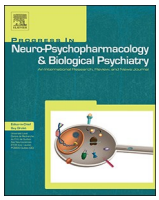
Progress in Neuropsychopharmacology & Biological Psychiatry 105 (2021) 110113

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Microbiome and substances of abuse

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

Target Journal Progress in Neuropsychopharmacology and Biological Psychiatry, Belgium

ARTICLE INFO

Keywords:
Substances of abuse
Alcohol-use-disorder
Opioids
Stimulants
Gut microbiota
Gut-brain axis
Intestinal permeability
Inflammation

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 gut-brain 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 behavior. 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 narrative literature review suggest a bidirectional influence in the pathogenesis of substance use disorders.

1. Introduction

Substance use and disorders in the use of substances (DUS) 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 (GBD, 2016). The attributable DALYs for tobacco smoking have been estimated to be 170.9 million in 2015 (Peacock et al., 2018). 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 (Volkow and Boyle, 2018).

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 (Chinna Meyyappan et al., 2020). In disease and stress states these pathways may become compromised, resulting in dysbiosis, changes in mood, behavior, cognition and altered inflammatory levels (Chinna Meyyappan et al., 2020). As such gut microbiota have been suggested to play an important role within the pathogenic processes underlying a broad variety of psychiatric disorders (Hayes et al., 2020).

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 (Haber and Kortt, 2020; Qamar et al., 2019; Rueda-Ruzafa et al., 2020).

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

* Corresponding author.
E-mail address: geert.dom@uantwerpen.be (G. Dom).

https://doi.org/10.1016/j.pnpbp.2020.110113
Received 18 July 2020; Received in revised form 7 September 2020; Accepted 14 September 2020
Available online 22 September 2020
0278-5846/

(Hillemacher et al., 2018).

2. Microbioma - gut – Brain axis: General mechanisms

The human gut microbiota has recently been the subject of extended studies establishing its impact on the immune system (Belkaid and Harrison, 2017; Rooks and Garrett, 2016; Zheng et al., 2020) and metabolism (Visconti et al., 2019; Ryan and Delzenne, 2016) 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 (Davenport et al., 2017) and a thousand (Shreiner et al., 2015) different identified species. The differing from the microbiota, the microbiome is defined as the total genetic material of the bacteria in this ecosystem (Bastiaanssen et al., 2018). Its composition is unique to each individual and is influenced by factors such as genetics, mode of delivery at birth (Dominguez-Bello et al., 2010), race, diet, living in an urban or rural environment (Tasnim et al., 2017) or the use of antibiotics (Levin et al., 2016; Bokulich et al., 2016). 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 (Jandhyala et al., 2015), but their relative proportions and the species present vary significantly between individuals (Lozupone et al., 2012). Alterations in the composition of the gut microbiota relate to several psychiatric disorders.

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, (2) the metabolic pathway, (3) the neuroendocrine pathway and the vagus nerve. 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. The composition of the gut microbiota influences intestinal barrier function, with bacterias such as *E.Coli* or *Clostridium difficile* increasing intestinal permeability (Bischoff et al., 2014), while other species, such as *Bifidobacterium* (Ling et al., *2016)* and *Butyricicoccus pullicaecorum* (Eeckhaut et al., *2013)* reinforcing the intestinal mucosae. Endotoxin and inflammatory mediators can then pass an intact blood-brain barrier (BBB) through an active transport (Banks et al., 1995; Skinner et al., 2009), but the microbiota also affects BBB permeability, facilitating inflammatory mediators entry in the brain (Braniste et al., 2014), and hence activating the microglia. Aside from releasing cytokines and chemokines to recruit local immune cells, microglia also recruit monocytes from the periphery to the brain (Cryan et al., 2019). The microbiota has been shown to influence microglia function (Hannestad et al., 2012; Rothhammer et al., 2016) and maturation (Erny, 2015). In rodents, sensitization of microglia and monocyte trafficking to the brain are regulators of recurring anxiety following exposure to prolonged stress (Wohleb et al., 2014). In humans, peripheric and central inflammation have been linked to psychological symptoms (Dowlati et al., 2010) **(Miller et al., 2009).,**

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 (Stilling et al., 2016). A specific role for SCFAs, and in particular butyrate, as promoters of the intestinal barrier integrity has recently been demonstrated (Elamin et al., 2013; Cresci et al., 2017; Ratajczak et al., 2019): 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 (Vijay and Morris, 2014) and influence brain function and behavior: butyrate reduces neuroinflammation through an action on microglial receptors (Bourassa et al., 2016); acetate modulates the appetite by binding to hippocampus (Frost et al., 2014); in mice SCFAs administration reduces symptoms of depression (van de Wouw et al., 2018). In keeping with these observations SCFAs depletion was observed in MDD patients (Jiang et al., 2015; Zheng et al., 2016; Skonieczna-Żydecka et al., 2018).

The microbiota also plays a role in the synthesis of tryptophan, the precursor of serotonin (Jenkins et al., 2016; O'Mahony et al., 2014; Yano et al., 2015) and of several neuromediators such as gamma-aminobutyric acid, norepinephrine, dopamine and serotonin (Mittal et al., 2017). 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. Under conditions of inflammation, tryptophan can also be diverted from the serotonin production into the kynurenin pathway (Badawy, 2017; O'Farrell and Harkin, 2017; Strasser et al., 2017), thus reducing the levels of serotonin and inducing depression-like behavior (Wichers and Maes, 2004) through the production of neuroactive metabolites.

2.3. The neuroendocrine pathway and the vagus nerve

Mice and human studies have shown that psychological stresses such as social disruption (Bailey et al., 2011), maternal separation (De Palma et al., 2015) or military service (Karl et al., 2017) 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 (Sudo et al., 2004). Microglial cells, whose maturation and activity can be influenced by bacterial products through peripheral inflammation, can activate the HPA axis (Rea et al., 2016). Conversely, direct HPA activation, through afferents of the vagus nerve, induces glucocorticoids production, whose receptors are highly expressed on microglial cells (Sierra et al., 2008), and activate brain microglia (Frank et al., 2007). The HPA axis, the stress response and the neuroinflammatory response are largely intertwined.

The vagus nerve is also related to gut microbiota regulation (Forsythe et al., 2014). Parasympathetic sensory afferents and efferents of the vagus nerve exist within the digestive tract. 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 (Bravo et al., 2011). Several bacterial species may increase firing rate in vagal afferents (Perez-Burgos et al., 2013; Goehler et al., 2005).

Although not in direct contact with the gut lumen, as they do not cross the epithelial layer (Wang and Powley, 2007), vagal afferents may detect bacterial products that diffuse through the epithelial wall through an interaction possibly mediated by entero-endocrine cells (Mayer, 2011), that express receptors which recognize bacterial products such as LPS (Abreu et al., 2005) and SCFAs (Samuel et al., 2008). Furthermore, vagal sensory gut neurons are connected to brain reward neurons, inducing the relase of dopamine and sustained self-stimulation (Han et al., 2018).

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 TNF-alpha in LPS stimulated human macrophage (Borovikova et al., 2000), reducing local inflammation; vagal nerve stimulation also attenuates disruptions of epithelial tight junctions in endotoxemic mice (Zhou et al., 2013), 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 (Hoban et al., 2016), synaptic development (Diaz Heijtz et al., 2011), dendritic morphology (Luczynski et al., 2016) and maturation of the hippocampal serotoninergic system (Clarke et al., 2013). On a behavioral level, GF mice show deficits in social cognitions (Gacias et al., 2016) and increased anxiety-like behaviors (Lu et al., 2018). A 24 h-exposure to an environment outside a sterile isolator makes GF mice less anxious (Nishino et al., 2013). 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 (Zheng et al., 2016). 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 (Sharon et al., 2019).

In humans, several clinical trials have demonstrated the benefits of probiotic (live microorganisms) and prebiotic (non-viable substrates such as dietary fibers) treatment on brain activity and psychological symptoms. A functional MRI (fMRI) 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 (Tillisch et al., 2013). A 4-week intake of probiotics helps reduce negative thoughts associated with sad mood (Steenbergen et al., 2015). A 8-week intake of *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* has a beneficial effect on depressive symptoms in patients with MDD (Akkasheh et al., 2016). Studies on prebiotics and probiotics treatment in ASD have showed limited efficacy in the treatment of behavioral symptoms in children with ASD (Ng et al., 2019).

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 (Bode et al., 1984) 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 (Mutlu et al., 2012). 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. Another study (Bjørkhaug et al., 2019) 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 (Chen et al., 2011) 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 (Dubinkina et al., 2017). A 2019 systematic review on microbiota composition in AUD (Bajaj, 2019) states a general increase in endotoxin-producing and decrease in autochtonous bacterial taxa. Several hypothesis have been proposed regarding the mechanism by which alcohol affects the microbiome: probably a combination of an increase of fecal pH (Bull-Otterson et al., 2013), a decrease of bile secretions (Monroe et al., 1981) and modifications of gastric acidity and gut motility (Fooks and Gibson, 2002). A recent study (Swanson et al., 2020) shows that alcohol decreases SCFAs levels, which play a major role in the homeostasis of the gastrointestinal wall. In vitro studies (Elamin et al., 2012) 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 still unclear, as it was still present after two weeks of abstinence in one study (Bjarnason et al., 1984), and completely recovered after three weeks in another (Leclercq et al., 2012). Alcohol also has a negative effect on mucus and antimicrobial peptide production (Yan et al., 2011). Overall, AUD patients show an increased intestinal permeability to several polysaccharides such as lactulose and mannitol (Arrieta et al., 2006; Shaikh et al., 2015). 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 (Vetreno et al., n.d.).

In keeping with these observations, a study (Leclercq et al., 2014a) 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 (Sokol et al., 2008). 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, 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. 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. Studies have found an elevated level of LPS in the blood of AUD patients (Leclercq et al., 2012) and in healthy subjects after binge drinking (Bala et al., 2014). 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 (Mutlu et al., 2009). 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. In the liver, Kupffer cells, the resident macrophages, are activated by LPS and produce pro-inflammatory chemokines, reactive oxygen species and leukotrienes (Kmieć, 2001), which can lead to liver injury. There is a strong correlation between endotoxin blood levels in both rats (Nanji et al., 1993) and humans (Bigatello et al., 1987) 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 (Leclercq et al., 2014b). 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 (Crews et al., 2006; Kane et al., 2014). Enhanced expression of TL receptors in brains, particularly those on microglia, were found in rats after adolescent binge drinking (Vetreno and Crews, 2012) and in AUD patients (Crews et al., 2017). In human post-mortem brains, increased levels of MCP-1 and increased microglial markers are found in heavy drinkers (He and Crews, 2008). It is important to note that part of this neuroinflammation could be related to a direct effect of ethanol on the brain (Zou and Crews, 2014; Fernandez-Lizarbe et al., 2009; Alfonso-Loeches et al., 2010). Other potent sources of inflammation including the gut itself, the liver or the adipose tissue have also been suggested (Kang et al., 2007). 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 scan studies that have been performed using TSPO ligand that is expected to measure the microglial activation (Kalk et al., 2017; Kim et al., 2018; Hillmer et al., 2017), showed controversial results with lower or equal levels of neuroinflammation compared to controls. This is clearly a shadow to the neuroinflammatory theory of addiction.

Alcohol-induced neuroinflammation could have many repercussions. There is a growing amount of evidence linking depressive behavior (Maes, 1995; Maes et al., 2012; Leonard and Maes, 2012) and anxiogenic-related behavior (Montesinos et al., 2016) to a low-grade inflammatory response and an activation of cell-mediated immunity. Furthermore, several animal studies show that an induced neuroinflammation could promote alcohol-seeking behavior (Blednov et al., 2011; Robinson et al., 2014). Several genes involved in immunity are overexpressed in strains of mice breeded for alcohol-preference (independently of ethanol administration) (Mulligan et al., 2006; Tabakoff et al., 2008), and there is an important overlap in the brain of mice between genes activated by LPS and by ethanol (Osterndorff-Kahanek et al., 2015). Further supporting the role of inflammation, genetic deletion of inflammatory genes in mice was associated with a decrease in alcohol preference and consumption (Blednov et al., 2012). 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) (Leclercq et al., 2014b). 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. There is an acute expression of proinflammatory mediators, both at the mRNA and the protein level, after 48 h of abstinence (Freeman et al., 2012). A study (Pascual et al., 2011) 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 behavior and cognitive impairments. Mice lacking TL4 receptors were protected against these effects. Patients undergoing alcohol withdrawal experience a number of emotional disturbances (Koob, 2015), which have been linked to a neuroinflammatory response in the central nucleus of the amygdala, a structure associated with the regulation of emotions (Freeman et al., 2012; Freeman et al., 2013). Leclercq et al. (Leclercq et al., 2012) 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 (Leclercq et al., 2014a) 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 (Volkow et al., 2019). In addition, recent evidence suggests that opioid use might be impairing somatic recovery as a result of their interactions with inflammatory processes (Hofford et al., 2019). However, the relationship between opioid use and immune responses seem to be complex and not consistent (Franchi et al., 2019). On the one hand, human studies indicate (peripherical) immunosuppressive effects of opioids, albeit not for all types of opioids (Hofford et al., 2019; Franchi et al., 2019). In contrast, 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 (Hofford et al., 2019; Salter and Stevens, 2017; Sofroniew, 2014). 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 (Hofford et al., 2019; Metz et al., 2017; Cooper et al., 2016).

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 (Rueda-Ruzafa et al., 2020). Pre-clinical 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* (Kang et al., 2017; Wang et al., 2018). Interestingly, morphine induced dysbiosis is antagonized by naltrexone, indicating the specificity of this action through the opioid receptors (Rueda-Ruzafa et al., 2020).

Chronic morphine administration induces changes in the intestinal

epithelium increasing permeability and bacterial translocation mediated by Toll-like receptor (TLR) (Meng et al., 2013; Banerjee et al., 2016). These mechanisms may underly a causal pathway linking chronic morphine administration associated gut dysbiosis with neuroinflammation, hyperalgesia, deficits in reward behavior and microglial activation (Lee et al., 2018; Wang et al., 2012). Of interest, pretreatment with a probiotic Lactobacillus acidophilus in a rat model was associated with increased pain threshold, improved hypersensitivity and expression of MOR (Rousseaux et al., 2007).

Taken together findings from pre-clinical 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 (Scorza et al., 2019; Chivero et al., 2019). 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 (Chivero et al., 2019). 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 (Kiraly et al., 2016; Meckel and Kiraly, 2019). 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 (Hofford et al., 2019). 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 (Hofford et al., 2019; Volpe et al., 2014). 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 (Savin et al., 2018), 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 (Papoutsopoulou et al., 2020; Kaur et al., 2019). Consistent with these hypotheses are findings indicating that smoking is associated not only with inflammatory Bowel Disease (IBD) (Papoutsopoulou et al., 2020; Somerville et al., 1984) but also periodontitis, asthma, chronic obstructive pulmonary disease, and cancer (Papoutsopoulou et al., 2020; Huang and Shi, 2019). So, the effects of smoking on the microbiome and subsequent somatic disorders is consistently demonstrated. However, the effect of smoking on the brain-gut 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 (Cussotto et al., 2019; Biedermann et al., 2013).

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 probiotics, prebiotics or fecal transplantation. In AUD, antibiotics such as minocyclin and rapamycin, that also present with anti-inflammatory properties, have shown positive neuroprotective effects and decreased alcohol intake in mice (Qin and Crews, 2012; Chen et al., 2012; Neasta et al., 2010; Agrawal et al., 2011). Studies on rats show that oats supplementation reduces gut leakiness and prevents alcohol-induced liver damage (Keshavarzian et al., 2001), while administration of probiotics such as *Lactobacillus rhamnosus* and *Bifidobacterium* seem to partially prevent gut leakiness, reduce endotoxin levels and attenuate the HPA response to stress (Ait-Belgnaoui et al., 2012; Forsyth et al., 2009). 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 (Kirpich et al., 2008). Consumption of prebiotics galacto-oligosaccharide or inulin-type fructans by healthy individuals increases the proportion of *Faecalibacterium prausnitzii* and *Bifidobacteria* (Dewulf et al., *2013*), both low in AUD patients with dysbiosis (Leclercq et al., 2014a), suggesting that that type of intervention might be fruitful in AUD patients, or at least in the subgroup that present with a dysbiosis.

7. Discussion

We have examined the general mechanisms involved in the gut-brain axis, and the impact of substances of abuse on these pathways. Most data, both preclinical and clinical, relate to alcohol use.

Generally, research supports an influence of the microbiota on gut permeability and the passage of bacterial products in the bloodstream, eliciting an inflammatory response in the periphery and in the central nervous system. Peripheral inflammation has been well demonstrated in AUD subjects, with at least part of this inflammation disputable to the microbiota. Alcohol consumption is associated with dysbiosis and increased intestinal permeability, but only in some patients, suggesting there are other factors involved, possibly even anterior to the beginning of alcohol consumption. At the central level, it is currently still unclear whether alcohol causes an actual inflammatory response in the brain, comparable to the one it causes in the liver, which involves an activation of resident macrophages, the secretion of potent inflammatory mediators and the remodeling of the extracellular matrix. Several animal studies point to an activation of microglia, but that was not confirmed in human PET-scan studies. It is more cautious for now to talk of 'neuromodulation' of the microglial system in AUD than of 'neuroinflammation'. The study of this neuromodulation and its relationship with the addiction process should be a next topic of focus, using brain structural and functional imaging.

Second, the metabolic factors. We have reviewed the role of SCFAs and tryptophan on neuroinflammation, brain function and behavior. A direct correlation between alcohol drinking and diminution of SCFAs has been established in a human study. Several studies have linked modifications of the microbiota, through the use of antibiotics or probiotic supplementation, to modifications in the kynurenin/tryptophan ratio (Cryan et al., 2019). The microbiota produces hundreds of metabolites that have not yet been studied but could play a role in brain function and maturation. Alcohol, through dysbiosis, probably influences several metabolic pathways. Studies focusing on metabolites that are specific of bacteria species frequently found in AUD dysbiosis could be interesting.

Third, the neuro-endocrine pathway. There is a demonstrated reciprocal relationship between the vagus nerve activity and the microbiota, and between the HPA axis activity and the microglia. In AUD, elevated levels of LPS are found, which can account for an activation of the HPA axis. A recent unpublished study (Leclercq, n.d.) suggests a link between microbiota composition and cortisol blood levels in both

humans and animals. Early stressful life events and alterations of the HPA axis have been shown to correlate with anxiety disorders (Faravelli et al., 2012); it would be interesting to study microbiota and HPA alterations in AUD patients with history of childhood trauma.

In contrast to the literature on alcohol, the number of studies on the use of opioids and stimulants and the microbiome remains very scarce. Preclinical studies indicate, consistently, a change in the microbiome after both acute and chronic use of these substances. Findings from these preclinical and (very scarce) human studies suggest similar effects along the pathways as described for alcohol use, i.e. immune, metabolic and neur-endocrine. However, findings are not consistent and given the limited number of studies interpretations remains difficult. The same accounts for nicotine smoking. Although already many studies highlight the effect of smoking on the microbiota in different body regions, most of these studies focus on the potential medical-somatic implications. Studies providing insight into the gut-brain effects of (chronic) smoking are still extremely rare.

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 (Hillemacher et al., 2018; Ren and Lotfipour, 2020). 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 serotonine, 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, all 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 can, without future research, not 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 (Cussotto et al., 2019). 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. Finally, 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, on 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 (Lee et al., 2018; Destoop et al., 2019; Coppens et al., 2019). However, none of the included studies in this review controlled for co-morbidity, warranting caution in the interpretation of these results.

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. Future studies need to use a translational approach, for example using fecal matter transplant between humans and animals, to determine the exact repercussions of an SUD dysbiosis on the individual.

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 pre-clinical studies, but the understanding of repercussions on the gut-brain axis and the symptomatology and behavior of SUD is still incomplete. Further human-focused studies need to examine more closely the vagus nerve as a potential pathway of communication, and the role of other circulating bacterial products, in order to develop a comprehensive view of the full impact of substances of abuse on the gut-brain axis. There is mounting evidence linking dysbiosis to other disorders such as depression (Jiang et al., 2015; Huang et al., 2016; Macedo et al., 2017), anxiety (O'Mahony et al., 2014; Foster and McVey Neufeld, 2013), autism (Ding et al., 2017; Nitschke et al., 2020) and schizophrenia (Nemani et al., 2015; Severance et al., 2012), suggesting that findings on SUD could be extrapolated for some extent to other psychiatric diseases.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abreu, M.T., Fukata, M., Arditi, M., 2005. TLR signaling in the gut in health and disease. J. Immunol. 174 (8), 4453–4460. https://doi.org/10.4049/jimmunol.174.8.4453.

Agrawal, R.G., Hewetson, A., George, C.M., Syapin, P.J., Bergeson, S.E., 2011. Minocycline reduces ethanol drinking. Brain Behav. Immun. 25 (Suppl. 1), S165–S169. https://doi.org/10.1016/j.bbi.2011.03.002.

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

Akkasheh, G., Kashani-Poor, Z., Tajabadi-Ebrahimi, M., et al., 2016. 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. 32 (3), 315–320. https://doi.org/10.1016/j.nut.2015.09.003.

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

Arrieta, M.C., Bistritz, L., Meddings, J.B., 2006. Alterations in intestinal permeability. Gut. 55 (10), 1512–1520. https://doi.org/10.1136/gut.2005.085373.

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

Bailey, M.T., Dowd, S.E., Galley, J.D., Hufnagle, A.R., Allen, R.G., Lyte, M., 2011. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. Brain Behav. Immun. 25 (3), 397–407. https://doi.org/10.1016/j.bbi.2010.10.023.

Bajaj, J.S., 2019. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol. 16 (4), 235–246. https://doi.org/10.1038/s41575-018-0099-1.

Bala, S., Marcos, M., Gattu, A., Catalano, D., Szabo, G., 2014. Acute binge drinking increases serum endotoxin and bacterial DNA levels in healthy individuals. PLoS One 9 (5), e96864. https://doi.org/10.1371/journal.pone.0096864.

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

Banks, W.A., Plotkin, S.R., Kastin, A.J., 1995. Permeability of the blood-brain barrier to soluble cytokine receptors. Neuroimmunomodulation. 2 (3), 161–165. https://doi.org/10.1159/000096887.

Bastiaanssen, T.F.S., Cowan, C.S.M., Claesson, M.J., Dinan, T.G., Cryan, J.F., 2018. Making sense of … the microbiome in psychiatry. Int. J. Neuropsychopharmacol. 22 (1), 37–52. https://doi.org/10.1093/ijnp/pyy067.

Belkaid, Y., Harrison, O.J., 2017. Homeostatic immunity and the microbiota. Immunity. 46 (4), 562–576. https://doi.org/10.1016/j.immuni.2017.04.008.
Biedermann, L., Zeitz, J., Mwinyi, J., et al., 2013. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. PLoS One 8 (3), e59260. https://doi.org/10.1371/journal.pone.0059260.
Bigatello, L.M., Broitman, S.A., Fattori, L., et al., 1987. Endotoxemia, encephalopathy, and mortality in cirrhotic patients. Am. J. Gastroenterol. 82 (1), 11–15.
Bischoff, S.C., Barbara, G., Buurman, W., et al., 2014. Intestinal permeability – a new target for disease prevention and therapy. BMC Gastroenterol. 14 (1), 1–25. https://doi.org/10.1186/s12876-014-0189-7.
Bjarnason, I., Peters, T.J., Wise, R.J., 1984. The leaky gut of alcoholism: possible route of entry for toxic compounds. Lancet Lond Engl. 1 (8370), 179–182. https://doi.org/10.1016/s0140-6736(84)92109-3.
Bjørkhaug, S.T., Aanes, H., Neupane, S.P., et al., 2019. Characterization of gut microbiota composition and functions in patients with chronic alcohol overconsumption. Gut Microbes 10 (6), 663–675. https://doi.org/10.1080/19490976.2019.1580097.
Blednov, Y.A., Benavidez, J.M., Geil, C., Perra, S., Morikawa, H., Harris, R.A., 2011. Activation of inflammatory signaling by lipopolysaccharide produces a prolonged increase of voluntary alcohol intake in mice. Brain Behav. Immun. 25 (Suppl. 1), S92–S105. https://doi.org/10.1016/j.bbi.2011.01.008.
Blednov, Y.A., Ponomarev, I., Geil, C., Bergeson, S., Koob, G.F., Harris, R.A., 2012. Neuroimmune regulation of alcohol consumption: behavioral validation of genes obtained from genomic studies. Addict. Biol. 17 (1), 108–120. https://doi.org/10.1111/j.1369-1600.2010.00284.x.
Bode, J.C., Bode, C., Heidelbach, R., Dürr, H.K., Martini, G.A., 1984. Jejunal microflora in patients with chronic alcohol abuse. Hepatogastroenterology. 31 (1), 30–34.
Bokulich, N.A., Chung, J., Battaglia, T., et al., 2016. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med. 8 (343), 343ra82. https://doi.org/10.1126/scitranslmed.aad7121.
Borovikova, L.V., Ivanova, S., Zhang, M., et al., 2000. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 405 (6785), 458–462. https://doi.org/10.1038/35013070.
Bourassa, M.W., Alim, I., Bultman, S.J., Ratan, R.R., 2016. Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health? Neurosci. Lett. 625, 56–63. https://doi.org/10.1016/j.neulet.2016.02.009.
Braniste, V., Al-Asmakh, M., Kowal, C., et al., 2014. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 6 (263), 263ra158. https://doi.org/10.1126/scitranslmed.3009759.
Bravo, J.A., Forsythe, P., Chew, M.V., et al., 2011. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc. Natl. Acad. Sci. 108 (38), 16050–16055. https://doi.org/10.1073/pnas.1102999108.
Bull-Otterson, L., Feng, W., Kirpich, I., et al., 2013. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. PLoS One 8 (1), e53028. https://doi.org/10.1371/journal.pone.0053028.
Chen, Y., Yang, F., Lu, H., et al., 2011. Characterization of fecal microbial communities in patients with liver cirrhosis. Hepatol Baltim Md. 54 (2), 562–572. https://doi.org/10.1002/hep.24423.
Chen, G., Ke, Z., Xu, M., et al., 2012. Autophagy is a protective response to ethanol neurotoxicity. Autophagy. 8 (11), 1577–1589. https://doi.org/10.4161/auto.21376.
Chinna Meyyappan, A., Forth, E., Wallace, C.J.K., Milev, R., 2020. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. BMC Psychiatry. 20 (1), 299. https://doi.org/10.1186/s12888-020-02654-5.
Chivero, E.T., Ahmad, R., Thangaraj, A., et al., 2019. Cocaine induces inflammatory gut milieu by compromising the mucosal barrier integrity and altering the gut microbiota colonization. Sci. Rep. 9 (1), 12187. https://doi.org/10.1038/s41598-019-48428-2.
Clarke, G., Grenham, S., Scully, P., et al., 2013. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Mol. Psychiatry 18 (6), 666–673. https://doi.org/10.1038/mp.2012.77.
Cooper, Z.D., Johnson, K.W., Pavlicova, M., et al., 2016. The effects of ibudilast, a glial activation inhibitor, on opioid withdrawal symptoms in opioid-dependent volunteers. Addict. Biol. 21 (4), 895–903. https://doi.org/10.1111/adb.12261.
Coppens, V., Morrens, M., Destoop, M., Dom, G., 2019. The interplay of inflammatory processes and cognition in alcohol use disorders-a systematic review. Front Psychiatry. 10, 632. https://doi.org/10.3389/fpsyt.2019.00632.
Cresci, G.A., Glueck, B., McMullen, M.R., Xin, W., Allende, D., Nagy, L.E., 2017. Prophylactic tributyrin treatment mitigates chronic-binge ethanol-induced intestinal barrier and liver injury. J. Gastroenterol. Hepatol. 32 (9), 1587–1597. https://doi.org/10.1111/jgh.13731.
Crews, F.T., Bechara, R., Brown, L.A., et al., 2006. Cytokines and alcohol. Alcohol. Clin. Exp. Res. 30 (4), 720–730. https://doi.org/10.1111/j.1530-0277.2006.00084.x.
Crews, F.T., Walter, T.J., Coleman, L.G., Vetreno, R.P., 2017. Toll-like receptor signaling and stages of addiction. Psychopharmacology 234 (9–10), 1483–1498. https://doi.org/10.1007/s00213-017-4560-6.
Cryan, J.F., O'Riordan, K.J., Cowan, C.S.M., et al., 2019. The microbiota-gut-brain Axis. Physiol. Rev. 99 (4), 1877–2013. https://doi.org/10.1152/physrev.00018.2018.
Cussotto, S., Clarke, G., Dinan, T.G., Cryan, J.F., 2019. Psychotropics and the Microbiome: a Chamber of Secrets. Psychopharmacology (Berl). 236 (5), 1411–1432. https://doi.org/10.1007/s00213-019-5185-8.
Davenport, E.R., Sanders, J.G., Song, S.J., Amato, K.R., Clark, A.G., Knight, R., 2017. The human microbiome in evolution. BMC Biol. 15. https://doi.org/10.1186/s12915-017-0454-7.
De Palma, G., Blennerhassett, P., Lu, J., et al., 2015. Microbiota and host determinants of behavioural phenotype in maternally separated mice. Nat. Commun. 6, 7735. https://doi.org/10.1038/ncomms8735.
Destoop, M., Morrens, M., Coppens, V., Dom, G., 2019. Addiction, anhedonia, and comorbid mood disorder. A Narrative Review. Front Psychiatry. 10, 311. https://doi.org/10.3389/fpsyt.2019.00311.
Dewulf, E.M., Cani, P.D., Claus, S.P., et al., 2013. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 62 (8), 1112–1121. https://doi.org/10.1136/gutjnl-2012-303304.
Diaz Heijtz, R., Wang, S., Anuar, F., et al., 2011. Normal gut microbiota modulates brain development and behavior. Proc. Natl. Acad. Sci. U. S. A. 108 (7), 3047–3052. https://doi.org/10.1073/pnas.1010529108.
Ding, H.T., Taur, Y., Walkup, J.T., 2017. Gut microbiota and autism: key concepts and findings. J. Autism Dev. Disord. 47 (2), 480–489. https://doi.org/10.1007/s10803-016-2960-9.
Dominguez-Bello, M.G., Costello, E.K., Contreras, M., et al., 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. U. S. A. 107 (26), 11971–11975. https://doi.org/10.1073/pnas.1002601107.
Dowlati, Y., Herrmann, N., Swardfager, W., et al., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67 (5), 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033.
Dubinkina, V.B., Tyakht, A.V., Odintsova, V.Y., et al., 2017. Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease. Microbiome. 5 (1), 141. https://doi.org/10.1186/s40168-017-0359-2.
Eeckhaut, V., Machiels, K., Perrier, C., et al., 2013. Butyricicoccus pullicaecorum in inflammatory bowel disease. Gut. 62 (12), 1745–1752. https://doi.org/10.1136/gutjnl-2012-303611.
Elamin, E., Jonkers, D., Juuti-Uusitalo, K., et al., 2012. Effects of Ethanol and Acetaldehyde on Tight Junction Integrity: In Vitro Study in a Three Dimensional Intestinal Epithelial Cell Culture Model. PLoS ONE. 7 (4). https://doi.org/10.1371/journal.pone.0035008.
Elamin, E.E., Masclee, A.A., Dekker, J., Pieters, H.-J., Jonkers, D.M., 2013. Short-chain fatty acids activate AMP-activated protein kinase and ameliorate ethanol-induced intestinal barrier dysfunction in Caco-2 cell monolayers. J. Nutr. 143 (12), 1872–1881. https://doi.org/10.3945/jn.113.179549.
Erny, D., 2015. Hrabě de Angelis AL, Jaitin D, et al. host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18 (7), 965–977. https://doi.org/10.1038/nn.4030.
Faravelli, C., Lo Sauro, C., Godini, L., et al., 2012. Childhood stressful events, HPA axis and anxiety disorders. World J Psychiatry. 2 (1), 13–25. https://doi.org/10.5498/wjp.v2.i1.13.
Fernandez-Lizarbe, S., Pascual, M., Guerri, C., 2009. Critical role of TLR4 response in the activation of microglia induced by ethanol. J Immunol Baltim Md 1950 183 (7), 4733–4744. https://doi.org/10.4049/jimmunol.0803590.
Fooks, L.J., Gibson, G.R., 2002. Probiotics as modulators of the gut flora. Br. J. Nutr. 88 (Suppl. 1), S39–S49. https://doi.org/10.1079/BJN2002628.
Forsyth, C.B., Farhadi, A., Jakate, S.M., Tang, Y., Shaikh, M., Keshavarzian, A., 2009. Lactobacillus GG treatment ameliorates alcohol-induced intestinal oxidative stress, gut leakiness, and liver injury in a rat model of alcoholic steatohepatitis. Alcohol Fayettev N. 43 (2), 163–172. https://doi.org/10.1016/j.alcohol.2008.12.009.
Forsythe, P., Bienenstock, J., Kunze, W.A., 2014. Vagal pathways for microbiome-brain-gut axis communication. Adv. Exp. Med. Biol. 817, 115–133. https://doi.org/10.1007/978-1-4939-0897-4_5.
Foster, J.A., McVey Neufeld, K.-A., 2013. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 36 (5), 305–312. https://doi.org/10.1016/j.tins.2013.01.005.
Franchi, S., Moschetti, G., Amodeo, G., Sacerdote, P., 2019. Do all opioid drugs share the same immunomodulatory properties? A Review From Animal and Human Studies. Front Immunol. 10, 2914. https://doi.org/10.3389/fimmu.2019.02914.
Frank, M.G., Baratta, M.V., Sprunger, D.B., Watkins, L.R., Maier, S.F., 2007. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. Brain Behav. Immun. 21 (1), 47–59. https://doi.org/10.1016/j.bbi.2006.03.005.
Freeman, K., Brureau, A., Vadigepalli, R., et al., 2012. Temporal changes in innate immune signals in a rat model of alcohol withdrawal in emotional and cardiorespiratory homeostatic nuclei. J. Neuroinflammation 9, 97. https://doi.org/10.1186/1742-2094-9-97.
Freeman, K., Staehle, M.M., Vadigepalli, R., et al., 2013. Coordinated dynamic gene expression changes in the central nucleus of the amygdala during alcohol withdrawal. Alcohol. Clin. Exp. Res. 37 (Suppl. 1), E88–100. https://doi.org/10.1111/j.1530-0277.2012.01910.x.
Frost, G., Sleeth, M.L., Sahuri-Arisoylu, M., et al., 2014. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat. Commun. 5 (1), 3611. https://doi.org/10.1038/ncomms4611.
Kaur, G., Begum, R., Thota, S., et al., 2019. A systematic review of smoking-related epigenetic alterations. Arch. Toxicol. 93, 2715–2740. https://doi.org/10.1007/s00204-019-02562-y.
Gacias, M., Gaspari, S., Santos, P.-M.G., et al., 2016. Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. eLife. 5. https://doi.org/10.7554/eLife.13442.
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. 5 (12), 987–1012. https://doi.org/10.1016/S2215-0366(18)30337-7.
Goehler, L.E., Gaykema, R.P.A., Opitz, N., Reddaway, R., Badr, N., Lyte, M., 2005. Activation in vagal afferents and central autonomic pathways: early responses to intestinal infection with campylobacter jejuni. Brain Behav. Immun. 19 (4), 334–344.

https://doi.org/10.1016/j.bbi.2004.09.002.
Haber, P.S., Kortt, N.C., 2020. Alcohol use disorder and the gut. Addict Abingdon Engl. 8https://doi.org/10.1111/add.15147. Published online June.
Han, W., Tellez, L.A., Perkins, M.H., et al., 2018. A Neural Circuit for Gut-Induced Reward. Cell 175 (3). https://doi.org/10.1016/j.cell.2018.08.049. 665-678.e23.
Hannestad, J., Gallezot, J.-D., Schafbauer, T., et al., 2012. Endotoxin-induced systemic inflammation activates microglia: [^{11}C]PBR28 positron emission tomography in nonhuman primates. NeuroImage. 63 (1), 232–239. https://doi.org/10.1016/j.neuroimage.2012.06.055.
Hayes, C.L., Peters, B.J., Foster, J.A., 2020. Microbes and mental health: Can the microbiome help explain clinical heterogeneity in psychiatry? Front Neuroendocrinol. 100849. https://doi.org/10.1016/j.yfrne.2020.100849. Published online June 1.
He, J., Crews, F.T., 2008. Increased MCP-1 and microglia in various regions of the human alcoholic brain. Exp. Neurol. 210 (2), 349–358. https://doi.org/10.1016/j.expneurol.2007.11.017.
Hillemacher, T., Bachmann, O., Kahl, K.G., Frieling, H., 2018. Alcohol, microbiome, and their effect on psychiatric disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 85, 105–115. https://doi.org/10.1016/j.pnpbp.2018.04.015.
Hillmer, A.T., Sandiego, C.M., Hannestad, J., et al., 2017. In vivo imaging of translocator protein, a marker of activated microglia, in alcohol dependence. Mol. Psychiatry 22 (12), 1759–1766. https://doi.org/10.1038/mp.2017.10.
Hoban, A.E., Stilling, R.M., Ryan, F.J., et al., 2016. Regulation of prefrontal cortex myelination by the microbiota. Transl. Psychiatry 6 (4), e774. https://doi.org/10.1038/tp.2016.42.
Hofford, R.S., Russo, S.J., Kiraly, D.D., 2019. Neuroimmune mechanisms of psychostimulant and opioid use disorders. Eur. J. Neurosci. 50 (3), 2562–2573. https://doi.org/10.1111/ejn.14143.
Huang, C., Shi, G., 2019. Smoking and microbiome in oral, airway, gut and some systemic diseases. J. Transl. Med. 17 (1), 225. https://doi.org/10.1186/s12967-019-1971-7.
Huang, R., Wang, K., Hu, J., 2016. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 8 (8). https://doi.org/10.3390/nu8080483.
Jandhyala, S.M., Talukdar, R., Subramanyam, C., Vuyyuru, H., Sasikala, M., Nageshwar, Reddy D., 2015. Role of the normal gut microbiota. World J. Gastroenterol. 21 (29), 8787–8803. https://doi.org/10.3748/wjg.v21.i29.8787.
Jenkins, T.A., Nguyen, J.C.D., Polglaze, K.E., Bertrand, P.P., 2016. Influence of Tryptophan and Serotonin on Mood and Cognition with a Possible Role of the Gut-Brain Axis. Nutrients 8 (1). https://doi.org/10.3390/nu8010056.
Jiang, H., Ling, Z., Zhang, Y., et al., 2015. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav. Immun. 48, 186–194. https://doi.org/10.1016/j.bbi.2015.03.016.
Kalk, N.J., Guo, Q., Owen, D., et al., 2017. Decreased hippocampal translocator protein (18 kDa) expression in alcohol dependence: a [11C]PBR28 PET study. Transl. Psychiatry 7 (1), e996. https://doi.org/10.1038/tp.2016.264.
Kane, C.J.M., Phelan, K.D., Douglas, J.C., et al., 2014. Effects of ethanol on immune response in the brain: region-specific changes in adolescent versus adult mice. Alcohol. Clin. Exp. Res. 38 (2), 384–391. https://doi.org/10.1111/acer.12244.
Kang, L., Sebastian, B.M., Pritchard, M.T., Pratt, B.T., Previs, S.F., Nagy, L.E., 2007. Chronic ethanol-induced insulin resistance is associated with macrophage infiltration into adipose tissue and altered expression of adipocytokines. Alcohol. Clin. Exp. Res. 31 (9), 1581–1588. https://doi.org/10.1111/j.1530-0277.2007.00452.x.
Kang, M., Mischel, R.A., Bhave, S., et al., 2017. The effect of gut microbiome on tolerance to morphine mediated antinociception in mice. Sci. Rep. 7, 42658. https://doi.org/10.1038/srep42658.
Karl, J.P., Margolis, L.M., Madslien, E.H., et al., 2017. Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress. Am. J. Physiol. Gastrointest. Liver Physiol. 312 (6), G559–G571. https://doi.org/10.1152/ajpgi.00066.2017.
Keshavarzian, A., Choudhary, S., Holmes, E.W., et al., 2001. Preventing gut leakiness by oats supplementation ameliorates alcohol-induced liver damage in rats. J. Pharmacol. Exp. Ther. 299 (2), 442–448.
Kim, S.W., Wiers, C.E., Tyler, R., et al., 2018. Influence of alcoholism and cholesterol on TSPO binding in brain: PET [11C]PBR28 studies in humans and rodents. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 43 (9), 1832–1839. https://doi.org/10.1038/s41386-018-0085-x.
Kiraly, D.D., Walker, D.M., Calipari, E.S., et al., 2016. Alterations of the host microbiome affect behavioral responses to cocaine. Sci. Rep. 6, 35455. https://doi.org/10.1038/srep35455.
Kirpich, I.A., Solovieva, N.V., Leikhter, S.N., et al., 2008. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. Alcohol Fayettev N. 42 (8), 675–682. https://doi.org/10.1016/j.alcohol.2008.08.006.
Kmieć, Z., 2001. Cooperation of liver cells in health and disease. *Adv Anat Embryol Cell Biol.* (161), 1–151. https://doi.org/10.1007/978-3-642-56553-3.
Koob, G.F., 2015. The dark side of emotion: the addiction perspective. Eur. J. Pharmacol. 753, 73–87. https://doi.org/10.1016/j.ejphar.2014.11.044.
Leclercq S. Unpublished.
Leclercq, S., Cani, P.D., Neyrinck, A.M., et al., 2012. Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. Brain Behav. Immun. 26 (6), 911–918. https://doi.org/10.1016/j.bbi.2012.04.001.
Leclercq, S., Matamoros, S., Cani, P.D., et al., 2014a. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc. Natl. Acad. Sci. U. S. A. 111 (42), E4485–E4493. https://doi.org/10.1073/pnas.1415174111.
Leclercq, S., De Saeger, C., Delzenne, N., de Timary, P., Stärkel, P., 2014b. Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. Biol. Psychiatry 76 (9), 725–733. https://doi.org/10.1016/j.biopsych.2014.02.003.
Lee, K., Vuong, H.E., Nusbaum, D.J., Hsiao, E.Y., Evans, C.J., Taylor, A.M.W., 2018. The gut microbiota mediates reward and sensory responses associated with regimen-selective morphine dependence. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 43 (13), 2606–2614. https://doi.org/10.1038/s41386-018-0211-9.
Leonard, B., Maes, M., 2012. 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. 36 (2), 764–785. https://doi.org/10.1016/j.neubiorev.2011.12.005.
Levin, A.M., Sitarik, A.R., Havstad, S.L., et al., 2016. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity. Sci. Rep. 6, 31775. https://doi.org/10.1038/srep31775.
Ling, X., Linglong, P., Weixia, D., Hong, W., 2016. 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 11 (8), e0161635. https://doi.org/10.1371/journal.pone.0161635.
Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature. 489 (7415), 220–230. https://doi.org/10.1038/nature11550.
Lu, J., Synowiec, S., Lu, L., et al., 2018. Microbiota influence the development of the brain and behaviors in C57BL/6J mice. PLoS ONE 13 (8). https://doi.org/10.1371/journal.pone.0201829.
Luczynski, P., Whelan, S.O., O'Sullivan, C., et al., 2016. Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. Eur. J. Neurosci. 44 (9), 2654–2666. https://doi.org/10.1111/ejn.13291.
Macedo, D., Filho, A.J.M.C., Soares de Sousa, C.N., et al., 2017. Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. J. Affect. Disord. 208, 22–32. https://doi.org/10.1016/j.jad.2016.09.012.
Maes, M., 1995. Evidence for an immune response in major depression: a review and hypothesis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 19 (1), 11–38. https://doi.org/10.1016/0278-5846(94)00101-m.
Maes, M., Berk, M., Goehler, L., et al., 2012. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med. 10, 66. https://doi.org/10.1186/1741-7015-10-66.
Mayer, E.A., 2011. Gut feelings: the emerging biology of gut-brain communication. Nat. Rev. Neurosci. 12 (8), 453–466. https://doi.org/10.1038/nrn3071.
Meckel, K.R., Kiraly, D.D., 2019. A potential role for the gut microbiome in substance use disorders. Psychopharmacology 236 (5), 1513–1530. https://doi.org/10.1007/s00213-019-05232-0.
Meng, J., Yu, H., Ma, J., et al., 2013. Morphine induces bacterial translocation in mice by compromising intestinal barrier function in a TLR-dependent manner. PLoS One 8 (1), e54040. https://doi.org/10.1371/journal.pone.0054040.
Metz, V.E., Jones, J.D., Manubay, J., et al., 2017. 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. 42 (9), 1825–1832. https://doi.org/10.1038/npp.2017.70.
Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65 (9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029.
Mittal, R., Debs, L.H., Patel, A.P., et al., 2017. Neurotransmitters: the critical modulators regulating gut-brain Axis. J. Cell. Physiol. 232 (9), 2359–2372. https://doi.org/10.1002/jcp.25518.
Monroe, P., Vlahcevic, Z.R., Swell, L., 1981. Effects of acute and chronic ethanol intake on bile acid metabolism. Alcohol. Clin. Exp. Res. 5 (1), 92–100. https://doi.org/10.1111/j.1530-0277.1981.tb04871.x.
Montesinos, J., Pascual, M., Rodríguez-Arias, M., Miñarro, J., Guerri, C., 2016. Involvement of TLR4 in the long-term epigenetic changes, rewarding and anxiety effects induced by intermittent ethanol treatment in adolescence. Brain Behav. Immun. 53, 159–171. https://doi.org/10.1016/j.bbi.2015.12.006.
Mulligan, M.K., Ponomarev, I., Hitzemann, R.J., et al., 2006. Toward understanding the genetics of alcohol drinking through transcriptome meta-analysis. Proc. Natl. Acad. Sci. U. S. A. 103 (16), 6368–6373. https://doi.org/10.1073/pnas.0510188103.
Mutlu, E., Keshavarzian, A., Engen, P., Forsyth, C.B., Sikaroodi, M., Gillevet, P., 2009. Intestinal dysbiosis: a possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. Alcohol. Clin. Exp. Res. 33 (10), 1836–1846. https://doi.org/10.1111/j.1530-0277.2009.01022.x.
Mutlu, E.A., Gillevet, P.M., Rangwala, H., et al., 2012. Colonic microbiome is altered in alcoholism. Am J Physiol-Gastrointest Liver Physiol. 302 (9), G966–G978. https://doi.org/10.1152/ajpgi.00380.2011.
Nanji, A.A., Khettry, U., Sadrzadeh, S.M., Yamanaka, T., 1993. Severity of liver injury in experimental alcoholic liver disease. Correlation with plasma endotoxin, prostaglandin E2, leukotriene B4, and thromboxane B2. Am. J. Pathol. 142 (2), 367–373.
Neasta, J., Ben Hamida, S., Yowell, Q., Carnicella, S., Ron, D., 2010. Role for mammalian target of rapamycin complex 1 signaling in neuroadaptations underlying alcohol-related disorders. Proc. Natl. Acad. Sci. U. S. A. 107 (46), 20093–20098. https://doi.org/10.1073/pnas.1005554107.
Nemani, K., Hosseini Ghomi, R., McCormick, B., Fan, X., 2015. Schizophrenia and the gut-brain axis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 56, 155–160. https://doi.org/10.1016/j.pnpbp.2014.08.018.
Ng, Q.X., Loke, W., Venkatanarayanan, N., Lim, D.Y., Soh, A.Y.S., Yeo, W.S., 2019. A Systematic Review of the Role of Prebiotics and Probiotics in Autism Spectrum Disorders. Medicina (Mex). 55 (5). https://doi.org/10.3390/medicina55050129.

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

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

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

O'Mahony, S.M., Felice, V.D., Nally, K., et al., 2014. 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. 277, 885–901. https://doi.org/10.1016/j.neuroscience.2014.07.054.

Osterndorff-Kahanek, E.A., Becker, H.C., Lopez, M.F., et al., 2015. Chronic ethanol exposure produces time- and brain region-dependent changes in gene coexpression networks. PLoS One 10 (3), e0121522. https://doi.org/10.1371/journal.pone.0121522.

Papoutsopoulou, S., Satsangi, J., Campbell, B.J., Probert, C.S., 2020. Review article: impact of cigarette smoking on intestinal inflammation-direct and indirect mechanisms. Aliment. Pharmacol. Ther. 51 (12), 1268–1285. https://doi.org/10.1111/apt.15774.

Pascual, M., Baliño, P., Alfonso-Loeches, S., Aragón, C.M.G., Guerri, C., 2011. Impact of TLR4 on behavioral and cognitive dysfunctions associated with alcohol-induced neuroinflammatory damage. Brain Behav. Immun. 25 (Suppl. 1), S80–S91. https://doi.org/10.1016/j.bbi.2011.02.012.

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

Perez-Burgos, A., Wang, B., Mao, Y.-K., et al., 2013. Psychoactive bacteria Lactobacillus rhamnosus (JB-1) elicits rapid frequency facilitation in vagal afferents. Am. J. Physiol. Gastrointest. Liver Physiol. 304 (2), G211–G220. https://doi.org/10.1152/ajpgi.00128.2012.

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

Qin, L., Crews, F.T., 2012. Chronic ethanol increases systemic TLR3 agonist-induced neuroinflammation and neurodegeneration. J. Neuroinflammation 9 (1), 130. https://doi.org/10.1186/1742-2094-9-130.

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

Rea, K., Dinan, T.G., Cryan, J.F., 2016. The microbiome: a key regulator of stress and neuroinflammation. Neurobiol Stress. 4, 23–33. https://doi.org/10.1016/j.ynstr.2016.03.001.

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

Robinson, G., Most, D., Ferguson, L.B., Mayfield, J., Harris, R.A., Blednov, Y.A., 2014. Neuroimmune pathways in alcohol consumption: evidence from behavioral and genetic studies in rodents and humans. Int. Rev. Neurobiol. 118, 13–39. https://doi.org/10.1016/B978-0-12-801284-0.00002-6.

Rooks, M.G., Garrett, W.S., 2016. Gut microbiota, metabolites and host immunity. Nat Rev Immunol. 16 (6), 341–352. https://doi.org/10.1038/nri.2016.42.

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

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

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

Ryan, P.M., Delzenne, N.M., 2016. Chapter 18 - Gut Microbiota and Metabolism. In: Hyland, N., Stanton, C. (Eds.), The Gut-Brain Axis. Academic Press, pp. 391–401. https://doi.org/10.1016/B978-0-12-802304-4.00018-9.

Salter, M.W., Stevens, B., 2017. Microglia emerge as central players in brain disease. Nat. Med. 23 (9), 1018–1027. https://doi.org/10.1038/nm.4397.

Samuel, B.S., Shaito, A., Motoike, T., et al., 2008. 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. 105 (43), 16767–16772. https://doi.org/10.1073/pnas.0808567105.

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

Scorza, C., Piccini, C., Martínez Busi, M., Abin Carriquiry, J.A., Zunino, P., 2019. Alterations in the gut microbiota of rats chronically exposed to volatilized cocaine and its active adulterants caffeine and phenacetin. Neurotox. Res. 35 (1), 111–121. https://doi.org/10.1007/s12640-018-9936-9.

Severance, E.G., Alaedini, A., Yang, S., et al., 2012. Gastrointestinal inflammation and associated immune activation in schizophrenia. Schizophr. Res. 138 (1), 48–53. https://doi.org/10.1016/j.schres.2012.02.025.

Shaikh, M., Rajan, K., Forsyth, C.B., Voigt, R.M., Keshavarzian, A., 2015. 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. 442, 24–32. https://doi.org/10.1016/j.cca.2014.12.040.

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

Shreiner, A.B., Kao, J.Y., Young, V.B., 2015. The gut microbiome in health and in disease. Curr. Opin. Gastroenterol. 31 (1), 69–75. https://doi.org/10.1097/MOG.0000000000000139.

Sierra, A., Gottfried-Blackmore, A., Milner, T.A., McEwen, B.S., Bulloch, K., 2008. Steroid hormone receptor expression and function in microglia. Glia. 56 (6), 659–674. https://doi.org/10.1002/glia.20644.

Skinner, R.A., Gibson, R.M., Rothwell, N.J., Pinteaux, E., Penny, J.I., 2009. Transport of interleukin-1 across cerebromicrovascular endothelial cells. Br. J. Pharmacol. 156 (7), 1115–1123. https://doi.org/10.1111/j.1476-5381.2008.00129.x.

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:https://doi.org/10.3390/nu10121939.

Sofroniew, M.V., 2014. Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neurosci Rev J Bringing Neurobiol Neurol Psychiatry. 20 (2), 160–172. https://doi.org/10.1177/1073858413504466.

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

Somerville, K.W., Logan, R.F., Edmond, M., Langman, M.J., 1984. Smoking and Crohn's disease. Br Med J Clin Res Ed. 289 (6450), 954–956. https://doi.org/10.1136/bmj.289.6450.954.

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

Stilling, R.M., van de Wouw, M., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2016. The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochem. Int. 99, 110–132. https://doi.org/10.1016/j.neuint.2016.06.011.

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

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

Swanson, G.R., Siskin, J., Gorenz, A., et al., 2020. 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. https://doi.org/10.1016/j.trsl.2020.04.004. Published online May 3.

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

Tasnim, N., Abulizi, N., Pither, J., Hart, M.M., Gibson, D.L., 2017. Linking the gut microbial ecosystem with the environment: does gut health depend on where we live? Front. Microbiol. 8. https://doi.org/10.3389/fmicb.2017.01935.

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

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

Vetreno, R.P., Crews, F.T., 2012. Adolescent binge drinking increases expression of the danger signal receptor agonist HMGB1 and toll-like receptors in the adult prefrontal cortex. Neuroscience. 226, 475–488. https://doi.org/10.1016/j.neuroscience.2012.08.046.

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:https://doi.org/10.1111/adb.12869.

Vijay, N., Morris, M.E., 2014. Role of monocarboxylate transporters in drug delivery to the brain. Curr. Pharm. Des. 20 (10), 1487–1498. https://doi.org/10.2174/13816128113199990462.

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

Volkow, N.D., Boyle, M., 2018. Neuroscience of addiction: relevance to prevention and treatment. Am. J. Psychiatry 175 (8), 729–740. https://doi.org/10.1176/appi.ajp.2018.17101174.

Volkow, N.D., Jones, E.B., Einstein, E.B., Wargo, E.M., 2019. Prevention and treatment of opioid misuse and addiction: a review. JAMA Psychiatry. 76 (2), 208–216. https://doi.org/10.1001/jamapsychiatry.2018.3126.

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

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

Wang, X., Loram, L.C., Ramos, K., et al., 2012. Morphine activates neuroinflammation in a manner parallel to endotoxin. Proc. Natl. Acad. Sci. U. S. A. 109 (16), 6325–6330. https://doi.org/10.1073/pnas.1200130109.

Wang, F., Meng, J., Zhang, L., Johnson, T., Chen, C., Roy, S., 2018. Morphine induces

changes in the gut microbiome and metabolome in a morphine dependence model. Sci. Rep. 8 (1), 3596. https://doi.org/10.1038/s41598-018-21915-8.

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

Wohleb, E.S., McKim, D.B., Sheridan, J.F., Godbout, J.P., 2014. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. Front. Neurosci. 8, 447. https://doi.org/10.3389/fnins.2014.00447.

Yan, A.W., Fouts, D.E., Brandl, J., et al., 2011. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. Hepatol Baltim Md. 53 (1), 96–105. https://doi.org/10.1002/hep.24018.

Yano, J.M., Yu, K., Donaldson, G.P., et al., 2015. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 161 (2), 264–276. https://doi.org/10.1016/j.cell.2015.02.047.

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

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

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

Zou, J.Y., Crews, F.T., 2014. Release of neuronal HMGB1 by ethanol through decreased HDAC activity activates brain neuroimmune signaling. PLoS One 9 (2), e87915. https://doi.org/10.1371/journal.pone.0087915.