DOI:
10.1016/j.jhep.2021.11.008

Document Version
Peer reviewed version

Title page

Title: Gut-derived systemic inflammation as a driver of depression in chronic liver disease

Authors: Victoria T. Kronsten[1], Thomas H. Tranah[1], Carmine Pariante[2], Debbie L. Shawcross[1]

Affiliations:

1. Institute of Liver Studies, 1st Floor James Black Centre, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, 125 Coldharbour Lane, London, UK, SE5 9NU

2. Institute of Psychiatry, Psychology and Neuroscience, King's College London,
The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London, SE5 9RT
London, UK, SE5 8AF

Corresponding author:

Victoria Tatiana Kronsten

Institute of Liver Studies, 1st Floor James Black Centre, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, 125 Coldharbour Lane, London, UK, SE5 9NU

victoria.kronsten@nhs.net

Keywords:

Depression; cirrhosis; systemic inflammation; gut dysbiosis; gut-liver-brain axis

Electronic word count: 5253 words**; Abstract:** 256 words.

Number of figures: 2

Number of tables: 3

Conflict of interest statement:

CP is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. CP has received research funding from Johnson & Johnson as part of a research programme on depression and inflammation, and from the Medical Research Council (UK) and the Wellcome Trust for research on depression and inflammation as part of two large consortia that also include Johnson & Johnson, GSK and Lundbeck; however, the present paper is independent from this funding. DLS has participated in advisory boards for Norgine Pharmaceuticals Ltd, EnteroBiotix, Kaleido Biosciences, Mallinckrodt and Shionogi and has delivered paid lectures for Norgine Pharmaceuticals Ltd, Falk Pharma and Alfa Sigma. THT and DLS have also received funding for an investigator-initiated study (EMITTIC Study) from Norgine Pharmaceuticals Ltd. THT has also received funding from the Medical Research Council (MRC). VTK has no COI to declare.

Financial support statement:

No funding was received for the preparation of this manuscript.

Author's contribution:

VTK drafted the manuscript. THT designed the figures. The manuscript was then revised extensively by THT, CP and DLS. All authors approved the final manuscript prior to submission.

Abstract:

Depression and chronic liver disease (CLD) are important causes of disability, morbidity and mortality worldwide and their prevalence continues to rise. The rate of depression in CLD is high compared to that of the general population and is comparable to the increased rates observed in other medical comorbidities and chronic inflammatory conditions. Notably, a comorbid diagnosis of depression has a detrimental effect on outcomes in cirrhosis.

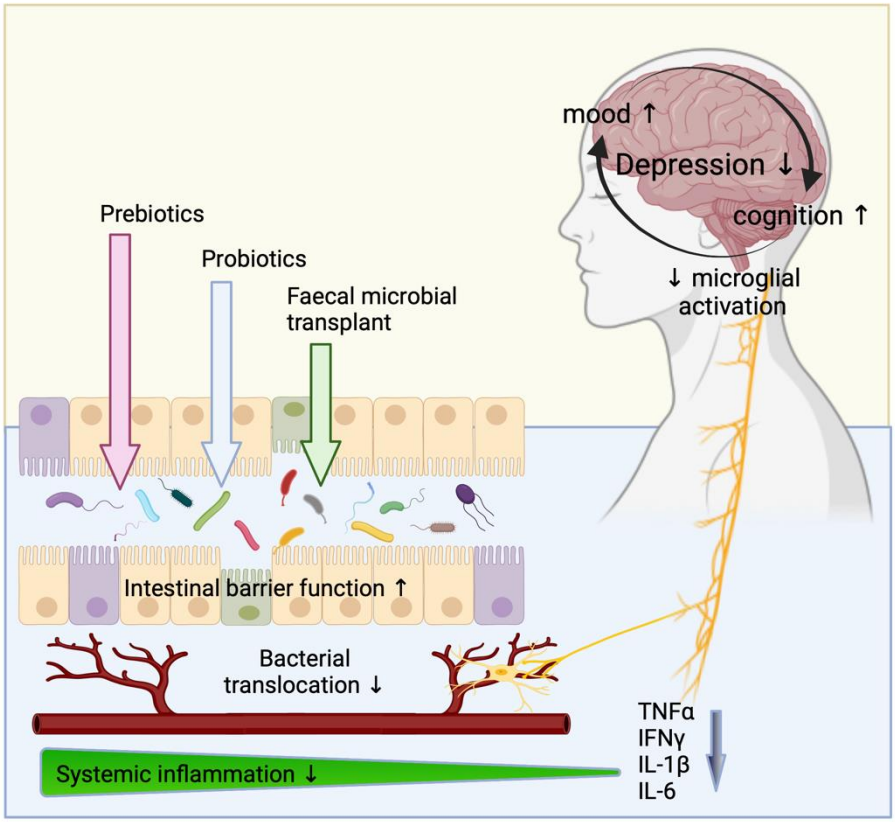
Systemic inflammation is pivotal in cirrhosis-associated immune dysfunction – a phenomenon present in advanced CLD (cirrhosis) and implicated in the development of complications, organ failure, disease progression, increased infection rates and poor outcome. The presence of systemic inflammation is also well documented in a cohort of depressed patients; peripheral cytokine signals can result in neuroinflammation, behavioural change and depressive symptoms via neural mechanisms, cerebral endothelial cell and circumventricular organ signaling, and peripheral immune cell-to-brain signaling. Gut dysbiosis has been observed in both depressed and cirrhotic patients. It leads to intestinal barrier dysfunction resulting in increased bacterial translocation, in turn activating circulating immune cells, leading to cytokine production and systemic inflammation. A perturbed gut-liver-brain axis may therefore explain the high rates of depression in patients with cirrhosis.

The underlying mechanisms explaining the critical relationship between depression and cirrhosis remain to be fully elucidated. Several other psychosocial and biological factors are likely to be involved, and therefore the cause is probably multifactorial. However, the role of the dysfunctional gut-liver-brain axis as a driver of gut-derived systemic inflammation requires further exploration and consideration as a target for therapy for depression in patients with cirrhosis.

KEY POINTS

- The prevalence of depression is high in cirrhosis and depression has an adverse impact on outcome and quality of life.
- Gut dysbiosis causes increased intestinal permeability and bacterial translocation.
- Gut dysbiosis and systemic inflammation are present in cirrhosis and depression.
- Gut-derived TNF-α, IL-1β and IL-6 can influence the brain resulting in depression.
- Favourably modifying the gut microbiome may decrease inflammation and depression in cirrhosis.

Graphical abstract (Figure 2)



1. Introduction

Depression is a principal cause of disability worldwide, affecting 350 million people annually, and frequently co-exists with chronic medical conditions.[1] Common symptoms include anhedonia, low mood, cognitive impairment and anxiety.[2]

Depression is diagnosed using the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria[3], which relies on the identification of a number of key symptoms, assessed via the Structured Clinical Interview for DSM-5 (SCID)[4], an objective psychiatric assessment. Depression screen questionnaires are helpful to detect and assess severity, and are commonly used in research studies, due to the time-consuming nature of structured interviews. Recommended tools include the Hospital Anxiety and Depression scale (HADS)[5] and Beck Depression Inventory second edition (BDI-II).[6] Functional neuroimaging studies have found that, in general, the amygdala and subgenual anterior cingulate have increased activity, but the insula and dorsal lateral prefrontal cortex are hypoactive, in patients with depression.[7,8] However, changes seen on functional neuroimaging are not consistent, and relate to a highly variable clinical presentation and are therefore not routinely used in clinical practice.[9,10]

Whilst the pathophysiology of depression remains to be fully elucidated, inflammation appears to be a key driver in its development.[11] A subgroup of patients with depression exhibit systemic inflammation. Increased levels of plasma pro-inflammatory cytokines and their receptors (including tumour necrosis alpha (TNF-α), interleukin (IL)-1β and IL-6), chemokines and acute phase reactants (such as C-reactive protein (CRP)) have been detected in the plasma of depressed patients.[12,13] Central (brain) inflammation has also been demonstrated; neuroinflammation, including microglial activation, has been found in the brains of depressed patients post-mortem,[14,15] and increased levels of pro-inflammatory cytokines (including TNF-

α and IL-6) have been detected in the cerebrospinal fluid (CSF) of patients with depression.[14]

Chronic liver disease (CLD) continues to rise globally with cirrhosis and the complications of viral hepatitis accounting for 2 million deaths per year, 3.5% of global mortality.[16] Cirrhosis is the pathological end-stage of CLD that leads to portal hypertension and liver failure, and an increased risk of developing hepatocellular carcinoma (HCC).[17]

Depression is more prevalent in patients with cirrhosis than the general population, and has an adverse impact on clinical outcomes.[18] Depression is therefore important to screen for in cirrhotic patients, and the underlying cause for its increased prevalence in cirrhosis needs to be determined to improve quality of life and outcomes in this large patient population.

2. The prevalence of depression in chronic liver disease and its effect on outcome

2.1 Depression and cirrhosis

Studies have emphasised the higher prevalence of depression in cirrhotic patients (18 – 58%)[18–21], compared to the general population (10%).[22] For comparison, studies have revealed 20% prevalence of depression in chronic kidney disease (CKD)[23], 22-57%, 33-50%, 1.5-46% and 11-44% prevalence in patients with oropharyngeal, pancreatic, breast and lung cancer, respectively[24], 17.6% prevalence in patients with Type 2 diabetes mellitus[25] and 21.5% prevalence in patients with heart failure.[26] CLD patients with an earlier fibrotic stage, and not yet cirrhosis, also have a higher rate of depression.[27] Whilst some studies have suggested that depression is associated with severity of liver disease[19,28,29], others have not reported this relationship.[30–32]

Depression in cirrhosis is an independent predictor of mortality, and a principal determinant of reduced health related quality of life (HRQoL), sleep disruption, increased fatigue and hospital readmission.[21,33] Depressed cirrhotic patients have worse health outcomes compared to matched patients without depression; Singh et al (1997) found that patients with depression and decompensated cirrhosis of different aetiologies undergoing liver transplant assessment had an increased mortality at 100 days compared to non-depressed patients, despite comparable incidence of specific features of decompensation and liver disease severity scores (Child Pugh).[32] A diagnosis of depression pre-liver transplant is also associated with decreased survival post-transplant.[33]

2.2 Depression and non-alcoholic fatty liver disease

The association between non-alcoholic fatty liver disease (NAFLD) and depression is well documented; several studies have reported increased prevalence of depression in NAFLD patients.[30,34,35] (**Table 1.**) Whilst the increased prevalence of depression in metabolic disorders, especially diabetes[36], is well recognised, these studies importantly controlled for these confounders.

Some studies have found that a diagnosis of depression correlates with NAFLD severity (based on histology)[28,29] and response to therapy.[28] (**Table 1.**) Conversely, Kim et al (2019) found that, whilst the prevalence of depression was higher in subjects with NAFLD (based on non-invasive indices) than those without, there was no difference in prevalence of depression between those with high probability of advanced fibrosis compared to those with low or intermediate risk. However, the assessment of NAFLD-related advanced fibrosis was assessed using a non-invasive index (Fibrosis-4 score) rather than histologically.[30]

Table 1.

2.3 Depression and other aetiologies of chronic liver disease

Depression is also more common at the pre-cirrhotic level in other aetiologies of CLD. Depression is more common in patients with chronic hepatitis C (HCV) infection, independent of anti-viral treatment use[37], with a prevalence of 30%.[38] Whilst there are numerous psychosocial factors that may contribute, the HCV itself may have a direct biological role on the development of depression[39], through peripherally induced cytokines[40] and direct neuropathic effects of HCV viral particles that can penetrate the blood brain barrier (BBB).[41]

Patients with cholestatic and autoimmune liver disease also exhibit higher rates of depression[42,43], which may be related to their state of immune activation.[44] Fatigue is a common symptom of cholestatic liver disease and has profound effects on quality of life.[45] Fatigue is also a core symptom of depression. A study of 92 patients with primary biliary cholangitis (PBC) found that 42% of patients had depressive symptoms based on Beck Depression Inventory (BDI) criteria, but only 3.7% had depression based on DSM-IV criteria. This discrepancy is likely related to the fact that fatigue and other somatic symptoms are assessed in BDI scores but not DSM-IV, and therefore it is difficult to distinguish if fatigue in PBC is a manifestation of depression, or of the underlying liver disease.[46]

3. Factors involved in the pathophysiology of depression in cirrhosis

3.1 Psychological and psychosocial mechanisms

It has been suggested that patients with depression and cirrhosis have similar health behaviours, including alcohol use, smoking, poor diet and increased treatment non-adherence[47], and have

more difficult social circumstances.[18] Some aetiologies of cirrhosis, such as HCV infection and alcohol misuse, have shared underlying roots with depression.[48,49] Nevertheless, studies have revealed no significant differences in the prevalence of the main lifestyle variables that are a factor in the development of depression (education level, marital status, employment, income and social support level) between depressed and non-depressed cirrhotic patients.[32]

3.2 Hepatic encephalopathy

Hepatic encephalopathy (HE) is a frequent debilitating complication of cirrhosis and is defined as 'brain dysfunction caused by liver insufficiency and/or portosystemic shunting' that presents with a wide array of clinical symptoms ranging from disturbance of sleep/wake cycle, non-specific cognitive impairment and personality changes through to acute confusion and coma.[50] Overt HE affects 20-40% of cirrhotic patients during their disease trajectory[51], and severely impacts on HRQoL and survival.[52] Minimal HE requires the use of neurophysiological or psychometric testing to diagnose, as it is clinically undetectable.[50]

HE and depression share a number of similar clinical signs and symptoms, including cognitive impairment, fatigue and psychomotor retardation, creating a diagnostic challenge. It is often difficult to recognise symptoms as a separate manifestation of the same condition or, conversely, to co-diagnose both conditions. Furthermore, studies involving single photon emission computed tomography (SPECT) have shown an overlap in the neuropathological origin of depression and HE.[18]

The literature on the association between HE and depression is conflicting, with some studies suggesting a positive association[53–60], whilst others refute this.[20,61] (**Table 2.**) Whilst cerebral accumulation of ammonia is central to the pathophysiology of HE, systemic inflammation,

which further exacerbates the toxic effect of ammonia on astrocytes, is also fundamental to its development.[62–64] Thus, whilst they are clearly separate clinical entities, systemic inflammation may be the common link between HE and depression.

Table 2.

3.3 Medications prescribed in cirrhosis

Another postulation is that commonly prescribed medications in cirrhosis may be contributory to the high rates of depression observed.[10] Notably, the anti-viral agent interferon-alpha (IFN-α), previously used to treat HCV, has a well-documented causal role in the development of depression.[65] However, major depression in chronic HCV has been demonstrated to be independent of anti-viral treatment use.[37] Though data regarding the association of beta-blockers, prescribed for primary or secondary prophylaxis for variceal bleeding, are conflicting, a recent systematic review of randomised controlled trials (RCTs) of beta-blockers versus placebo revealed that patients on beta-blockers had lower rates of depression.[66]

Significant pharmacokinetic and pharmacodynamic changes occur in cirrhosis[67], and therefore there is significant concern amongst clinicians when considering antidepressant prescription to cirrhotic patients, due to the potential risk of drug-induced liver injury (DILI) and adverse events.[18] Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenergic reuptake inhibitors (SNRIs), particularly SSRIs, are safe and effective pharmacotherapeutic options to treat depression in cirrhosis, though the maintenance dose of some SSRIs should be halved due to prolonged half-life and reduction in drug clearance.[67]

3.4 Unifying biological theories

The increased prevalence of depression in liver disease, and its detrimental effect on patient outcome, cannot solely be explained by psychological and social factors, severity of liver disease and presence of HE.

Increased rates of depression have been noted in most aetiologies of CLD, including; NAFLD[30,35], alcohol-related cirrhosis[68], viral hepatitis[37,53] and cholestatic and autoimmune liver disease.[42,43] These diseases vary considerably in their pathogenesis, and therefore the increased rates of depression observed over-all suggest a unifying biological mechanism.[18]

Biological theories centre on the dysregulated immune system and pro-inflammatory state observed in both depression[12,14] and cirrhosis.[69] An imbalance in the gut microbiome, and increased bacterial translocation, contribute to the similar inflammatory pathophysiology of both depression and cirrhosis.

4. The role of the immune system and inflammation

4.1 Cirrhosis-associated immune dysfunction

Cirrhosis-associated immune dysfunction (CAID) describes key abnormalities observed in the immune system of patients with cirrhosis; firstly, acquired immunodeficiency with impaired response to pathogens, and secondly, overt systemic inflammation. Whilst innate immune dysfunction has mainly been described, adaptive immune defects have also been established.[70] CAID describes a dynamic pattern; over time the immune response shifts from a pro-inflammatory to anti-inflammatory compensatory response. CAID contributes to disease progression in cirrhosis, increases the propensity to develop infection and is associated with

the progression to acute decompensation (AD) and acute-on-chronic liver failure (ACLF). Furthermore, CAID occurs across the spectrum of all aetiologies of cirrhosis.[69]

Systemic inflammation, in the absence of infection, is the hallmark of CAID and is likely instigated by bacterial translocation from the gut to the systemic circulation.[71] Increased bacteria and resultant pathogen-associated molecular patterns (PAMPs), from enteric microbes, stimulate PRRs on innate immune cells. Increased generation of damage-associated molecular patterns (DAMPs), from necrotic liver cells, also stimulates immune cells. Once stimulated, PRRs activate a transcriptional response inducing gene expression and the synthesis of pro-inflammatory cytokines, chemokines and cell adhesion molecules involved in the adaptive immune response.[72] Further activated PRR responses include; vascular endothelial injury[73], acute phase protein synthesis in the liver[73], leucocyte recruitment to sites of inflammation[69] and augmented phagocytic activity. Such pathways lead to systemic inflammation, without overt sepsis, which carries a poor prognosis. There is a wealth of research data demonstrating evidence of systemic inflammation in cirrhosis including; but not limited to, increased serum level of acute phase reactants (CRP) [72], increased serum levels of markers of endothelial activation (vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), nitrates/nitrites)[69,73,74] increased pro-inflammatory cytokine production (TNF-α, IL-17, interferon-gamma (IFNγ)) by circulating immune cells[69,75] and increased serum levels of pro-inflammatory cytokines (TNF-α, IFNγ, IL-1β, IL-6, IL-17, IL-18).[69,73–77]

4.2 Non-alcoholic fatty liver disease and inflammation

Whilst the detrimental role of systemic inflammation in cirrhosis of all aetiologies has been discussed, special mention is required in relation to NAFLD.

NAFLD covers a spectrum of disease ranging from excessive fat accumulation/steatosis without necroinflammatory injury to significant hepatocellular injury and inflammation (non-alcoholic steatohepatitis (NASH)) to cirrhosis, and is closely related with obesity, insulin resistance (IR) and the components of the metabolic syndrome; hypertension, type 2 diabetes mellitus and dyslipidaemia.[78]

Whilst the pathophysiology of NAFLD and the metabolic syndrome is outside of the scope of this review, oxidative stress and inflammation appear key to their development. Chronic low-level inflammation along with visceral adipose tissue, adipocyte dysfunction and IR impair lipid and glucose homeostasis in insulin-sensitive tissues[79], and the gene expression of adipose-derived inflammatory cytokines (such as TNF-α and IL-6) is increased in obese patients.[80] Ectopic fat accumulates in NAFLD, and this is linked to increased hepatokine secretion, augmented gluconeogenesis, reduced glycogen synthesis and insulin signaling inhibition.[81] Hepatokines, proteins that are secreted by hepatocytes, can manipulate metabolic processes through autocrine, paracrine and endocrine signaling.[82] Hepatic steatosis provokes changes in hepatokine secretion which result in metabolic dysfunction, promoting IR, and drive systemic inflammation by activating pro-inflammatory pathways.[83] Levels of Fetuin A, a glycoprotein present in the plasma, are increased in NAFLD and increase the risk of IR.[82] Fetuin A also stimulates the production of pro-inflammatory cytokines from adipocytes and macrophages.[84] Excess hepatic lipid also adds to IR, and leads to oxidative stress, chronic inflammation and lipotoxicity, increasing the risk of fibrosis and cirrhosis development.[85] Alongside liver lipid metabolism, adipose tissue dysfunction and inflammation, as in the metabolic syndrome, appear to be central to the development of NAFLD.[78]

Many studies have demonstrated the increased levels of pro-inflammatory cytokines, including TNF-α and IL-6, in the development of NASH.[86,87] Hepatocytes and immune cells produce TNF-α. TNF-α stimulates liver steatosis, and also activates Kupffer cells which promote liver fibrosis.[85] Adipose tissue is the main secretor of IL-6. IL-6 is involved in fatty acid metabolism and, whilst the IL-6 signaling pathway protects against liver steatosis development, it may paradoxically stimulate hepatic inflammation.[88]

Hence, the systemic inflammation observed in NAFLD and NASH may be separate from that seen in CAID, and may therefore explain the increased rates of depression seen NAFLD as well as NASH cirrhosis.

4.3 The role of systemic inflammation in depression in cirrhosis

Whilst the theory that the dysregulated immune system and overt systemic inflammation is key to the increased prevalence of depression in cirrhosis, there are few studies examining this (summarised in **Table 3.**).

Hepatic and systemic inflammation have been shown to trigger neuroinflammation and depressive symptoms in two studies employing mouse models. (**Table 3.**)[89,90]

Human studies are lacking. Ko et al. (2013) demonstrated that depression scores correlate with serum levels of aspartate transaminase (AST) in cirrhotic patients.[31] AST is a cytoplasmic enzyme, its extracellular presence signals cell necrosis and, whilst not specific to the liver, suggests hepatic inflammation and damage. In a separate study Ko et al. (2013) demonstrated that the percentage of CD8 T-cells, but not CD3 or CD4, positively correlated with depression in cirrhotic patients (**Table 3**).[91] The functional state of T-lymphocytes often depends on T-

lymphocyte subset percentage distribution, and they are involved in cell-mediated immunity. An imbalance in T-lymphocyte subsets may therefore facilitate depression in cirrhosis, potentially through increased pro-inflammatory cytokine release (such as TNF-α) or increased permeability of the BBB.[92] Of note, studies have implicated phenotypic and functional changes in CD8 T-cells in cirrhotic patients which may contribute to CAID.[70]

Thus, the innate and adaptive immune system are activated in cirrhosis, resulting in a pro-inflammatory state, similar to that seen in depression.[11] Whilst no published studies have compared the levels of pro-inflammatory cytokines in cirrhotic patients with and without depression, the main pro-inflammatory cytokines implicated in the development of depression (TNF-α, IL-1β and IL-6)[14,93–95] are also notably raised in cirrhotic patients.[77,96]

Table 3.

4.4 The pathway between peripheral and central inflammation

The pathway between peripheral inflammation, neuroinflammation and clinical symptoms of depression remains to be fully elucidated.

Systemic inflammation and oxidative stress increase BBB permeability driving neuroinflammation.[97] Animal models have identified three main cytokines, TNF-α, IL-1β and IL-6 (all of which are increased in cirrhosis)[69] that enable peripheral to central communication in systemic inflammation. There are four well-documented pathways by which peripheral cytokines communicate with the brain; neural routes via peripheral afferent nerve fibre cytokine receptors (such as the vagus nerve)[98], permeable areas of the BBB such as circumventricular organs (CVOs), peripheral immune cell-to-brain signaling and cerebrovascular endothelial cells (CECs).[99] CECs at the BBB become activated by circulating

peripheral inflammatory chemokines, resulting in pro-inflammatory mediator release into the brain. CECs have TNF-α and IL-1β receptors. Their activation generates intracerebral synthesis of nitric oxide (NO) and prostanoids[100] which, in turn, stimulate microglial cells and astrocytes.[101]

In brief, these peripheral cytokine signals can then affect practically all central nervous system (CNS) fields involved in depression, including; neuroendocrine function (by activating the hypothalamic-pituitary-adrenal axis), neurotransmitter metabolism (serotonin, dopamine, noradrenaline, glutamate and kynurenine pathways), and neural plasticity.[11] Furthermore, they can act directly on microglia and astrocytes, the CNS glial cells chiefly implicated in the neuroinflammation of depression.[12]

Microglia are resident cerebral immune cells, essential for mounting a neuroinflammatory response and comprise 5-10% of total brain cells.[102] When activated microglia produce their own pro-inflammatory cytokines which, in health, are vital modulators of various CNS functions.[103] However, excessive pro-inflammatory cytokine activity in the brain disturbs many neuronal functions, including neurotransmitter signaling,[104,105] ultimately affecting the neurocircuits involved in cognition and mood.[106]

5. The role of gut microbiome

There is growing evidence that the gut microbiome plays a central role in the development of the pro-inflammatory state observed cirrhosis[71,107] and the microbiota-gut-brain axis is also proving increasingly important in the pathophysiology of depression.[108]

5.1 The gut-liver-immune axis and inflammation in chronic liver disease and cirrhosis

Patients with cirrhosis have an imbalance between healthy and pathogenic bacteria affecting the microbiome structure and function, termed enteric dysbiosis, which is associated with impaired intestinal barrier function and dysregulated immune homeostasis.[71]

The gut microbiome has been implicated in the development of NAFLD; animal and human studies have revealed an association between intestinal dysbiosis and NAFLD and its severity.[109,110] NAFLD patients have reduced microbial diversity, increased *Firmicutes* and reduced *Bacteriodetes.*[109] Furthermore, differential abundance of *Firmicutes, Bacteriodetes* and *Proteobacteria* phyla has been shown to predict advanced fibrosis in NAFLD patients.[111]

Gut microbiome modifications have been observed in patients with alcohol misuse, alcohol-related liver disease (ARLD) and alcohol-related cirrhosis.[112] Higher proportions of *Enterobacteriaceae* and lower proportions of *Lachnospiraceae, Ruminococcaceae* and *Clostridiales XIV* are observed in patients with alcohol-related cirrhosis.[113] Chronic alcohol abuse can modulate faecal pH which encourages pathogen overgrowth and is also associated with alterations in metabolite secretions affecting gut microbiota function.[112] Alcohol use also impairs the function of the intestinal barrier. Alcohol and acetaldehyde, the toxic metabolite of alcohol, increase intestinal permeability by altering the expression of tight-junction proteins.[114] Patients with chronic alcohol use display higher levels of pro-inflammatory cytokines[115] and are at greater risk of depression. The modified gut microbiome with alcohol use may result in increased bacterial translocation, an activated innate immune system, subsequent systemic inflammation and increase in pro-inflammatory cytokines[115] which signal to the brain and induce depressive symptoms.[99]

Cirrhotic patients exhibit gut dysbiosis, encompassing a significantly reduced bacterial diversity, overexpression of pathogens such as *Fusobacteria, Proteobacteria* and *Streptococaccae* and reduction in species central to healthy microbiome function such as *Bacteriodetes*, *Lachnospiracae* and *Firmicutes.*[116,117] This dysbiosis worsens with more advanced disease.[113] Patients with cirrhosis also exhibit small bowel bacterial overgrowth. Quantitative metagenomics have revealed 75,245 microbial genes differ between cirrhotic patients and healthy subjects.[117] Dysbiosis is greater in cirrhotic patients who develop complications and correlates with plasma endotoxin levels and 30-day mortality.[113]

Cirrhotic dysbiosis encourages intestinal barrier dysfunction in cirrhosis, which allows pathogens to adhere to the mucosa and enables bacteria, their products (such as lipopolysaccharide (LPS), flagellin, peptidoglycan and bacterial DNA) and PAMPs to translocate into the portal circulation. The portal hypertension and endothelial dysfunction that develop in cirrhosis further increase this intestinal permeability.[118] Portal hypertension, in both cirrhotic and non-cirrhotic patients, results in venous congestion and splanchnic neoangiogenesis, which lead to impaired microcirculation and gut barrier dysfunction.[119] Bacterial translocation leads to endotoxemia, and delivers gut-derived pathogens and their products directly to the liver, via the portal vein, activating the innate immune response.[71] Portosystemic shunting in cirrhosis further enables direct delivery of immune-activating bacterial degradation products to the systemic circulation.[120] Endotoxins activate hepatic macrophages via toll-like receptors (TLRs) and stimulate the production of pro-inflammatory cytokines, including TNF-α and IL-8, which recruit monocytes and neutrophils to the liver.[121] Ultimately this drives hepatic injury, systemic inflammation and CAID, promoting the development of infection, decompensation and disease progression.[113]

Research is now focused on restoring gut eubiosis, for example via faecal microbial transplantation (FMT), and repairing intestinal barrier function to prevent complications, infection and decompensation in patients with cirrhosis.[107]

5.2 The gut-microbiota-brain axis and inflammation in depression

The microbiota-gut-brain axis influences behaviour, and is also implicated in the development of depression. Most evidence has come from pre-clinical models[122]; the absence of a gut microbiota induces depression-like behaviour in mice and germ-free (GF) mice transplanted with stool rich from patients with depression resulted in depression-like behaviours not seen with FMT of 'healthy microbiota' from controls.[123]

Human studies have also found significant differences in the gut microbiome in depressed patients compared to healthy individuals.[108,124–126] However, there is disparity in their findings with one study noting *Bifidobacterium* and *Lactobacillus* were reduced in depressed patients[124], another noting that *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were increased, and *Firmicutes* were decreased in depressed individuals[125] and another noting that the family *Lachnospiraceae* was significantly decreased in depressed patients versus healthy controls.[126] Further studies have reported reduced microbial richness.[108] Interestingly some of these changes, such as decreased *Lachnospiraceae* (involved in short chain fatty acid (SCFA) production) and decreased microbial richness are similar to those observed in cirrhotic patients.[71] A recent observational study determined that depressed patients deemed non-responders to conventional treatment had a lower alpha diversity in the Phylogenetic diversity whole tree index compared to responders during treatment, and also increased microbiome glutamate synthesis.[127]

The exact communication pathways between the gut microbiome and brain need further clarification, but the activated immune system is likely a significant pathway leading to depressive symptoms.[108] Dysbiosis results in gut immune cell activation, cytokine production and increased permeability of intestinal mucosa, leading to increased translocation of bacteria.[71] This triggers cytokine production by circulating immune cells, an exaggerated immune response and resultant neuroinflammation.

Together with the activation of the innate immune system, gut microbiota can produce a variety of metabolites, including neurotransmitters, secondary bile acids, choline, SCFAs, bacteriocins and branched chain amino acids[108] which are immunomodulatory. Mounting evidence suggests that microbiota-host interactions at the gut level result in cytokine, chemokine, neuropeptide, neurotransmitter, endocrine and by-product release that can travel via the systemic circulation and lymphatics, or communicate with the brain via the autonomic nervous system and influence behaviour.[108] The effect of the gut microbiome on microglial homeostasis appears to be key to the gut-microbiota-brain axis and behavioural changes.[128]

The gut is the main source of serotonin in the body.[129] The gut microbiota may also be crucial in the regulation of tryptophan metabolism, affecting serotonin synthesis and downstream kynurenine pathway metabolism in both the periphery and the CNS, affecting behaviour and depressive symptoms.[130]

The vagus nerve, the principal component of the parasympathetic nervous system, is one of the vital modes of communication between the gut and the brain.[131] Vagal afferent fibres are located in the gastrointestinal tract wall but do not cross the epithelium, thus are not in direct contact with gut microbiota.[132] Instead, metabolites can travel across the epithelial cell layer and act directly on vagus nerve afferent fibres to signal to the brain.[133] The luminal wall is also

richly innervated by the enteric nervous system (ENS), which is predominantly responsible for gut motility, and can be targeted by SCFAs and neurotransmitters.[131]

The implication of the gut microbiome in the pathophysiology of depression has led to the notion of psychobiotics –microbiota-targeted interventions, mainly focussing on prebiotics and probiotics, affecting the gut-microbiota-brain axis, used in the treatment of mental health and neurological disorders. Several bacterial strains or combinations, mainly containing *Lactobacillus* and *Bifidobacterium* species, have proved efficacious in multiple studies at treating psychiatric disorders, and have been shown to reduce depression scores and enhance cognition.[108,134,135] Probiotics have been shown to reduce systemic levels of inflammatory biomarkers and pro-inflammatory cytokines.[117]

FMT aims to restore the microbiome of an unhealthy individual to a healthy state, via faecal bacteria transfer from healthy donor to recipient. Whilst the use of FMT is still in its infancy, a recent systematic review, analysing the effect of FMT on psychiatric disorder symptoms from 28 pre-clinical and clinical studies, found a decrease in depressive symptoms post FMT in all studies.[136]

5.3 Targeting the gut microbiome and inflammation in depression and liver disease

Probiotic administration has been shown to improve quality of life, symptom burden and infection rates in cirrhotic patients, but not mortality.[137,138] Furthermore, probiotic administration has been associated with a decrease in pro-inflammatory cytokine levels, such as TNF-α, in patients with CLD.[139] A pre-clinical study found that administering VSL#3 (a proprietary name for a group of eight probiotics) improved 'fatigue-like' behaviours in mice with liver inflammation, independent of changes in liver injury severity. Furthermore the mice treated with VSL#3 had decreased levels of TNFα which was linked to reduced microglial

activation, monocyte:CEC interactions and cerebral monocyte infiltration.[140] Such observations suggest that altering the gut microbiome can modify systemic immunity in liver disease, which can consequently affect the brain and behaviour.

Similarly, in a cirrhotic mouse model, transfer of faecal material from cirrhotic patients resulted in higher levels of neuroinflammation, microglial activation and dysbiosis than faecal material from healthy controls. There was no change in liver histology severity. This neuroinflammation was then reduced significantly when faecal material obtained from the same patients 15 days after undergoing FMT from healthy controls was transplanted into the same mice.[141] This demonstrated that the attenuation of neuroinflammation by FMT is independent of liver inflammation.

Trials of FMT in cirrhosis are ongoing and have mainly focused on its safety. However, FMT has been shown to have a beneficial impact on cirrhotic patients with HE, with improvement in cognition, and on patients with alcohol-related cirrhosis and alcohol use disorder (AUD) with again improved cognition, improved psychosocial quality of life and a reduction in serum IL-6 levels.[142]

As such, our exploration of the literature lends further weight to the hypothesis that the gut dysbiosis observed in cirrhosis, and resultant systemic inflammation, may explain the increased rates of depression seen (**Figure 1.**). The observations and trials described demonstrate the potential role of the gut microbiome and immune dysfunction in driving the behavioural changes and increased rates of depression observed in cirrhosis and highlight the need for further work, involving larger clinical trials investigating potential psychobiotic treatments (**Figure 2.**).

Figure 1.

Figure 2.

6. Future developments in the field

The gut-liver-immune axis in cirrhosis is well documented[107] and research into this area is growing exponentially. The microbiota-gut-brain axis has also been clearly demonstrated.[108]

Whilst our hypothesis that the high rates of depression seen in cirrhosis are a consequence of gut-derived systemic inflammation is logical, and certainly is not contradictory to current literature, there is a paucity of direct evidence to date. As depicted in **Table 3.** published studies examining the relationship between systemic inflammation, depression and liver disease are few, and arise from two research teams. One research group demonstrated the link between hepatic inflammation and sickness behaviour in bile duct ligated (BDL) mice, with evidence of microglial activation.[89,90] Cross-sectional data from a separate team corroborated the relationship between depression and inflammation in cirrhosis, though correlation was not strong.[31,91] Further mechanistic work, including prospective longitudinal studies in cirrhotic patients to assess the gut microbiome, immune system and depression (confirmed by clinical psychiatric evaluations such as the Structure Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5 (SCID))[4], is required to lend further support to this hypothesis.

Therapeutic interventions that target dysbiosis are being investigated in cirrhosis, and targeting the microbiome may be key to improving mood and alleviating depression in cirrhosis.

6.1 FMT

FMT has shown beneficial effects in cirrhotic patients, with improved cognition in patients with HE, reduction in episodes of overt HE[143,144] and improved quality of life.[142] The effect of FMT on psychiatric disorder symptoms in other illnesses, such as depression and irritable bowel syndrome (IBS), is promising[136], however has not been evaluated in cirrhosis. The upcoming UK multicentre randomised controlled PROMISE (PROspective double-blind placebo-controlled multicentre trial of faecal MIcrobiota tranSplantation to improve outcomEs in patients with cirrhosis) [https://fundingawards.nihr.ac.uk/award/NIHR130730] trial will assess efficacy of encapsulated FMT to reduce infection and mortality in ARLD and NAFLD cirrhosis. Primary endpoint is time to hospitalisation with infection, however secondary endpoints include change in depression and anxiety (measure by HADS score) and change in quality of life (measured by EQ-5D-3L score). As such, this study should yield crucial data on the effect of FMT on depression in cirrhosis.

6.2 Rifaximin

Rifaximin is an oral non-absorbable gut-selective antibiotic, used effectively to treat HE in cirrhosis.[145] It has been shown to modulate the gut microbiome, reduce endotoxemia and improve cognitive performance in cirrhotic patients[146] raising its potential as a psychobiotic-like treatment. The recently published RIFSYS trial, a placebo-controlled RCT of rifaximin in cirrhotic patients with HE, revealed significantly reduced TNF-α levels at 30-days in the treatment arm, in conjunction with a reduction in markers of gut-derived systemic inflammation, abundance of metagenomic species in both faecal and salivary compartments and resolution of HE.[147]

Non-selective beta-blockers

Non-selective B-blockers (NSBBs) are a well-established treatment for portal hypertension and reduce splanchnic blood flow. NSBBs ameliorate intestinal permeability and reduce bacterial translocation, by modulating gut motility[148], demonstrated by lower levels of IL-6 and LBP in cirrhotic patients receiving NSBBs.[119] The M-BOP mechanistic sub-study to the current UK multicentre randomized controlled BOPPP trial (NCT03776955), investigating the use of NSBBs or placebo for primary prophylaxis of oesophageal varices, will further explore the effect of NSBBs on bacterial translocation and risk of decompensation in BOPPP participants.

Albumin

Whilst human albumin solution is commonly used for various indications in cirrhosis, it has further immune-restorative effects that may prove beneficial in cirrhosis.[149] Trials of albumin infusion in decompensated cirrhosis have shown conflicting results. The open-label randomised ANSWER trial resulted in a 38% reduction in the mortality hazard ratio in cirrhotic patients receiving weekly albumin infusions.[150] The recent UK multicentre randomised open-label ATTIRE study investigated the effect of intravenous 20% albumin infusions in hospitalised patients with cirrhosis (targeting a serum albumin level ≥30 g/L) compared to standard of care. Conversely, there was no benefit, and no difference in composite end point (new infection, renal dysfunction and death at 15-days) was observed.[151] The current MICROB-PREDICT study, which aims to validate microbiome-based markers to predict treatment response to albumin, may shed further light on this area.

7. Conclusion

The prevalence of depression is high in liver disease. Importantly, a comorbid diagnosis of depression appears to have an adverse impact on outcomes in cirrhosis.

Gut dysbiosis results in increased permeability of the intestinal mucosa, resulting in increased bacterial translocation culminating in the activation of circulating immune cells, cytokine production and systemic inflammation. Such pathways are central to CAID, and are implicated in the increased incidence of infection in cirrhosis, disease progression and the development of organ failure and complications. Peripheral inflammation can extend to the CNS and brain via neural mechanisms, CEC and CVO signaling, and peripheral immune cell-to-brain signalling resulting in depressive symptoms. The overt systemic inflammation present in cirrhosis may therefore explain the high rates of depression.

Whilst the mechanism underlying the crucial link between depression and cirrhosis remains to be fully elucidated, and given the various psychosocial and other biological factors involved, is likely to be multifactorial, the role of the gut microbiome and inflammation requires further exploration and consideration as a target for therapy.

Abbreviations:

ACLF: acute-on-chronic liver failure

ARLD: alcohol-related liver disease

AST: aspartate transaminase

AUD: alcohol use disorder

BBB: blood brain barrier

BDL: bile duct ligated

BDIL Beck Depression Inventory

BDI-II: Beck Depression Inventory second edition

CAID: cirrhosis-associated immune dysfunction

CECs: cerebrovascular endothelial cells

CLD: chronic liver disease

CKD: chronic kidney disease

CNS: central nervous system

CRP: C-reactive protein

CVOs: circumventricular organs

DAMPs: damage-associated molecular patterns

DILI drug induced liver injury

DSM-5 Diagnostic and Statistical Manual of Mental Disorders 5

ENS enteric nervous system

FMT: faecal microbial transplantation

GALT: gut-associated lymphoid tissue

GF: germ-free

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

HE: hepatic encephalopathy

HRQoL: health related quality of life

IBS: irritable bowel syndrome

ICAM-1: intercellular adhesion molecule-1

IFN-α: interferon alpha

IFN-γ: interferon-gamma

IL: interleukin

IR: insulin resistance

LPS: lipopolysaccharide

LBP: lipopolysaccharide-binding protein

NAFL: non-alcoholic fatty liver

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

NK: natural killer

NO: nitric oxide

NSBB: Non-selective beta-blocker

PAMPs: pathogen-associated molecular patterns

PBC: primary biliary cholangitis

PRRs: pattern recognition receptors

RCT: randomised controlled trial

SCFA: short chain fatty acid

SCID Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5

SNRI selective noradrenergic reuptake inhibitors

SPECT: single photon emission computed tomography

SSRI Selective serotonin reuptake inhibitors

TLR: toll-like receptors

TNF-α: tumour necrosis factor alpha

VEGF: vascular endothelial growth factor

VCAM-1: vascular cell adhesion molecule 1

Acknowledgements

Figure 2 was “created with BioRender.com.”

References

[1] Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. PLoS Med 2013;10:e1001547. https://doi.org/10.1371/journal.pmed.1001547.

[2] Cruz-Pereira JS, Rea K, Nolan YM, O'Leary OF, Dinan TG, Cryan JF. Depression's unholy trinity: Dysregulated stress, immunity, and the microbiome. Annu Rev Psychol 2020;71:49–78. https://doi.org/10.1146/annurev-psych-122216-011613.

[3] American Psychiatry Association. Diagnostic and statistical manual of mental disorders (5th ed.). 2013.

[4] First MB. Structured Clinical Interview for the *DSM* (SCID). Encycl. Clin. Psychol., Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2015, p. 1–6. https://doi.org/10.1002/9781118625392.wbecp351.

[5] Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed) 1986;292:344. https://doi.org/10.1136/BMJ.292.6516.344.

[6] Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588–97. https://doi.org/10.1207/S15327752JPA6703_13.

[7] Pizzagalli DA. Depression, stress, and anhedonia: Toward a synthesis and integrated model. Annu Rev Clin Psychol 2014;10:393–423. https://doi.org/10.1146/ANNUREV-CLINPSY-050212-185606.

[8] Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of baseline activation and neural response data. Am J Psychiatry 2012;169:693–703. https://doi.org/10.1176/APPI.AJP.2012.11071105.

[9] Müller VI, Cieslik EC, Serbanescu I, Laird AR, Fox PT, Eickhoff SB. Altered brain activity in unipolar depression revisited: Meta-analyses of neuroimaging studies. JAMA Psychiatry 2017;74:47–55. https://doi.org/10.1001/JAMAPSYCHIATRY.2016.2783.

[10] Malhi GS, Mann JJ. Depression. Lancet 2018;392:2299–312. https://doi.org/10.1016/S0140-6736(18)31948-2.

[11] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016;16:22–34. https://doi.org/10.1038/nri.2015.5.

[12] Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Biol Psychiatry 2009;65:732–41. https://doi.org/10.1016/j.biopsych.2008.11.029.

[13] Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, et al. The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immun 2001;15:199–226. https://doi.org/10.1006/brbi.2000.0597.

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

[15] Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miler L, Rajkowska G, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiatry 2015;72:268–75. https://doi.org/10.1001/jamapsychiatry.2014.2427.

[16] Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014 121 2014;12:1–24. https://doi.org/10.1186/S12916-014-0145-Y.

[17] Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. Br Med J (Clin Res Ed) 1981;282:263–6.

[18] Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. Aliment Pharmacol Ther 2014;40:880–92. https://doi.org/10.1111/apt.12925.

[19] Bianchi G, Marchesini G, Nicolino F, Graziani R, Sgarbi D, Loguercio C, et al. Psychological status and depression in patients with liver cirrhosis. Dig Liver Dis 2005;37:593–600. https://doi.org/10.1016/j.dld.2005.01.020.

[20] Nardelli S, Pentassuglio I, Pasquale C, Ridola L, Moscucci F, Merli M, et al. Depression, anxiety and alexithymia symptoms are major determinants of health related quality of life (HRQoL) in cirrhotic patients. Metab. Brain Dis., vol. 28, Metab Brain Dis; 2013, p. 239–43. https://doi.org/10.1007/s11011-012-9364-0.

[21] Buganza-Torio E, Mitchell N, Abraldes JG, Thomas L, Ma M, Bailey RJ, et al. Depression in cirrhosis - a prospective evaluation of the prevalence, predictors and development of a screening nomogram. Aliment Pharmacol Ther 2019;49:194–201. https://doi.org/10.1111/apt.15068.

[22] Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743–800. https://doi.org/10.1016/S0140-6736(15)60692-4.

[23] Bautovich A, Katz I, Smith M, Loo CK, Harvey SB. Depression and chronic kidney disease: A review for clinicians: Http://DxDoiOrg/101177/0004867414528589 2014;48:530–41. https://doi.org/10.1177/0004867414528589.

[24] Massie MJ. Prevalence of Depression in Patients With Cancer. JNCI Monogr

2004;2004:57–71. https://doi.org/10.1093/JNCIMONOGRAPHS/LGH014.

[25] Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2006;23:1165–73. https://doi.org/10.1111/J.1464-5491.2006.01943.X.

[26] Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48:1527–37. https://doi.org/10.1016/J.JACC.2006.06.055.

[27] Dirks M, Haag K, Pflugrad H, Tryc AB, Schuppner R, Wedemeyer H, et al. Neuropsychiatric symptoms in hepatitis C patients resemble those of patients with autoimmune liver disease but are different from those in hepatitis B patients. J Viral Hepat 2019;26:422–31. https://doi.org/10.1111/jvh.12979.

[28] Tomeno W, Kawashima K, Yoneda M, Saito S, Ogawa Y, Honda Y, et al. Non-alcoholic fatty liver disease comorbid with major depressive disorder: The pathological features and poor therapeutic efficacy. J Gastroenterol Hepatol 2015;30:1009–14. https://doi.org/10.1111/jgh.12897.

[29] Youssef NA, Abdelmalek MF, Binks M, Guy CD, Omenetti A, Smith AD, et al. Associations of depression, anxiety and antidepressants with histological severity of nonalcoholic fatty liver disease. Liver Int 2013;33:1062–70. https://doi.org/10.1111/liv.12165.

[30] Kim D, Yoo ER, Li AA, Tighe SP, Cholankeril G, Harrison SA, et al. Depression is associated with non-alcoholic fatty liver disease among adults in the United States. Aliment Pharmacol Ther 2019;50:590–8. https://doi.org/10.1111/apt.15395.

[31] Ko FY, Yang AC, Tsai SJ, Zhou Y, Xu LM. Physiologic and laboratory correlates of depression, anxiety, and poor sleep in liver cirrhosis. BMC Gastroenterol 2013;13:18.

https://doi.org/10.1186/1471-230X-13-18.

[32] Singh N, Gayowski T, Wagener MM, Marino IR. Depression in patients with cirrhosis. Impact on outcome. Dig Dis Sci 1997;42:1421–7.

[33] Rogal SS, Mankaney G, Udawatta V, Chinman M, Good CB, Zickmund S, et al. Pre-Transplant Depression Is Associated with Length of Hospitalization, Discharge Disposition, and Survival after Liver Transplantation. PLoS One 2016;11. https://doi.org/10.1371/JOURNAL.PONE.0165517.

[34] Weinstein AA, Kallman Price J, Stepanova M, Poms LW, Fang Y, Moon J, et al. Depression in Patients with Nonalcoholic Fatty Liver Disease and Chronic Viral Hepatitis B and C. Psychosomatics 2011;52:127–32. https://doi.org/10.1016/j.psym.2010.12.019.

[35] Labenz C, Huber Y, Michel M, Nagel M, Galle PR, Kostev K, et al. Nonalcoholic Fatty Liver Disease Increases the Risk of Anxiety and Depression. Hepatol Commun 2020;4:1293–301. https://doi.org/10.1002/hep4.1541.

[36] Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: Overview, mechanisms, and implications. Dialogues Clin Neurosci 2018;20:63–73. https://doi.org/10.31887/dcns.2018.20.1/bpenninx.

[37] Carta MG, Hardoy MC, Garofalo A, Pisano E, Nonnoi V, Intilla G, et al. Association of chronic hepatitis C with major depressive disorders: Irrespective of interferon-alpha therapy. Clin Pract Epidemiol Ment Heal 2007;3. https://doi.org/10.1186/1745-0179-3-22.

[38] Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaeys G, Neri S, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J Hepatol 2012;57:1379–90. https://doi.org/10.1016/J.JHEP.2012.07.037.

[39] Grover VP, Pavese N, Koh S-B, Wylezinska M, Saxby BK, Gerhard A, et al. Cerebral

microglial activation in patients with hepatitis C: in vivo evidence of neuroinflammation. J Viral Hepat 2012;19. https://doi.org/10.1111/J.1365-2893.2011.01510.X.

[40] Huckans M, Fuller BE, Olavarria H, Sasaki AM, Chang M, Flora KD, et al. Multi-analyte profile analysis of plasma immune proteins: altered expression of peripheral immune factors is associated with neuropsychiatric symptom severity in adults with and without chronic hepatitis C virus infection. Brain Behav 2014;4:123–42. https://doi.org/10.1002/BRB3.200.

[41] Adair DM, Radkowski M, Jablonska J, Pawelczyk A, Wilkinson J, Rakela J, et al. Differential display analysis of gene expression in brains from hepatitis C-infected patients. AIDS 2005;19 Suppl 3. https://doi.org/10.1097/01.AIDS.0000192084.79679.E4.

[42] Biagini MR, Tozzi A, Milani S, Grippo A, Amantini A, Capanni M, et al. Fatigue in primary biliary cirrhosis: A possible role of comorbidities. Eur J Gastroenterol Hepatol 2008;20:122–6. https://doi.org/10.1097/MEG.0B013E3282F1CBDA.

[43] Schramm C, Wahl I, Weiler-Normann C, Voigt K, Wiegard C, Glaubke C, et al. Health-related quality of life, depression, and anxiety in patients with autoimmune hepatitis. J Hepatol 2014;60:618–24. https://doi.org/10.1016/J.JHEP.2013.10.035.

[44] Pryce CR, Fontana A. Depression in Autoimmune Diseases. Curr Top Behav Neurosci 2016;31:139–54. https://doi.org/10.1007/7854_2016_7.

[45] Poupon RE, Chrétien Y, Chazouillères O, Poupon R, Chwalow J. Quality of life in patients with primary biliary cirrhosis. Hepatology 2004;40:489–94. https://doi.org/10.1002/HEP.20276.

[46] Van Os E, Van den Broek WW, Mulder PG, ter Borg PC, Bruijn JA, Van Buuren HR. Depression in patients with primary biliary cirrhosis and primary sclerosing cholangitis.

J Hepatol 2007;46:1099–103. https://doi.org/10.1016/J.JHEP.2007.01.036.

[47] DiMatteo MR, Lepper HS, Croghan TW. Depression Is a Risk Factor for Noncompliance With Medical Treatment. Arch Intern Med 2000;160:2101. https://doi.org/10.1001/archinte.160.14.2101.

[48] Boden JM, Fergusson DM. Alcohol and depression. Addiction 2011;106:906–14. https://doi.org/10.1111/j.1360-0443.2010.03351.x.

[49] Butt AA, Khan UA, McGinnis KA, Skanderson M, Kent Kwoh C. Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. J Viral Hepat 2007;14:890–6. https://doi.org/10.1111/j.1365-2893.2007.00885.x.

[50] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014;61:642–59. https://doi.org/10.1016/j.jhep.2014.05.042.

[51] Amodio P, Del Piccolo F, Pettenò E, Mapelli D, Angeli P, Iemmolo R, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001;35:37–45. https://doi.org/10.1016/S0168-8278(01)00129-5.

[52] Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: A Danish population-based cohort study. Hepatology 2010;51:1675–82. https://doi.org/10.1002/hep.23500.

[53] Barboza KC, Salinas LM, Sahebjam F, Jesudian AB, Weisberg IL, Sigal SH. Impact of depressive symptoms and hepatic encephalopathy on health-related quality of life in cirrhotic hepatitis C patients. Metab Brain Dis 2016;31:869–80. https://doi.org/10.1007/s11011-016-9817-y.

[54] Hilsabeck RC, Hassanein TI, Carlson MD, Ziegler EA, Perry W. Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. J Int Neuropsychol

Soc 2003;9:847–54. https://doi.org/10.1017/S1355617703960048.

[55] Malaguarnera M, Bella R, Vacante M, Giordano M, Malaguarnera G, Gargante MP, et al. Acetyl-l-carnitine reduces depression and improves quality of life in patients with minimal hepatic encephalopathy. Scand J Gastroenterol 2011;46:750–9. https://doi.org/10.3109/00365521.2011.565067.

[56] Malaguarnera G, Pennisi M, Bertino G, Motta M, Borzì AM, Vicari E, et al. Resveratrol in patients with minimal hepatic encephalopathy. Nutrients 2018;10:329. https://doi.org/10.3390/nu10030329.

[57] Stewart CA, Enders FTB, Mitchell MM, Felmlee-Devine D, Smith GE. The cognitive profile of depressed patients with cirrhosis. Prim Care Companion J Clin Psychiatry 2011;13:0–0. https://doi.org/10.4088/PCC.10m01090.

[58] Telles-Correia D, João Freire M, Mega I, Barreiras D, Cortez Pinto H. Anxiety and depression symptoms in hepatic encephalopathy: Are they psychiatric or organic? Transplant. Proc., vol. 47, Elsevier USA; 2015, p. 1005–7. https://doi.org/10.1016/j.transproceed.2015.03.011.

[59] Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–73. https://doi.org/10.1016/S0168-8278(01)00026-5.

[60] Xiao G, Ye Q, Han T, Yan J, Sun L, Wang F. Study of the sleep quality and psychological state of patients with hepatitis B liver cirrhosis. Hepatol Res 2018;48:E275–82. https://doi.org/10.1111/hepr.12981.

[61] Hassan EA, Abd El-Rehim AS, Seifeldein GS, Shehata GA. Minimal hepatic encephalopathy in patients with liver cirrhosis: Magnetic resonance spectroscopic brain findings versus neuropsychological changes. Arab J Gastroenterol 2014;15:108–13. https://doi.org/10.1016/j.ajg.2014.09.003.

[62] Keiding S, Sørensen M, Bender D, Munk OL, Ott P, Vilstrup H. Brain metabolism of 13N-ammonia during acute hepatic encephalopathy in cirrhosis measured by positron emission tomography. Hepatology 2006;43:42–50. https://doi.org/10.1002/hep.21001.

[63] Norenberg MD. A light and electron microscopic study of experimental portal systemic (ammonia) encephalopathy. Progression and reversal of the disorder. Lab Investig 1977;36:618–27.

[64] Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol 2004;40:247–54. https://doi.org/10.1016/J.JHEP.2003.10.016.

[65] Sockalingam S, Abbey SE. Managing Depression During Hepatitis C Treatment n.d.

[66] Barron AJ, Zaman N, Cole GD, Wensel R, Okonko DO, Francis DP. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: Recommendations for patient information. Int J Cardiol 2013;168:3572–9. https://doi.org/10.1016/j.ijcard.2013.05.068.

[67] Lewis JH, Stine JG. Review article: Prescribing medications in patients with cirrhosis - A practical guide. Aliment Pharmacol Ther 2013;37:1132–56. https://doi.org/10.1111/APT.12324.

[68] Ewusi-Mensah I, Saunders JB, Wodak AD, Murray RM, Williams R. Psychiatric morbidity in patients with alcoholic liver disease. Br Med J 1983;287:1417–9. https://doi.org/10.1136/bmj.287.6403.1417.

[69] Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. J Hepatol 2014;61:1385–96. https://doi.org/10.1016/J.JHEP.2014.08.010.

[70] Lebossé F, Gudd C, Tunc E, Singanayagam A, Nathwani R, Triantafyllou E, et al. CD8+ T cells from patients with cirrhosis display a phenotype that may contribute to cirrhosis-

associated immune dysfunction. EBioMedicine 2019;49:258–68. https://doi.org/10.1016/j.ebiom.2019.10.011.

[71] Woodhouse CA, Patel VC, Singanayagam A, Shawcross DL. Review article: the gut microbiome as a therapeutic target in the pathogenesis and treatment of chronic liver disease. Aliment Pharmacol Ther 2018;47:192–202. https://doi.org/10.1111/apt.14397.

[72] Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 2010;10:826–37. https://doi.org/10.1038/nri2873.

[73] Buck M, Garcia-Tsao G, Groszmann RJ, Stalling C, Grace ND, Burroughs AK, et al. Novel inflammatory biomarkers of portal pressure in compensated cirrhosis patients. Hepatology 2014;59:1052–9. https://doi.org/10.1002/hep.26755.

[74] Girón-González JA, Martínez-Sierra C, Rodriguez-Ramos C, Rendón P, Macías MA, Fernández-Gutiérrez C, et al. Adhesion molecules as a prognostic marker of liver cirrhosis. Scand J Gastroenterol 2005;40:217–24. https://doi.org/10.1080/00365520510011470.

[75] Lemmers A, Moreno C, Gustot T, Maréchal R, Degré D, Demetter P, et al. The interleukin-17 pathway is involved in human alcoholic liver disease. Hepatology 2009;49:646–57. https://doi.org/10.1002/hep.22680.

[76] Albillos A, De La Hera A, Reyes E, Monserrat J, Muñoz L, Nieto M, 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;40:624–31. https://doi.org/10.1016/j.jhep.2003.12.010.

[77] Lee FY, Lu RH, Tsai YT, Lin HC, Hou MC, Li CP, et al. Plasma Interleukin-6 Levels in Patients with Cirrhosis: Relationship to Endotoxemia, Tumor Necrosis Factor-α, and Hyperdynamic Circulation. Scand J Gastroenterol 1996;31:500–5. https://doi.org/10.3109/00365529609006772.

[78] Byrne CD, Targher G. NAFLD: A multisystem disease. J Hepatol 2015;62:S47–64. https://doi.org/10.1016/j.jhep.2014.12.012.

[79] Zafar U, Khaliq S, Ahmad HU, Manzoor S, Lone KP. Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links. Hormones 2018;17:299–313. https://doi.org/10.1007/s42000-018-0051-3.

[80] Mohammadi M, Gozashti MH, Aghadavood M, Mehdizadeh MR, Hayatbakhsh MM. Clinical significance of serum IL-6 and TNF-α levels in patients with metabolic syndrome. Reports Biochem Mol Biol 2017;6:74–9.

[81] Samuel VT, Liu Z-X, Qu X, Elder BD, Bilz S, Befroy D, et al. Mechanism of Hepatic Insulin Resistance in Non-alcoholic Fatty Liver Disease* Downloaded from. J Biol Chem 2004;279:32345–53. https://doi.org/10.1074/jbc.M313478200.

[82] Meex RCR, Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. Nat Rev Endocrinol 2017 139 2017;13:509–20. https://doi.org/10.1038/nrendo.2017.56.

[83] Meex RC, Hoy AJ, Morris A, Brown RD, Lo JC, Burke M, et al. Fetuin B Is a Secreted Hepatocyte Factor Linking Steatosis to Impaired Glucose Metabolism. Cell Metab 2015;22:1078–89. https://doi.org/10.1016/J.CMET.2015.09.023.

[84] Mukhopadhyay S, Bhattacharya S. Plasma fetuin-A triggers inflammatory changes in macrophages and adipocytes by acting as an adaptor protein between NEFA and TLR-4. Diabetologia 2016;59:859–60. https://doi.org/10.1007/S00125-016-3866-Y.

[85] Shao M, Ye Z, Qin Y, Wu T. Abnormal metabolic processes involved in the pathogenesis of non-alcoholic fatty liver disease (Review). Exp Ther Med 2020;20:1–1. https://doi.org/10.3892/etm.2020.9154.

[86] Bocsan IC, Milaciu MV, Pop RM, Vesa SC, Ciumarnean L, Matei DM, et al. Cytokines Genotype-Phenotype Correlation in Nonalcoholic Steatohepatitis. Oxid Med Cell

Longev 2017;2017. https://doi.org/10.1155/2017/4297206.

[87] Zahran WE, Salah El-Dien KA, Kamel PG, El-Sawaby AS. Efficacy of tumor necrosis factor and interleukin-10 analysis in the follow-up of nonalcoholic fatty liver disease progression. Indian J Clin Biochem 2013;28:141–6. https://doi.org/10.1007/s12291-012-0236-5.

[88] Vida M, Gavito AL, Pavoń FJ, Bautista D, Serrano A, Suarez J, et al. Chronic administration of recombinant IL-6 upregulates lipogenic enzyme expression and aggravates high-fat-diet-induced steatosis in IL-6-deficient mice. DMM Dis Model Mech 2015;8:721–31. https://doi.org/10.1242/dmm.019166.

[89] D'Mello C, Riazi K, Le T, Stevens KM, Wang A, McKay DM, et al. P-selectin-mediated monocyte-cerebral endothelium adhesive interactions link peripheral organ inflammation to sickness behaviors. J Neurosci 2013;33:14878–88. https://doi.org/10.1523/JNEUROSCI.1329-13.2013.

[90] D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factora signaling during peripheral organ inflammation. J Neurosci 2009;29:2089–102. https://doi.org/10.1523/JNEUROSCI.3567-08.2009.

[91] Ko F-Y, Tsai S-J, Yang AC, Zhou Y, Xu L-M. Association of CD8 T Cells with Depression and Anxiety in Patients with Liver Cirrhosis. Int J Psychiatry Med 2013;45:15–29. https://doi.org/10.2190/PM.45.1.b.

[92] Huseby ES, Liggitt D, Brabb T, Schnabel B, Öhlén C, Goverman J. A pathogenic role for myelin-specific CD8+ T cells in a model for multiple sclerosis. J Exp Med 2001;194:669–76. https://doi.org/10.1084/jem.194.5.669.

[93] Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. vol. 34. J Affect Disord; 1995.

https://doi.org/10.1016/0165-0327(95)00028-L.

[94] Penninx BWJH, Kritchevsky SB, Yaffe K, Newman AB, Simonsick EM, Rubin S, et al. Inflammatory markers and depressed mood in older persons: Results from the health, aging and body composition study. Biol Psychiatry 2003;54:566–72. https://doi.org/10.1016/S0006-3223(02)01811-5.

[95] Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in interleukin-1β in late-life depression. Am J Psychiatry 2005;162:175–7. https://doi.org/10.1176/appi.ajp.162.1.175.

[96] Solé C, Solà E, Morales-Ruiz M, Fernàndez G, Huelin P, Graupera I, et al. Characterization of Inflammatory Response in Acute-on-Chronic Liver Failure and Relationship with Prognosis. Sci Rep 2016;6:32341. https://doi.org/10.1038/srep32341.

[97] Dröge W. Free radicals in the physiological control of cell function. Physiol Rev 2002;82:47–95. https://doi.org/10.1152/physrev.00018.2001.

[98] Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review & analysis of alternative mechanisms. Life Sci 1995;57:1011–26. https://doi.org/10.1016/0024-3205(95)02047-M.

[99] D'Mello C, Swain MG. Immune-to-brain communication pathways in inflammation-associated sickness and depression. Curr. Top. Behav. Neurosci., vol. 31, Springer Verlag; 2017, p. 73–94. https://doi.org/10.1007/7854_2016_37.

[100] Schiltz JC, Sawchenko PE. Signaling the brain in systemic inflammation: The role of perivascular cells. Front Biosci 2003;8. https://doi.org/10.2741/1211.

[101] Coltart I, Tranah TH, Shawcross DL. Inflammation and hepatic encephalopathy. Arch Biochem Biophys 2013;536:189–96. https://doi.org/10.1016/j.abb.2013.03.016.

[102] Kim SU, de Vellis J. Microglia in health and disease. J Neurosci Res 2005;81:302–13. https://doi.org/10.1002/JNR.20562.

[103] Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron 2020;107:234. https://doi.org/10.1016/J.NEURON.2020.06.002.

[104] Deverman BE, Patterson PH. Cytokines and CNS development. Neuron 2009;64:61–78. https://doi.org/10.1016/J.NEURON.2009.09.002.

[105] Stephan AH, Barres BA, Stevens B. The complement system: an unexpected role in synaptic pruning during development and disease. Annu Rev Neurosci 2012;35:369–89. https://doi.org/10.1146/ANNUREV-NEURO-061010-113810.

[106] Dantzer R, O'Connor JC, Freund GG, Johnson JW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–56. https://doi.org/10.1038/NRN2297.

[107] Tranah TH, Edwards LA, Schnabl B, Shawcross DL. Targeting the gut-liver-immune axis to treat cirrhosis. Gut 2020;0:1–13. https://doi.org/10.1136/gutjnl-2020-320786.

[108] Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu K V., Bastiaanssen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. Physiol Rev 2019;99:1877–2013. https://doi.org/10.1152/physrev.00018.2018.

[109] Mouzaki M, Comelli EM, Arendt BM, Bonengel J, Fung SK, Fischer SE, et al. Intestinal microbiota in patients with nonalcoholic fatty liver disease. Hepatology 2013;58:120–7. https://doi.org/10.1002/hep.26319.

[110] Wigg AJ, Roberts-Thomson IC, Grose RH, Cummins AG, Dymock RB, McCarthy PJ. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor α in the pathogenesis of non-alcoholic steatohepatitis. Gut 2001;48:206–11. https://doi.org/10.1136/gut.48.2.206.

[111] Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, et al. Gut Microbiome-Based Metagenomic Signature for Non-invasive Detection of Advanced Fibrosis in

Human Nonalcoholic Fatty Liver Disease. Cell Metab 2017;25:1054-1062.e5. https://doi.org/10.1016/j.cmet.2017.04.001.

[112] Wang SC, Chen YC, Chen SJ, Lee CH, Cheng CM. Alcohol addiction, gut microbiota, and alcoholism treatment: A review. Int J Mol Sci 2020;21:1–11. https://doi.org/10.3390/ijms21176413.

[113] Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940–7. https://doi.org/10.1016/j.jhep.2013.12.019.

[114] Ying W, Jing T, Bing C, Baifang W, Dai Z, Bingyuan W. Effects of alcohol on intestinal epithelial barrier permeability and expression of tight junction-associated proteins. Mol Med Rep 2014;9:2352–6. https://doi.org/10.3892/mmr.2014.2126.

[115] 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 dependenc. Biol Psychiatry 2014;76:725–33. https://doi.org/10.1016/j.biopsych.2014.02.003.

[116] Chen Y, Yang F, Lu H, Wang B, Chen Y, Lei D, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. Hepatology 2011;54:562–72. https://doi.org/10.1002/hep.24423.

[117] Qin N, Yang F, Li A, Prifti E, Chen YY, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature 2014;513:59–64. https://doi.org/10.1038/nature13568.

[118] Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology 2005;41:422–33. https://doi.org/10.1002/HEP.20632.

[119] Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP

and IL-6 in patients with cirrhosis. J Hepatol 2013;58:911–21. https://doi.org/10.1016/J.JHEP.2012.12.011.

[120] Cirera I, Martin Bauer T, Miguel N, Vila J, Grande L, Taurá P, et al. Bacterial translocation of enteric organisms in patients with cirrhosis 2001;34:32–7. https://doi.org/10.1016/S0168-8278(00)00013-1.

[121] Singh R, Bullard J, Kalra M, Assefa S, Kaul AK, Vonfeldt K, et al. Status of bacterial colonization, Toll-like receptor expression and nuclear factor-kappa B activation in normal and diseased human livers. Clin Immunol 2011;138:41–9.

[122] Dinan TG, Cryan JF. Gut-brain axis in 2016: Brain-gut-microbiota axis-mood, metabolism and behaviour. Nat Rev Gastroenterol Hepatol 2017;14:69–70. https://doi.org/10.1038/nrgastro.2016.200.

[123] Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry 2016;21:786–96. https://doi.org/10.1038/mp.2016.44.

[124] Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, et al. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder. J Affect Disord 2016;202:254–7. https://doi.org/10.1016/j.jad.2016.05.038.

[125] Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 2015;48:186–94. https://doi.org/10.1016/j.bbi.2015.03.016.

[126] Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linløkken A, Wilson R, et al. Correlation between the human fecal microbiota and depression. Neurogastroenterol Motil 2014;26:1155–62. https://doi.org/10.1111/nmo.12378.

[127] Kurokawa S, Tomizawa Y, Miyaho K, Ishii D, Takamiya A, Ishii C, et al. Fecal

Microbial and Metabolomic Change during Treatment Course for Depression: An Observational Study. J Psychiatr Res 2021. https://doi.org/10.1016/j.jpsychires.2021.05.009.

[128] Erny D, De Angelis ALH, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci 2015;18:965–77. https://doi.org/10.1038/nn.4030.

[129] Erspamer V. Occurrence of indolealkylamines in nature. 5-Hydroxytryptamine Relat Indolealkylamines 1966:132–81. https://doi.org/10.1007/978-3-642-85467-5_4.

[130] Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Kynurenine pathway metabolism and the microbiota-gut-brain axis. Neuropharmacology 2017;112:399–412. https://doi.org/10.1016/J.NEUROPHARM.2016.07.002.

[131] Long-Smith C, O'Riordan KJ, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota-Gut-Brain Axis: New Therapeutic Opportunities. Annu Rev Pharmacol Toxicol 2020;60:annurev-pharmtox-010919-023628. https://doi.org/10.1146/annurev-pharmtox-010919-023628.

[132] Wang FB, Powley TL. Vagal innervation of intestines: afferent pathways mapped with new en bloc horseradish peroxidase adaptation. Cell Tissue Res 2007;329:221–30. https://doi.org/10.1007/S00441-007-0413-7.

[133] Fülling C, Dinan TG, Cryan JF. Gut Microbe to Brain Signaling: What Happens in Vagus…. Neuron 2019;101:998–1002. https://doi.org/10.1016/J.NEURON.2019.02.008.

[134] Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition 2016;32:315–20. https://doi.org/10.1016/j.nut.2015.09.003.

[135] Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. Clin Nutr 2019;38:522–8. https://doi.org/10.1016/j.clnu.2018.04.010.

[136] Meyyappan AC, Forth E, Wallace CJK, Milev R. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. BMC Psychiatry 2020;20. https://doi.org/10.1186/S12888-020-02654-5.

[137] Dalal R, Mcgee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database Syst Rev 2017;2017. https://doi.org/10.1002/14651858.CD008716.pub3.

[138] Mittal VV, Sharma BC, Sharma P, Sarin SK. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol 2011;23:725–32. https://doi.org/10.1097/MEG.0b013e32834696f5.

[139] Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: A randomized, controlled trial. Gastroenterology 2014;147:1327-1337.e3. https://doi.org/10.1053/j.gastro.2014.08.031.

[140] D'Mello C, Ronaghan N, Zaheer R, Dicay M, Le T, MacNaughton WK, et al. Probiotics improve inflammation-associated sickness behavior by altering communication between the peripheral immune system and the brain. J Neurosci 2015;35:10821–30. https://doi.org/10.1523/JNEUROSCI.0575-15.2015.

[141] Liu R, Kang JD, Sartor RB, Sikaroodi M, Fagan A, Gavis EA, et al. Neuroinflammation in Murine Cirrhosis Is Dependent on the Gut Microbiome and Is Attenuated by Fecal Transplant. Hepatology 2020;71:611–26. https://doi.org/10.1002/hep.30827.

[142] Bajaj JS, Gavis EA, Fagan A, Wade JB, Thacker LR, Fuchs M, et al. A Randomized Clinical Trial of Fecal Microbiota Transplant for Alcohol Use Disorder. Hepatology 2020:hep.31496. https://doi.org/10.1002/hep.31496.

[143] Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology 2017;66:1727–38. https://doi.org/10.1002/hep.29306.

[144] Bajaj JS, Salzman NH, Acharya C, Sterling RK, White MB, Gavis EA, et al. Fecal Microbial Transplant Capsules Are Safe in Hepatic Encephalopathy: A Phase 1, Randomized, Placebo-Controlled Trial. Hepatology 2019;70:1690–703. https://doi.org/10.1002/hep.30690.

[145] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–81. https://doi.org/10.1056/NEJMOA0907893.

[146] Bajaj JS, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, et al. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. PLoS One 2013;8:e60042. https://doi.org/10.1371/journal.pone.0060042.

[147] Patel V, Lee S, McPhail M, Da Silva K, Guilly S, Zamalloa A, et al. Rifaximin reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. J Hepatol 2021. https://doi.org/10.1016/J.JHEP.2021.09.010.

[148] Senzolo M, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, et al. beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. Liver Int 2009;29:1189–93. https://doi.org/10.1111/J.1478-3231.2009.02038.X.

[149] China L, Maini A, Skene SS, Shabir Z, Sylvestre Y, Colas RA, et al. Albumin Counteracts Immune-Suppressive Effects of Lipid Mediators in Patients With Advanced Liver Disease. Clin Gastroenterol Hepatol 2018;16:738-747.e7. https://doi.org/10.1016/J.CGH.2017.08.027.

[150] Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet (London, England) 2018;391:2417–29. https://doi.org/10.1016/S0140-6736(18)30840-7.

[151] China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med 2021;384:808–17. https://doi.org/10.1056/NEJMOA2022166.

Tables

Table 1.

Author and Year	Study design	Subjects	NAFLD diagnosis	Psychiatric assessment	Findings and significance
Kim et al (2019)[30]	Cross-sectional	10 484 subjects Identified from a national database	FLI, HSI, USFLI	PHQ-9	Prevalence of depression higher in subjects with NAFLD. Patients with depression 1.6-2.2 fold more likely to have NAFLD. Depression was not associated with NAFLD-related advanced fibrosis.
Labenz et al (2020)[35]	Retrospective cohort	19,871 patients with NAFLD, 19,871 matched controls	Database ICD-10 coding (NAFLD/NASH)	Database ICD-10 code (depression)	Within 10 years, 21.2% patients with NAFLD were diagnosed with depression, compared to 18.2% controls (p<0.001). HR for depression was 1.21 (p<0.001) and for first prescription of antidepressant medication (HR 1.21, p<0.001).
Tomeno et al (2015)[28]	Prospective cohort	258 patients with NAFLD	Histological	MDD diagnosis based on DSM-IV-TR. Stable/unstable based on being in full/partial remission as per DSM-IV-TR criteria.	12% comorbid with MDD. MDD NAFLD patients had more severe histological steatosis, higher NAFLD score, high levels of AST, GGT and ferritin. MDD NAFLD patients had poorer response to standard of care for NAFLD, including weight loss.
Weinstein et al (2011)[34]	Cross-sectional	878 CLD patients	Pathology and/or radiologic	Self-reported depression (yes/no) and	23.6% of CLD patients had a diagnosis of

		(184 NAFLD, 190 HBV, 504 HCV)	testing (not specified)	use of antidepressant medication	depression, 27.2% of NAFLD patients had a diagnosis of depression.
Youssef et al (2013)[29]	Cross-sectional	567 patients with NAFLD	Histological	HADS	Subclinical and clinical depression observed in 53% and 14% of patients, respectively. Depression associated with more severe hepatocyte ballooning in dose-dependent manner.

Table 1. Published studies analysing NAFLD and depression.

Abbreviations; AST: aspartate aminotransferase; CLD: chronic liver disease; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision; FLI: Fatty Liver Index; GGT: gamma glutamyl transferase; HADS: Hospital Anxiety and Depression Scale; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: Hazard Ratio; HSI: Hepatic Steatosis Index; ICD-10 International Classification of Diseases; MDD: Major Depressive Disorder; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; PHQ-9: Patient Health Questionnaire-9; USFLI: US Fatty Liver Index.

Table 2.

Author and Year	Study design	Subjects	Psychiatric assessment	Neuro-psychological assessment	Findings and significance
Barboza et al (2016)[53]	Observational	43, HCV cirrhosis	BDI-II	D-KEFS TMT NCT WAIS-III	Positive association between depressive symptoms and HE severity.
Hassan et al (2014)[61]	Case - control	35, HCV cirrhosis	HAM-D	CASI	No association between depression and mHE.
Hilsabeck at al (2003)[54]	Observational	21, chronic HCV	BDI-II	BVMT-R SDMT TMT WAIS-III	Trend towards higher BDI-II scores in patients with more cognitive complaints.
Malaguarnera et al (2011)[55]	Randomised double blind placebo controlled	33 + 34 (placebo), cirrhosis and mHE	BDI	PHES TMT	BDI score pre intervention indicative of moderate depression.
Malaguarnera et al (2018)[56]	Randomised placebo controlled, observational	35 + 35 (placebo), cirrhosis and mHE	BDI	PHES	BDI score pre intervention indicative of moderate depression.
Nardelli et al (2013)[20]	Observational	60, cirrhosis	Zung-STH	PHES	No differences in psychological test score between patients with or without minimal HE.
Stewart et al (2011)[57]	Observational	75, cirrhosis	BDI-II	CVLT TMT WAIS-III	Higher BDI-II scores in patients with decrease in cognitive function in domains of working memory.
Telles-Correia et al (2015)[58]	Observational	60, cirrhosis	HADS	PHES	No correlation between HADS and PHES, but correlation

					between anhedonia, loss of energy and some parts of PHES.
Xiao et al (2018)[60]	Cross-sectional	341, HBV cirrhosis	HADS	NCT-A	HADS-D subscore higher in NCT-A positive patients.

Table 2. Published studies analysing depression and hepatic encephalopathy in cirrhosis.

Abbreviations: BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory second edition; BVMT-R, Brief Visuospatial Memory Test – Revised; CASI, Cognitive Abilities Screening Instrument; CVLT, California Verbal Learning Test; D-KEFS TMT, Delis-Kaplan Executive Function System Trail Making Test; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; HE, hepatic encephalopathy; HBV, hepatitis B; virus; HCV, hepatitis C virus; mHE, minimal hepatic encephalopathy; NCT-A, Number Connection Test – A; NCT, Number Connection Test; PHES, Psychometric Hepatic Encephalopathy Score; SDMT, Symbol Digital Modalities Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale third revision; Zung-STH, Zung Self Rating Depression Scale.

Table 3.

Author and Year	Study design	Subjects	Psychiatric assessment	Findings and significance
D'Mello et al (2009)[90]	Animal study	Mouse model of inflammatory liver injury (BDL ligated)	Sickness behaviour	In the presence of hepatic inflammation, TNF-α signaling stimulated cerebral microglia to produce MCP-1/CCL2 to recruit monocytes into the brain. Inhibition of monocyte recruitment led to improvement in sickness behaviour of the mice.
D'Mello et al (2013)[89]	Animal study	Mouse model of inflammatory liver injury (BDL ligated)	Sickness behaviour	Increased monocyte specific rolling and adhesion along CECs was observed in mice with hepatic inflammation. Peripheral TNF-TNFR1 signaling and P-selectin were found to be central to monocyte-CEC adhesion which led to microglial activation and development of sickness behaviour.
Ko et al (2013)[31]	Cross-sectional	125 patients with cirrhosis (varying aetiologies)	HAM-D	HAM-D was correlated with AST, but not Child Pugh score.
Ko et al (2013)[91]	Cross-sectional	59 patients with cirrhosis (varying aetiologies)	HAM-D	The percentage of CD8 T-cells, but not CD3 nor CD4 cells, positively correlated with depression, after controlling for age and Child Pugh score.

Table 3. Published studies examining the relationship between systemic inflammation, depression and liver disease.

Abbreviations; AST: aspartate aminotransferase; BDL: bile duct ligated; CECs; cerebrovascular endothelial cells; HAM-D: Hamilton Depression Rating Scale; MCP-1/CCL2:

monocyte chemoattractant protein-1; TNF – α: tumour necrosis factor alpha; TNFR1: tumour necrosis factor receptor 1.

Figure Legends

Fig. 1. The role of gut-derived systemic inflammation in the pathophysiology of cirrhosis and depression.

Gut dysbiosis occurs in cirrhosis with decreased microbial diversity, increased pathogenic microbes and small bowel bacterial overgrowth. This reduces intestinal barrier function resulting in increased translocation of bacteria (and their products (LPS, peptidoglycan, flagellin, bacterial DNA)) and PAMPs into the portal circulation leading to endotoxaemia. This results in systemic inflammation and increased levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6). These cytokines communicate with the brain via neural pathways, CEC ad CVO signaling and peripheral immune cell-to-brain signaling leading to microglial activation, changes in neural activity and ultimately depressive symptoms.

In cirrhosis reduced synthetic and reticuloendothelial function results in an acquired immunodeficiency and innate immune dysfunction which, coupled with systemic inflammation, is referred to as cirrhosis-associated immune dysfunction (CAID).

Fig. 2. Potential treatment options to restore gut eubiosis and treat depression in cirrhosis.

The administration of prebiotics, probiotics and faecal microbiota transplant results in favourable gut microbiota composition, decreased bacterial translocation and reduced systemic inflammation. The consequent reduction in pro-inflammatory cytokines may lead to decreased

microglial activation, improved cognition and mood and fewer depressive symptoms. Created with BioRender.com.

Abbreviations: TNF-α: tumour necrosis factor alpha; IFN-γ: interferon-gamma; IL-1β: interleukin 1 beta; IL-6: interleukin 6.

Figures

Figure 1.

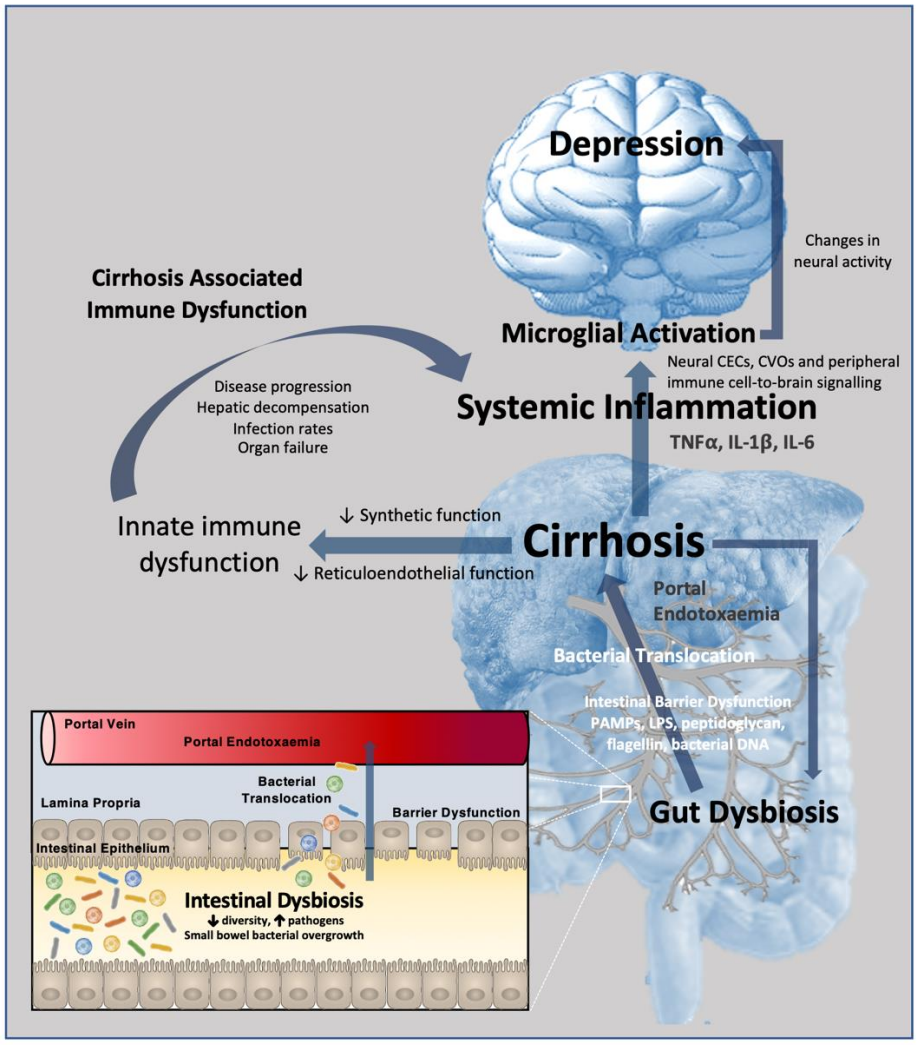
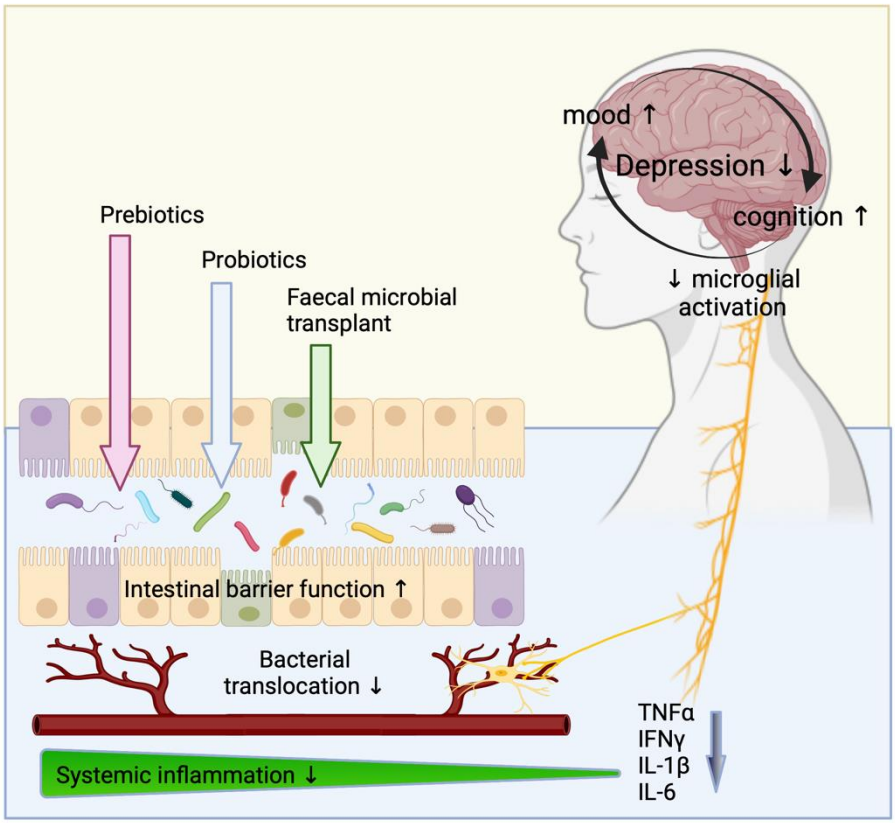


Figure 2.


mood ↑
Depression ↓
cognition ↑
↓ microglial activation
Prebiotics
Probiotics
Faecal microbial transplant
Intestinal barrier function ↑
Bacterial translocation ↓
Systemic inflammation ↓
TNFα
IFNγ
IL-1β
IL-6