook GAW, Lowry CA. Tryptophan metabolism in the central nervous system: medical implications. *Expert Rev Mol Med*. 2006;8(20):1-27. doi:10.1017/S1462399406000068

75. Badawy AA-B. Tryptophan availability for kynurenine pathway metabolism across the life span: Control mechanisms and focus on aging, exercise, diet and nutritional supplements. *Neuropharmacology*. 2017;112(Pt B):248-263. doi:10.1016/j.neuropharm.2015.11.015

76. O'Farrell K, Harkin A. Stress-related regulation of the kynurenine pathway: Relevance to neuropsychiatric and degenerative disorders. *Neuropharmacology*. 2017;112(Pt B):307-323. doi:10.1016/j.neuropharm.2015.12.004

77. Strasser B, Becker K, Fuchs D, Gostner JM. Kynurenine pathway metabolism and immune activation: Peripheral measurements in psychiatric and co-morbid conditions. *Neuropharmacology*. 2017;112(Pt B):286-296. doi:10.1016/j.neuropharm.2016.02.030

78. Wichers MC, Maes M. The role of indoleamine 2,3-dioxygenase (IDO) in the pathophysiology of interferon-α-induced depression. *J Psychiatry Neurosci*. 2004;29(1):11-17.

79. Chong HX, Yusoff N a. A, Hor Y-Y, et al. Lactobacillus plantarum DR7 alleviates stress and anxiety in adults: a randomised, double-blind, placebo-controlled study. *Benef Microbes*. 2019;10(4):355-373. doi:10.3920/BM2018.0135

80. Desbonnet L, Clarke G, Traplin A, et al. Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain Behav Immun*. 2015;48:165-173. doi:10.1016/j.bbi.2015.04.004

81. Rudzki L, Ostrowska L, Pawlak D, et al. Probiotic Lactobacillus Plantarum 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: A double-blind, randomized, placebo controlled study. *Psychoneuroendocrinology*. 2019;100:213-222. doi:10.1016/j.psyneuen.2018.10.010

82. Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a Social Stressor Alters the Structure of the Intestinal Microbiota: Implications for Stressor-Induced Immunomodulation. *Brain Behav Immun*. 2011;25(3):397-407. doi:10.1016/j.bbi.2010.10.023

83. De Palma G, Blennerhassett P, Lu J, et al. Microbiota and host determinants of behavioural phenotype in maternally separated mice. *Nat Commun*. 2015;6:7735. doi:10.1038/ncomms8735

84. Karl JP, Margolis LM, Madslien EH, et al. 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*. 2017;312(6):G559-G571. doi:10.1152/ajpgi.00066.2017

85. Leclercq S. Unpublished.

86. Sierra A, Gottfried-Blackmore A, Milner TA, McEwen BS, Bulloch K. Steroid hormone receptor expression and function in microglia. *Glia*. 2008;56(6):659-674. doi:10.1002/glia.20644

87. Frank MG, Baratta MV, Sprunger DB, Watkins LR, Maier SF. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. *Brain Behav Immun*. 2007;21(1):47-59. doi:10.1016/j.bbi.2006.03.005

88. Browning KN, Verheijden S, Boeckxstaens GE. The vagus nerve in appetite regulation, mood and intestinal inflammation. *Gastroenterology*. 2017;152(4):730-744. doi:10.1053/j.gastro.2016.10.046

89. Wang F-B, Powley TL. Vagal innervation of intestines: afferent pathways mapped with new en bloc horseradish peroxidase adaptation. *Cell Tissue Res*. 2007;329(2):221-230. doi:10.1007/s00441-007-0413-7

90. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci*. 2011;12(8):453-466. doi:10.1038/nrn3071

91. Abreu MT, Fukata M, Arditi M. TLR Signaling in the Gut in Health and Disease. *J Immunol*. 2005;174(8):4453-4460. doi:10.4049/jimmunol.174.8.4453

92. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci U S A*. 2008;105(43):16767-16772. doi:10.1073/pnas.0808567105

93. Han W, Tellez LA, Perkins MH, et al. A Neural Circuit for Gut-Induced Reward. *Cell*. 2018;175(3):665-678.e23. doi:10.1016/j.cell.2018.08.049

94. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405(6785):458-462. doi:10.1038/35013070

95. Zhou H, Liang H, Li Z-F, Xiang H, Liu W, Li J-G. Vagus nerve stimulation attenuates intestinal epithelial tight junctions disruption in endotoxemic mice through α7 nicotinic acetylcholine receptors. *Shock Augusta Ga*. 2013;40(2):144-151. doi:10.1097/SHK.0b013e318299e9c0

96. Hoban AE, Stilling RM, Ryan FJ, et al. Regulation of prefrontal cortex myelination by the microbiota. *Transl Psychiatry*. 2016;6(4):e774-e774. doi:10.1038/tp.2016.42

97. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A*. 2011;108(7):3047-3052. doi:10.1073/pnas.1010529108

98. Luczynski P, Whelan SO, O'Sullivan C, et al. Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. *Eur J Neurosci*. 2016;44(9):2654-2666. doi:10.1111/ejn.13291

99. Clarke G, Grenham S, Scully P, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry*. 2013;18(6):666-673. doi:10.1038/mp.2012.77

100. Gacias M, Gaspari S, Santos P-MG, et al. Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. *eLife*. 2016;5. doi:10.7554/eLife.13442

101. Lu J, Synowiec S, Lu L, et al. Microbiota influence the development of the brain and behaviors in C57BL/6J mice. *PLoS ONE*. 2018;13(8). doi:10.1371/journal.pone.0201829

102. Nishino R, Mikami K, Takahashi H, et al. Commensal microbiota modulate murine behaviors in a strictly contamination-free environment confirmed by culture-based methods. *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc*. 2013;25(6):521-528. doi:10.1111/nmo.12110

103. Sharon G, Cruz NJ, Kang D-W, et al. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell*. 2019;177(6):1600-1618.e17. doi:10.1016/j.cell.2019.05.004

104. Bode JC, Bode C, Heidelbach R, Dürr HK, Martini GA. Jejunal microflora in patients with chronic alcohol abuse. *Hepatogastroenterology*. 1984;31(1):30-34.

105. Mutlu EA, Gillevet PM, Rangwala H, et al. Colonic microbiome is altered in alcoholism. *Am J Physiol-Gastrointest Liver Physiol*. 2012;302(9):G966-G978. doi:10.1152/ajpgi.00380.2011

106. Bjørkhaug ST, Aanes H, Neupane SP, et al. Characterization of gut microbiota composition and functions in patients with chronic alcohol overconsumption. *Gut Microbes*. 2019;10(6):663-675. doi:10.1080/19490976.2019.1580097

107. Chen Y, Yang F, Lu H, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatol Baltim Md*. 2011;54(2):562-572. doi:10.1002/hep.24423

108. Dubinkina VB, Tyakht AV, Odintsova VY, et al. Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease. *Microbiome*. 2017;5(1):141. doi:10.1186/s40168-017-0359-2

109. Bajaj JS. Alcohol, liver disease and the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2019;16(4):235-246. doi:10.1038/s41575-018-0099-1

110. Bull-Otterson L, Feng W, Kirpich I, et al. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PloS One*. 2013;8(1):e53028. doi:10.1371/journal.pone.0053028

111. Monroe P, Vlahcevic ZR, Swell L. Effects of acute and chronic ethanol intake on bile acid metabolism. *Alcohol Clin Exp Res*. 1981;5(1):92-100. doi:10.1111/j.1530-0277.1981.tb04871.x

112. Fooks LJ, Gibson GR. Probiotics as modulators of the gut flora. *Br J Nutr*. 2002;88 Suppl 1:S39-49. doi:10.1079/BJN2002628

113. Swanson GR, Siskin J, Gorenz A, et al. Disrupted Diurnal Oscillation of Gut-Derived Short Chain Fatty Acids in Shift Workers Drinking Alcohol: Possible Mechanism for Loss of Resiliency of Intestinal Barrier in Disrupted Circadian Host. *Transl Res J Lab Clin Med*. Published online May 3, 2020. doi:10.1016/j.trsl.2020.04.004

114. Bjarnason I, Peters TJ, Wise RJ. The leaky gut of alcoholism: possible route of entry for toxic compounds. *Lancet Lond Engl*. 1984;1(8370):179-182. doi:10.1016/s0140-6736(84)92109-3

115. Leclercq S, Cani PD, Neyrinck AM, et al. Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. *Brain Behav Immun*. 2012;26(6):911-918. doi:10.1016/j.bbi.2012.04.001

116. Yan AW, Fouts DE, Brandl J, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatol Baltim Md*. 2011;53(1):96-105. doi:10.1002/hep.24018

117. Arrieta MC, Bistritz L, Meddings JB. Alterations in intestinal permeability. *Gut*. 2006;55(10):1512-1520. doi:10.1136/gut.2005.085373

118. Shaikh M, Rajan K, Forsyth CB, Voigt RM, Keshavarzian A. Simultaneous gas-chromatographic urinary measurement of sugar probes to assess intestinal permeability: use of time course analysis to optimize its use to assess regional gut permeability. *Clin Chim Acta Int J Clin Chem*. 2015;442:24-32. doi:10.1016/j.cca.2014.12.040

119. Vetreno RP, Massey V, Crews FT. Long-lasting microbial dysbiosis and altered enteric neurotransmitters in adult rats following adolescent binge ethanol exposure. *Addict Biol*. n/a(n/a):e12869. doi:10.1111/adb.12869

120. Leclercq S, Matamoros S, Cani PD, et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity.

Proc Natl Acad Sci U S A. 2014;111(42):E4485-4493. doi:10.1073/pnas.1415174111

121. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A*. 2008;105(43):16731-16736. doi:10.1073/pnas.0804812105

122. Wang HJ, Zakhari S, Jung MK. Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. *World J Gastroenterol WJG*. 2010;16(11):1304-1313. doi:10.3748/wjg.v16.i11.1304

123. Rizzatti G, Lopetuso LR, Gibiino G, Binda C, Gasbarrini A. Proteobacteria: A Common Factor in Human Diseases. BioMed Research International. doi:https://doi.org/10.1155/2017/9351507

124. Bala S, Marcos M, Gattu A, Catalano D, Szabo G. Acute Binge Drinking Increases Serum Endotoxin and Bacterial DNA Levels in Healthy Individuals. *PLOS ONE*. 2014;9(5):e96864. doi:10.1371/journal.pone.0096864

125. Mutlu E, Keshavarzian A, Engen P, Forsyth CB, Sikaroodi M, Gillevet P. Intestinal dysbiosis: a possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. *Alcohol Clin Exp Res*. 2009;33(10):1836-1846. doi:10.1111/j.1530-0277.2009.01022.x

126. Kanczkowski W, Alexaki V-I, Tran N, et al. Hypothalamo-pituitary and immune-dependent adrenal regulation during systemic inflammation. *Proc Natl Acad Sci U S A*. 2013;110(36):14801-14806. doi:10.1073/pnas.1313945110

127. Kmieć Z. Cooperation of liver cells in health and disease. *Adv Anat Embryol Cell Biol*. 2001;161:III-XIII, 1-151. doi:10.1007/978-3-642-56553-3

128. Nanji AA, Khettry U, Sadrzadeh SM, Yamanaka T. Severity of liver injury in experimental alcoholic liver disease. Correlation with plasma endotoxin, prostaglandin E2, leukotriene B4, and thromboxane B2. *Am J Pathol*. 1993;142(2):367-373.

129. Bigatello LM, Broitman SA, Fattori L, et al. Endotoxemia, encephalopathy, and mortality in cirrhotic patients. *Am J Gastroenterol*. 1987;82(1):11-15.

130. Leclercq S, De Saeger C, Delzenne N, de Timary P, Stärkel P. Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. *Biol Psychiatry*. 2014;76(9):725-733. doi:10.1016/j.biopsych.2014.02.003

131. Crews FT, Bechara R, Brown LA, et al. Cytokines and alcohol. *Alcohol Clin Exp Res*. 2006;30(4):720-730. doi:10.1111/j.1530-0277.2006.00084.x

132. Kane CJM, Phelan KD, Douglas JC, et al. Effects of ethanol on immune response in the brain: region-specific changes in adolescent versus adult mice. *Alcohol Clin Exp Res*. 2014;38(2):384-391. doi:10.1111/acer.12244

133. Vetreno RP, Crews FT. Adolescent binge drinking increases expression of the danger signal receptor agonist HMGB1 and toll-like receptors in the adult prefrontal cortex. *Neuroscience*. 2012;226:475-488. doi:10.1016/j.neuroscience.2012.08.046

134. Crews FT, Walter TJ, Coleman LG, Vetreno RP. Toll-like receptor signaling and stages of addiction. *Psychopharmacology (Berl)*. 2017;234(9-10):1483-1498. doi:10.1007/s00213-017-4560-6

135. He J, Crews FT. Increased MCP-1 and microglia in various regions of the human alcoholic brain. *Exp Neurol*. 2008;210(2):349-358. doi:10.1016/j.expneurol.2007.11.017

136. Zou JY, Crews FT. Release of neuronal HMGB1 by ethanol through decreased HDAC activity activates brain neuroimmune signaling. *PloS One*. 2014;9(2):e87915. doi:10.1371/journal.pone.0087915

137. Fernandez-Lizarbe S, Pascual M, Guerri C. Critical role of TLR4 response in the activation of microglia induced by ethanol. *J Immunol Baltim Md 1950*. 2009;183(7):4733-4744. doi:10.4049/jimmunol.0803590

138. Alfonso-Loeches S, Pascual-Lucas M, Blanco AM, Sanchez-Vera I, Guerri C. Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain damage. *J Neurosci Off J Soc Neurosci*. 2010;30(24):8285-8295. doi:10.1523/JNEUROSCI.0976-10.2010

139. Kang L, Sebastian BM, Pritchard MT, Pratt BT, Previs SF, Nagy LE. Chronic ethanol-induced insulin resistance is associated with macrophage infiltration into adipose tissue and altered expression of adipocytokines. *Alcohol Clin Exp Res*. 2007;31(9):1581-1588. doi:10.1111/j.1530-0277.2007.00452.x

140. Kalk NJ, Guo Q, Owen D, et al. Decreased hippocampal translocator protein (18 kDa) expression in alcohol dependence: a [11C]PBR28 PET study. *Transl Psychiatry*. 2017;7(1):e996. doi:10.1038/tp.2016.264

141. Kim SW, Wiers CE, Tyler R, et al. Influence of alcoholism and cholesterol on TSPO binding in brain: PET [11C]PBR28 studies in humans and rodents. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2018;43(9):1832-1839. doi:10.1038/s41386-018-0085-x

142. Hillmer AT, Sandiego CM, Hannestad J, et al. In vivo imaging of translocator protein, a marker of activated microglia, in alcohol dependence. *Mol Psychiatry*. 2017;22(12):1759-1766. doi:10.1038/mp.2017.10

143. Maes M. Evidence for an immune response in major depression: a review and hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry*. 1995;19(1):11-38. doi:10.1016/0278-5846(94)00101-m

144. Maes M, Berk M, Goehler L, et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med*. 2012;10:66. doi:10.1186/1741-7015-10-66

145. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev*. 2012;36(2):764-785. doi:10.1016/j.neubiorev.2011.12.005

146. Montesinos J, Pascual M, Rodríguez-Arias M, Miñarro J, Guerri C. Involvement of TLR4 in the long-term epigenetic changes, rewarding and anxiety effects induced by intermittent ethanol treatment in adolescence. *Brain Behav Immun*. 2016;53:159-171. doi:10.1016/j.bbi.2015.12.006

147. Blednov YA, Benavidez JM, Geil C, Perra S, Morikawa H, Harris RA. Activation of inflammatory signaling by lipopolysaccharide produces a prolonged increase of voluntary alcohol intake in mice. *Brain Behav Immun*. 2011;25 Suppl 1:S92-S105. doi:10.1016/j.bbi.2011.01.008

148. Robinson G, Most D, Ferguson LB, Mayfield J, Harris RA, Blednov YA. Neuroimmune pathways in alcohol consumption: evidence from behavioral and genetic studies in rodents and humans. *Int Rev Neurobiol*. 2014;118:13-39. doi:10.1016/B978-0-12-801284-0.00002-6

149. Mulligan MK, Ponomarev I, Hitzemann RJ, et al. Toward understanding the genetics of alcohol drinking through transcriptome meta-analysis. *Proc Natl Acad Sci U S A*. 2006;103(16):6368-6373. doi:10.1073/pnas.0510188103

150. Tabakoff B, Saba L, Kechris K, et al. The genomic determinants of alcohol preference in mice. *Mamm Genome Off J Int Mamm Genome Soc*. 2008;19(5):352-365. doi:10.1007/s00335-008-9115-z

151. Osterndorff-Kahanek EA, Becker HC, Lopez MF, et al. Chronic ethanol exposure produces time- and brain region-dependent changes in gene coexpression networks. *PloS One*. 2015;10(3):e0121522. doi:10.1371/journal.pone.0121522

152. Blednov YA, Ponomarev I, Geil C, Bergeson S, Koob GF, Harris RA. Neuroimmune regulation of alcohol consumption: behavioral validation of genes obtained from genomic studies. *Addict Biol*. 2012;17(1):108-120. doi:10.1111/j.1369-1600.2010.00284.x

153. Freeman K, Brureau A, Vadigepalli R, et al. Temporal changes in innate immune signals in a rat model of alcohol withdrawal in emotional and cardiorespiratory homeostatic nuclei. *J Neuroinflammation*. 2012;9:97. doi:10.1186/1742-2094-9-97

154. Pascual M, Baliño P, Alfonso-Loeches S, Aragón CMG, Guerri C. Impact of TLR4 on behavioral and cognitive dysfunctions associated with alcohol-

induced neuroinflammatory damage. *Brain Behav Immun*. 2011;25 Suppl 1:S80-91. doi:10.1016/j.bbi.2011.02.012

155. Koob GF. The dark side of emotion: the addiction perspective. *Eur J Pharmacol*. 2015;753:73-87. doi:10.1016/j.ejphar.2014.11.044

156. Freeman K, Staehle MM, Vadigepalli R, et al. Coordinated dynamic gene expression changes in the central nucleus of the amygdala during alcohol withdrawal. *Alcohol Clin Exp Res*. 2013;37 Suppl 1:E88-100. doi:10.1111/j.1530-0277.2012.01910.x

157. Volkow ND, Jones EB, Einstein EB, Wargo EM. Prevention and Treatment of Opioid Misuse and Addiction: A Review. *JAMA Psychiatry*. 2019;76(2):208-216. doi:10.1001/jamapsychiatry.2018.3126

158. Hofford RS, Russo SJ, Kiraly DD. Neuroimmune mechanisms of psychostimulant and opioid use disorders. *Eur J Neurosci*. 2019;50(3):2562-2573. doi:10.1111/ejn.14143

159. Franchi S, Moschetti G, Amodeo G, Sacerdote P. Do All Opioid Drugs Share the Same Immunomodulatory Properties? A Review From Animal and Human Studies. *Front Immunol*. 2019;10:2914. doi:10.3389/fimmu.2019.02914

160. Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med*. 2017;23(9):1018-1027. doi:10.1038/nm.4397

161. Sofroniew MV. Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry*. 2014;20(2):160-172. doi:10.1177/1073858413504466

162. Metz VE, Jones JD, Manubay J, et al. Effects of Ibudilast on the Subjective, Reinforcing, and Analgesic Effects of Oxycodone in Recently Detoxified Adults with Opioid Dependence. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2017;42(9):1825-1832. doi:10.1038/npp.2017.70

163. Cooper ZD, Johnson KW, Pavlicova M, et al. The effects of ibudilast, a glial activation inhibitor, on opioid withdrawal symptoms in opioid-dependent volunteers. *Addict Biol*. 2016;21(4):895-903. doi:10.1111/adb.12261

164. Kang M, Mischel RA, Bhave S, et al. The effect of gut microbiome on tolerance to morphine mediated antinociception in mice. *Sci Rep*. 2017;7:42658. doi:10.1038/srep42658

165. Wang F, Meng J, Zhang L, Johnson T, Chen C, Roy S. Morphine induces changes in the gut microbiome and metabolome in a morphine dependence model. *Sci Rep*. 2018;8(1):3596. doi:10.1038/s41598-018-21915-8

166. Meng J, Yu H, Ma J, et al. Morphine induces bacterial translocation in mice by compromising intestinal barrier function in a TLR-dependent manner. *PloS One*. 2013;8(1):e54040. doi:10.1371/journal.pone.0054040

167. Banerjee S, Sindberg G, Wang F, et al. Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compromise and sustained systemic inflammation. *Mucosal Immunol*. 2016;9(6):1418-1428. doi:10.1038/mi.2016.9

168. Lee K, Vuong HE, Nusbaum DJ, Hsiao EY, Evans CJ, Taylor AMW. The gut microbiota mediates reward and sensory responses associated with regimen-selective morphine dependence. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2018;43(13):2606-2614. doi:10.1038/s41386-018-0211-9

169. Wang X, Loram LC, Ramos K, et al. Morphine activates neuroinflammation in a manner parallel to endotoxin. *Proc Natl Acad Sci U S A*. 2012;109(16):6325-6330. doi:10.1073/pnas.1200130109

170. Rousseaux C, Thuru X, Gelot A, et al. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med*. 2007;13(1):35-37. doi:10.1038/nm1521

171. Scorza C, Piccini C, Martínez Busi M, Abin Carriquiry JA, Zunino P. Alterations in the Gut Microbiota of Rats Chronically Exposed to Volatilized Cocaine and Its Active Adulterants Caffeine and Phenacetin. *Neurotox Res*. 2019;35(1):111-121. doi:10.1007/s12640-018-9936-9

172. Chivero ET, Ahmad R, Thangaraj A, et al. Cocaine Induces Inflammatory Gut Milieu by Compromising the Mucosal Barrier Integrity and Altering the Gut Microbiota Colonization. *Sci Rep*. 2019;9(1):12187. doi:10.1038/s41598-019-48428-2

173. Kiraly DD, Walker DM, Calipari ES, et al. Alterations of the Host Microbiome Affect Behavioral Responses to Cocaine. *Sci Rep*. 2016;6:35455. doi:10.1038/srep35455

174. Meckel KR, Kiraly DD. A potential role for the gut microbiome in substance use disorders. *Psychopharmacology (Berl)*. 2019;236(5):1513-1530. doi:10.1007/s00213-019-05232-0

175. Volpe GE, Ward H, Mwamburi M, et al. Associations of cocaine use and HIV infection with the intestinal microbiota, microbial translocation, and inflammation. *J Stud Alcohol Drugs*. 2014;75(2):347-357. doi:10.15288/jsad.2014.75.347

176. Savin Z, Kivity S, Yonath H, Yehuda S. Smoking and the intestinal microbiome. *Arch Microbiol*. 2018;200(5):677-684. doi:10.1007/s00203-018-1506-2

177. Papoutsopoulou S, Satsangi J, Campbell BJ, Probert CS. Review article: impact of cigarette smoking on intestinal inflammation-direct and indirect mechanisms. *Aliment Pharmacol Ther*. 2020;51(12):1268-1285. doi:10.1111/apt.15774

178. G K, R B, S T, S B. A Systematic Review of Smoking-Related Epigenetic Alterations. Archives of toxicology. doi:10.1007/s00204-019-02562-y

179. Somerville KW, Logan RF, Edmond M, Langman MJ. Smoking and Crohn's disease. *Br Med J Clin Res Ed*. 1984;289(6450):954-956. doi:10.1136/bmj.289.6450.954

180. Huang C, Shi G. Smoking and microbiome in oral, airway, gut and some systemic diseases. *J Transl Med*. 2019;17(1):225. doi:10.1186/s12967-019-1971-7

181. Cussotto S, Clarke G, Dinan TG, Cryan JF. Psychotropics and the Microbiome: a Chamber of Secrets…. *Psychopharmacology (Berl)*. 2019;236(5):1411-1432. doi:10.1007/s00213-019-5185-8

182. Biedermann L, Zeitz J, Mwinyi J, et al. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PloS One*. 2013;8(3):e59260. doi:10.1371/journal.pone.0059260

183. Adachi Y, Moore LE, Bradford BU, Gao W, Thurman RG. Antibiotics prevent liver injury in rats following long-term exposure to ethanol. *Gastroenterology*. 1995;108(1):218-224. doi:10.1016/0016-5085(95)90027-6

184. Albillos A, Hera Ad A de la, Reyes E, et al. Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. *J Hepatol*. 2004;40(4):624-631. doi:10.1016/j.jhep.2003.12.010

185. Qin L, Crews FT. Chronic ethanol increases systemic TLR3 agonist-induced neuroinflammation and neurodegeneration. *J Neuroinflammation*. 2012;9(1):130. doi:10.1186/1742-2094-9-130

186. Chen G, Ke Z, Xu M, et al. Autophagy is a protective response to ethanol neurotoxicity. *Autophagy*. 2012;8(11):1577-1589. doi:10.4161/auto.21376

187. Neasta J, Ben Hamida S, Yowell Q, Carnicella S, Ron D. Role for mammalian target of rapamycin complex 1 signaling in neuroadaptations underlying alcohol-related disorders. *Proc Natl Acad Sci U S A*. 2010;107(46):20093-20098. doi:10.1073/pnas.1005554107

188. Agrawal RG, Hewetson A, George CM, Syapin PJ, Bergeson SE. Minocycline reduces ethanol drinking. *Brain Behav Immun*. 2011;25 Suppl 1:S165-169. doi:10.1016/j.bbi.2011.03.002

189. de Timary P, Stärkel P, Delzenne NM, Leclercq S. A role for the peripheral immune system in the development of alcohol use disorders? *Neuropharmacology*. 2017;122:148-160. doi:10.1016/j.neuropharm.2017.04.013

190. Ait-Belgnaoui A, Durand H, Cartier C, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*. 2012;37(11):1885-1895. doi:10.1016/j.psyneuen.2012.03.024

191. Forsyth CB, Farhadi A, Jakate SM, Tang Y, Shaikh M, Keshavarzian A. Lactobacillus GG treatment ameliorates alcohol-induced intestinal oxidative stress, gut leakiness, and liver injury in a rat model of alcoholic steatohepatitis. *Alcohol Fayettev N*. 2009;43(2):163-172. doi:10.1016/j.alcohol.2008.12.009

192. Kirpich IA, Solovieva NV, Leikhter SN, et al. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. *Alcohol Fayettev N*. 2008;42(8):675-682. doi:10.1016/j.alcohol.2008.08.006

193. Han SH, Suk KT, Kim DJ, et al. Effects of probiotics (cultured Lactobacillus subtilis/Streptococcus faecium) in the treatment of alcoholic hepatitis: randomized-controlled multicenter study. *Eur J Gastroenterol Hepatol*. 2015;27(11):1300-1306. doi:10.1097/MEG.0000000000000458

194. Stadlbauer V, Mookerjee RP, Hodges S, Wright GAK, Davies NA, Jalan R. Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. *J Hepatol*. 2008;48(6):945-951. doi:10.1016/j.jhep.2008.02.015

195. Loguercio C, Federico A, Tuccillo C, et al. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol*. 2005;39(6):540-543. doi:10.1097/01.mcg.0000165671.25272.0f

196. Tillisch K, Labus J, Kilpatrick L, et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*. 2013;144(7):1394-1401, 1401.e1-4. doi:10.1053/j.gastro.2013.02.043

197. Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain Behav Immun*. 2015;48:258-264. doi:10.1016/j.bbi.2015.04.003

198. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutr Burbank Los Angel Cty Calif*. 2016;32(3):315-320. doi:10.1016/j.nut.2015.09.003

199. Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;14(8):491-502. doi:10.1038/nrgastro.2017.75

200. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer R-J. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther*. 2008;27(2):104-119. doi:10.1111/j.1365-2036.2007.03562.x

201. Gibson GR, Beatty ER, Wang X, Cummings JH. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology*. 1995;108(4):975-982. doi:10.1016/0016-5085(95)90192-2

202. Everard A, Lazarevic V, Derrien M, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes*. 2011;60(11):2775-2786. doi:10.2337/db11-0227

203. Dewulf EM, Cani PD, Claus SP, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut*. 2013;62(8):1112-1121. doi:10.1136/gutjnl-2012-303304

204. Keshavarzian A, Choudhary S, Holmes EW, et al. Preventing gut leakiness by oats supplementation ameliorates alcohol-induced liver damage in rats. *J Pharmacol Exp Ther*. 2001;299(2):442-448.

205. Han S, Shannahan S, Pellish R. Fecal Microbiota Transplant: Treatment Options for Clostridium difficile Infection in the Intensive Care Unit. *J Intensive Care Med*. 2016;31(9):577-586. doi:10.1177/0885066615594344

206. Ferrere G, Wrzosek L, Cailleux F, et al. Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice. *J Hepatol*. 2017;66(4):806-815. doi:10.1016/j.jhep.2016.11.008

207. Philips CA, Pande A, Shasthry SM, et al. Healthy Donor Fecal Microbiota Transplantation in Steroid-Ineligible Severe Alcoholic Hepatitis: A Pilot Study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2017;15(4):600-602. doi:10.1016/j.cgh.2016.10.029

208. Shasthry SM. Fecal microbiota transplantation in alcohol related liver diseases. *Clin Mol Hepatol*. 2020;26(3):294-301. doi:10.3350/cmh.2020.0057

209. Ren M, Lotfipour S. The role of the gut microbiome in opioid use. *Behav Pharmacol*. 2020;31(2 & 3):113-121. doi:10.1097/FBP.0000000000000538

210. Destoop M, Morrens M, Coppens V, Dom G. Addiction, Anhedonia, and Comorbid Mood Disorder. A Narrative Review. *Front Psychiatry*. 2019;10:311. doi:10.3389/fpsyt.2019.00311

211. Coppens V, Morrens M, Destoop M, Dom G. The Interplay of Inflammatory Processes and Cognition in Alcohol Use Disorders-A Systematic Review. *Front Psychiatry*. 2019;10:632. doi:10.3389/fpsyt.2019.00632

212. Faravelli C, Lo Sauro C, Godini L, et al. Childhood stressful events, HPA axis and anxiety disorders. *World J Psychiatry*. 2012;2(1):13-25. doi:10.5498/wjp.v2.i1.13