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From Liver to Brain: How MAFLD/MASLD Impacts Cognitive Function

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Metabolic dysfunction-associated fatty liver disease or metabolic dysfunction-associated steatotic liver disease (MAFLD/MASLD), is a common chronic liver condition affecting a substantial global population. Beyond its primary impact on liver function, MAFLD/MASLD is associated with a myriad of extrahepatic manifestations, including cognitive impairment. The scope of cognitive impairment within the realm of MAFLD/MASLD is a matter of escalating concern. Positioned as an intermediate stage between the normal aging process and the onset of dementia, cognitive impairment manifests as a substantial challenge associated with this liver condition. Insights from studies underscore the presence of compromised executive function and a global decline in cognitive capabilities among individuals identified as being at risk of progressing to liver fibrosis. Importantly, this cognitive impairment transcends mere association with metabolic factors, delving deep into the intricate pathophysiology characterizing MAFLD/MASLD. The multifaceted nature of cognitive impairment in the context of MAFLD/MASLD is underlined by a spectrum of factors, prominently featuring insulin resistance, lipotoxicity, and systemic inflammation as pivotal contributors. These factors interplay within the intricate landscape of MAFLD/MASLD, fostering a nuanced understanding of the links between hepatic health and cognitive function. By synthesizing the available evidence, exploring potential mechanisms, and assessing clinical implications, the overarching aim of this review is to contribute to a more complete understanding of the impact of MAFLD/MASLD on cognitive function.

Keywords: Abdominal Obesity Metabolic Syndrome • Cognitive Dysfunction • Insulin Resistance • Metabolic Syndrome • Non-Alcoholic Fatty Liver Disease • Oxidative Stress

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Background

Metabolic dysfunction-associated fatty liver disease, or metabolic dysfunction-associated steatotic liver disease (MAFLD/MASLD), is the most common cause of chronic liver disease, affecting a large part of the global population [1]. The global prevalence of MAFLD/MASLD is estimated at 25-30% globally, likely influenced by the escalating epidemics of type 2 diabetes mellitus (T2DM) and obesity [2,3].

Beyond its main involvement in liver function, MAFLD/MASLD is closely related to a spectrum of extrahepatic manifestations that affect several organs and systems, underscoring the complexity of MAFLD/MASLD [4]. Individuals with MAFLD/MASLD often develop a constellation of metabolic abnormalities, such as insulin resistance (IR), dyslipidemia, and obesity, which form a complex interplay that contributes to disease progression [5,6]. In addition, MAFLD/MASLD has been associated with an increased risk of cardiovascular disease, T2DM, and chronic kidney disease [7,8]. In this regard, poor cognitive performance might be an extrahepatic manifestation in MAFLD/MASLD individuals.

Mild cognitive impairment is an intermediate stage between typical aging and dementia. This transitional phase can evolve into dementia, frequently manifesting as Alzheimer disease [9]. Observational studies have revealed that individuals at high risk of liver fibrosis have impaired executive function, abstract reasoning, and global cognitive function (**Table 1**) [10-16]. The underlying mechanisms of this impairment have not been fully elucidated, but may be related to the pathophysiology of MAFLD/MASLD, led by insulin resistance (IR), lipotoxicity, progressive lipid deposition, lipid peroxidation, and systemic inflammation; all of which have been associated with intestinal dysbiosis, leaky gut, and progressive liver fibrosis [17]. Through a comprehensive review of published research, this review aims to provide a detailed understanding of the intricate relationship between MAFLD/MASLD and cognitive impairment. By synthesizing the available evidence, exploring possible mechanisms, and assessing clinical implications, the aim is to contribute to a more complete understanding of the impact of MAFLD/MASLD on cognitive function.

Epidemiology

Observational studies have provided insights into the relationship between MAFLD/MASLD and cognitive impairment [10,11,13,18,19]. Currently there are no reliable data on the prevalence and incidence of cognitive impairment in individuals with MAFLD/MASLD due to the relatively recent recognition of this condition and the continuing evolution of diagnostic criteria. However, emerging research suggests a potential association between metabolic dysfunction and cognitive impairment in individuals with MAFLD. Seo et al found that people with MAFLD/MASLD had inferior learning, recall, and concentration functions in comparison to those without the liver condition. Importantly, these cognitive deficits were observed independently of the metabolic factors typically associated with MAFLD/MASLD [13]. While Seo et al highlighted the independent cognitive effects of MAFLD/MASLD, later investigations brought attention to the cumulative impact of underlying metabolic factors associated with MAFLD/MASLD [10,11,20]. Weinstein et al observed that individuals with MAFLD/MASLD and T2DM had impaired visuospatial function, while individuals with MAFLD/MASLD without T2DM had no impaired performance on any of the cognitive tests [20]. Additionally, the association with cognitive impairment was found to be more pronounced in individuals at higher risk of liver fibrosis, introducing the concept that the severity of liver involvement could amplify cognitive consequences [10,11]. Cognitive impairment typically manifests at the age of 60 years or older and the risk increases with age [21]. Recent findings from a systematic review have added a temporal dimension to this association, revealing that cognitive impairment in individuals with MAFLD/MASLD tends to exacerbate with age. In particular, cognitive impairment is more pronounced in those aged 37-61 years, suggesting that this disease can contribute to the early onset of cognitive impairment [17].

Risk Factors: The Interplay of MetS, MAFLD/MASLD, and Cognitive Function

The association between MAFLD/MASLD and cognitive impairment is influenced by various risk factors, predominately those associated with metabolic syndrome (MetS) [22]. MetS is a complex and increasingly prevalent disease that encompasses a set of interconnected metabolic risk factors such as obesity, hypertension, dyslipidemia, and insulin resistance (IR) [23].

Insulin Resistance

IR poses a substantial risk as it not only affects glucose metabolism but also exerts influences on cognitive processes [24]. Although insulin can pass the blood–brain barrier (BBB), insulin receptors are not uniformly distributed across the brain; instead, they are concentrated in specific regions such as the olfactory bulb, hypothalamus, hippocampus, cerebral cortex, and cerebellum [25]. The presence of hyperglycemia associated with IR triggers detrimental effects on brain function, involving the accumulation of advanced glycation end products, oxidative stress, and glucose neurotoxicity [26]. Furthermore, the disruption of insulin signaling in the brain can lead to cognitive impairment by downregulating BBB insulin receptors and reducing the transport of insulin into the brain [27].

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Table 1. Insights from studies MAFLD/MASLD and cognitive impairment.

Author	Study design	Group	Purpose	Measuring instrument for cognitive impairment	Results
Elliott et al (2013) [12]	Cohort	224 NAFLD 100 controls	To assess functional physical capacity and cognitive abilities	Psychological Health Assessment Questionnaire (PHAQ) y Cognitive Failures Questionnaire (CFQ)	NAFLD patients: • Significantly worse functional capacities (p<0.001) • Greater cognitive difficulty (p<0.0001) • Age (p=0.0001) • Fatigue (p=0.01) • Lower albumin (p=0.02) • Total bilirubin (p=0.04)
Seo et al (2016) [13]	Cross sectional	4472 participants from 20 to 59 years old	To evaluate liver enzyme activity and cognitive assessment	SRRT SDLT SDST	NAFLD patients: • Lower SDLT performance (β=0.726, 95% confidence interval [CI]: 0.105-1.347) • Increased ALT (β=0.018, 95% CI 0.006-0.030) and AST (β=0.021, 95% CI 0.005-0.037) activity correlated with lower SDLT performance • Increased ALT was also correlated with decreased performance on the SDST (β=0.002, 95% CI 0.0001-0.004)
Tuttolomondo et al (2018) [14]	Case-control	80 NAFLD 83 without liver or cardiovascular disease	To assess cognitive performance in patients with NAFLD	MMSE (74 with MAFL y 65 controls)	NAFLD patients: • Lower mean score on the MMSE (26.9±1.6 vs 28.0±1.36; p=0.005) compared with patients without NAFLD. • No significant differences were observed regarding the MMSE score according to the severity of fibrosis (fibrosis 0-1: 27.8±2.2 and fibrosis >1: 26.9±2.9) p 0.131
Weinstein et al (2019) [10]	Cross sectional	1287 participants 378 (29%) with NAFLD	To assess the relationship of NAFLD and its severity, using the NAFLD Fibrosis Score (NFS) with cognitive performance.	Trail – making test Abstract reasoning tests Hooper's Visual Organization Test (visual perception)	NAFLD and cognitive performance were not associated; however patients with poorer cognitive performance on tests were associated with higher risk of advanced fibrosis in patients with NAFLD (β=-0.11±0.05; P=0.028)

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Table 1 continued. Insights from studies MAFLD/MASLD and cognitive impairment.

Author	Study design	Group	Purpose	Measuring instrument for cognitive impairment	Results
Moretti et al (2019) [15]	Cross sectional	671 NAFLD 687 controls	To assess the relationship between NAFLD and performance with frontal, executive functions, behavior changes (mood, apathy, and anxiety)	FAB Test (Frontal Assessment Battery) Becks test HAM-A test AES-C	NAFLD patients: • Worse executive and frontal functions • (FAB Test F chi² 0.87, DF: 2.43, p: 0.01) • Behavioral changes: depressive state, anxiety and apathy
Celikbilek et al (2018) [16]	Cross sectional	70 NAFLD and 73 controls matched by age and sex from 18 to 70 years	To assess cognitive functions	Turkish version of the MoCa test	NAFLD patients: • Deficits in each cognitive domain: visuospatial (p<0.05) and executive (p<0.05) functioning • Significantly lower MoCA test scores (p<0.05) • Multivariate model, educational level [2.79 (1.12-6.96); P<0.05] and area of residence [5.68 (2.24-14.38); P<0.001] were independently associated with cognitive dysfunction in both the NAFLD and healthy groups • MoCA scores were negatively correlated with fibrosis scores 4 in participants with NAFLD (r=-0.359; P<0.05)

AES-C – Apathy Evaluation Scale – Clinician Version; CFQ: Cognitive Failures Questionnaire; FAB Test – Frontal Assessment Battery Test; HAM-A Test – Hamilton Anxiety Rating Scale; MAFLD – metabolic dysfunction-associated fatty liver disease; MMSE – mini-mental state examination; MoCA – Montreal Cognitive Assessment; NAFLD – non-alcoholic fatty liver disease, NFS – NAFLD fibrosis score; PHAQ – Psychological Health Assessment Questionnaire; SDLT – Stroop Color and Word Test – Delayed Recall; SDST – Stroop Color and Word Test – Sustained Attention; SRRT – Symbol Digit Modalities Test.

Hypertension

Cognitive impairment is commonly associated with hypertension [28]. Recognized as a well-established risk factor for cerebrovascular disease, recent findings emphasize the significant impact of hypertension on the progression of cognitive impairment, vascular dementia, and Alzheimer disease [29]. The adverse effects of hypertension extend to the structural and functional aspects of the cerebral microcirculation, leading to microvascular rarefaction, cerebromicrovascular endothelial dysfunction, and neurovascular uncoupling. These changes collectively compromise the integrity of the cerebral blood supply [30].

Obesity

Obesity is a well-established risk factor for cognitive impairment [31]. Adipose tissue-derived inflammatory signals and adipokines can impact the brain, leading to neuroinflammation and cognitive dysfunction [32-34]. Moreover, obesity is often accompanied by systemic inflammation, which is recognized as a key player in the development of cognitive disorders [35,36].

Systemic Atherosclerosis

MAFLD/MASLD is marked by systemic atherosclerosis, manifesting as a procoagulation state accompanied by inflammation,

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endothelial dysfunction, reactive oxidative stress, and heightened platelet activity. These factors collectively contribute to the development of atherosclerotic lesions and microvascular disease [37-39]. Additionally, MAFLD/MASLD is associated with asymptomatic brain lesions and changes in cerebral perfusion, which contribute to the risk of vascular dementia [37].

Mechanisms Underlying Cognitive Impairment in MAFLD/MASLD

MAFLD/MASLD has been proposed as a "multiple-hit pathogenesis" due to its various causative factors, such as genetic and epigenetic factors, gut microbiota, metabolic pathways, nutritional factors, and IR [40-42]. Nevertheless, the pathological mechanisms by which MAFLD/MASLD affects other systems, especially the central nervous system (CNS), have not yet been fully elucidated [43]. The key components contributing to cognitive dysfunction in MAFLD/MASLD include IR, systemic inflammation, lipotoxicity, vascular dysfunction, and dysbiosis [37,38]. Recent studies have helped broaden the perspective to fully understand the relationship between MAFLD/MASLD and cognitive dysfunction [19,44].

Vascular Alterations and Inflammation

Individuals with MAFLD/MASLD typically exhibit chronic low-grade inflammation, which extends systemically [45]. The association between inflammatory status and cognitive decline was shown in a cross-sectional study including 50-64-year-old patients with MAFLD/MASLD who had high indicators of inflammation: white blood cell count (WBC) and high-sensitivity C-reactive protein (hsCRP) [46]. This association may be attributed to the accumulation of intrahepatic fat, causing damaged hepatocytes to release abundant proinflammatory cytokines, leading to recruitment of macrophages to the liver [47]. The ongoing proinflammatory cycle of macrophage recruitment in the liver is maintained in a positive feedback loop by the secretion of cytokines and chemokines into the systemic circulation, contributing to the development of persistent low-grade systemic inflammation [48]. Under normal conditions, the CNS is functionally segregated from the systemic circulation by the BBB [49]. Nevertheless, cytokines and other proinflammatory factors can penetrate the brain through active transportation or by directly entering circumventricular regions, unique communication points between the bloodstream, brain tissue, and cerebrospinal fluid (CSF), characterized by absence of the BBB [50]. Once damage-associated molecular patterns (DAMPs) and proinflammatory cytokines reach the CNS, they activate microglia, increasing BBB permeability and thus promoting release of proinflammatory cytokines and initiating a complex immune response in the CNS. This process leads to migration of immune cells and inflammatory factors, resulting in a neurotoxic effect [51]. Together, these factors promote chronic neuroinflammation and formation of beta-amyloid plaques, which trigger cognitive deterioration due to neuronal death and injury [52].

Insulin Resistance

Another important metabolic indicator that has been associated with cognitive impairment in patients with MAFLD/MASLD is IR, as demonstrated in an observational study that evaluated the determinants of memory function in obese middle-aged patients with T2DM or newly diagnosed prediabetes with MAFLD/MASLD [44]. The findings indicated a direct correlation between memory performance and the extent of IR. This can be attributed to reduced expression of insulin receptors in the brain, leading to a subsequent decline in neuronal plasticity, neuroprotection, neuronal growth, and energy metabolism –functions typically supported by insulin under normal physiological conditions [53]. Additionally, lower memory function was linked to increased ectopic liver fat, which is itself associated with exposure to a high-fat diet (HFD), thereby negatively impacting memory function dependent on the hippocampus [44].

To comprehend the metabolic processes, it is essential to position the liver as the central organ responsible for metabolizing sugars such as fructose and glucose [54]. Additionally, once hepatic glycogen stores are saturated, the metabolic pathways of fructose lead to de novo synthesis of triglycerides [5]. Consequently, the impact of high-fructose diets (HFr) on hepatic metabolism mirrors that of a high-fat diet (HFD), amplifying the progression of MAFLD/MASLD. This escalation is attributed to disruptions such as oxidative stress, IR, lipid peroxidation, mitochondrial dysfunction, proinflammatory cytokines, and adipokines [55,56]. Furthermore, hippocampal-dependent and -independent memory disorders have been described in fructose-fed rodents, which is caused by hippocampal neuronal expression of GLUT4 and 5, which are specific transporters for fructose [57] by increasing the intake of fructose by neurons, neutralization mechanisms and redox balance decay, producing an overall increase in free radicals, advanced glycation products, glycoxidation, and oxidative stress. These biochemical effects are related to mitochondrial dysfunction, lipid peroxidation, posttranslational alterations of proteins, reduction of acetylcholinesterase, brain dysfunction, and reduced plasticity [58].

Lipotoxicity

The concept of lipotoxicity emerges as a crucial factor in understanding the pathophysiological mechanisms associated with metabolic diseases such as MAFLD/MASLD [59]. Lipotoxicity, defined as adverse effects resulting from accumulation of lipids in non-adipose tissues, particularly manifests in the liver, leading

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to 2 distinct phenotypes: MAFLD/MASLD and metabolic dysfunction-associated steatohepatitis (MASH) [60]. This process involves the release of free fatty acids (FFAs) from insulin-resistant adipocytes, triggering inflammatory pathways, cellular dysfunction, and lipoapoptosis. The liver, unable to eliminate excess FFAs, undergoes hepatocyte dysfunction and injury, contributing to the progression of lipotoxic conditions [61]. Lipotoxicity extends its impact beyond the liver, affecting various organs due to factors like HFr and HFD, leading to obesity and IR [62]. In the context of HFr and HFD, lipid accumulation increases intrahepatic triglycerides, activating enzymes like 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), and promoting inflammation. Furthermore, SFAs like palmitic acid from HFD induce chronic low-grade inflammation, leading to cognitive decline and neurodegenerative diseases [63]. Furthermore, the dysregulation caused by lipotoxicity in the brain involves orexin, a neuropeptide crucial for cognitive functions, executive function, and learning. Loss of orexin signaling, particularly type A, is associated with memory impairment, obesity, learning deficits, and neuroinflammation. Targeting the orexin system may offer a potential avenue for mitigating diet-induced cognitive decline and addressing neurodegenerative diseases characterized by orexin loss [64].

Dysbiosis

Another pathophysiological aspect identified in MAFLD/MASLD-related cognitive impairment is alteration of the intestinal microbiota (dysbiosis). The intricate balance of the microbiota is influenced not only by dietary choices but also by various lifestyle factors, including exercise and sleep [65]. In fact, physical activity is crucial to maintain gut microbiota equilibrium, nourishing its diversity, which increases hippocampal volume [66]. Dysbiosis is associated with increased intestinal permeability to pathogen-associated molecular patterns (PAMPS), such as lipopolysaccharides (LPS), and other bacterial products [43]. The heightened influx of PAMPs through the portal vein initiates activation of TLR4 receptors located in Kupffer liver cells (KC) and hepatic stellate cells (HSC). This activation sets off the generation of pro-inflammatory cytokines implicated in the development of metabolic-dysfunction-associated steatohepatitis (MASH) [67]. The impact of dysbiosis extends beyond the liver, as TLR expression and activation are also observed in neurons, which experience the systemic inflammatory conditions associated with MAFLD/MASLD [68]. Additionally, low levels of short-chain fatty acids (SCFAs), along with hyperammonemia and microbial taxa alterations, lead to gut neuroinflammation and dysbiosis, impacting brain metabolism through the microbiota-gut–brain axis [69].

The Brain–Gut–Liver Axis

The gut–brain axis is a bidirectional communication system that involves information exchange between the CNS and the gastrointestinal tract. This intricate network incorporates neural, endocrine, and immune systems (**Figure 1**) [70]. Communication between the gut microbiome and the CNS is facilitated by microbiome-derived intermediates, which include compounds such as short-chain fatty acids, secondary bile acids, tryptophan metabolites, glutamate, γ-aminobutyric acid (GABA), dopamine, norepinephrine, serotonin, and histamine [71]. These bioactive substances act as messengers, playing a crucial role in modulating various physiological and neurological processes [72]. Conversely, communication from the brain to the gastrointestinal tract is facilitated by the vagal nerve, the autonomic nervous system, and the hypothalamic–pituitary–adrenal (HPA) axis [73].

Neurological Pathways

Physiologically, the enteric nervous system (ENS), through vagal sensory nerves and sympathetic neurons, directly or indirectly senses the intestinal microenvironment and consequently convert chemical signals from the environment into nerve impulses, which spread to the entire intestine and the CNS through the vagal nerve [74,75]. Vagal afferent neurons play a crucial role in this regulatory process by expressing receptors for several intestinal peptides, such as cholecystokinin (CCK), ghrelin, leptin, peptide tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1), and 5-hydroxytryptamine (5-HT), among others. These peptides are secreted by enteroendocrine cells (EEC) of the gastrointestinal tract [76]. Once specific gut peptides are detected by vagal afferent neurons, the relevant gut information is transmitted to the CNS, triggering various reactions [11]. The gut microbiota also plays a key role in modulating the levels of these gut peptides, such as CCK, ghrelin, leptin, PYY, GLP-1 and 5-HT., and this microbial influence extends to the vagal afferent pathway [77].

Endocrine Pathways

The HPA-axis is a crucial component of the endocrine pathways within the brain–gut–liver axis, playing a central role in the body's response to stress [78]. When the brain detects stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which signals the pituitary gland to release adrenocorticotropic hormone (ACTH) [79]. ACTH, in turn, stimulates the adrenal glands to produce cortisol and other stress-related hormones. These hormones not only influence various physiological processes throughout the body, but also affect the gut [80].

Cortisol receptors are expressed on various cells in the intestine, which directly influences their function [81]. Additionally, cortisol can influence the gut microbiota by modifying factors such as intestinal transit time, intestinal permeability, and nutrient availability. These alterations subsequently contribute to changes in the composition and diversity of the gut microbiome [82,83]. In the brain, cortisol exerts its influence by

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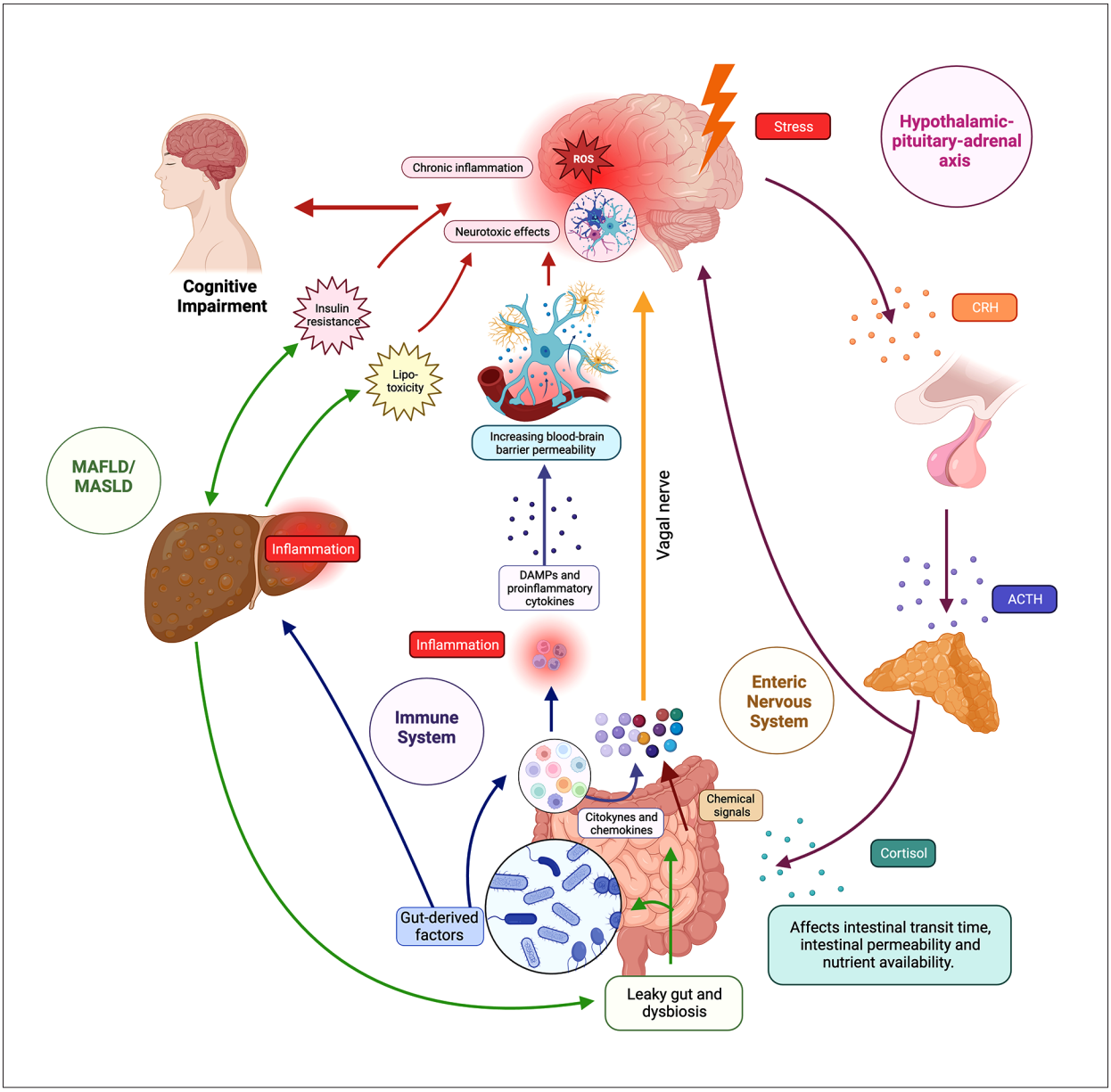

Figure 1. The brain–gut–liver axis. The figure illustrates the intricate network of the brain–gut–liver axis, showing bidirectional communication pathways between the central nervous system (CNS), gastrointestinal tract, and liver. The axis involves neurological, endocrine, and immune components, influencing physiological and cognitive processes. In the neurological pathways, the enteric nervous system (ENS) senses the intestinal microenvironment, transmitting signals via vagal sensory nerves to the afferent neurons that express receptors for gut peptides (eg, CCK, ghrelin, leptin), influencing reactions and gut microbiota modulates gut peptide levels. In endocrine pathways, the hypothalamic–pituitary–adrenal (HPA) axis responds to stress, releasing corticotropin-releasing hormone (CRH) and stimulating cortisol production; cortisol impacts physiological processes, gut microbiota, and binds to glucocorticoid receptors (GR) in the brain. In immune pathways, gut-associated lymphoid tissue (GALT) communicates with the CNS through signaling molecules, influencing neuroimmune responses. Microbiome-derived products modulate immune cells and inflammation locally and systemically. Regarding the liver and cognitive impairment, the liver is connected to the gut via the portal vein and receives signals affecting liver health and the gut–brain axis. Disruptions in the axis, as seen in metabolic-associated fatty liver disease (MAFLD) and metabolic-associated steatosis of liver disease (MASLD), lead to "leaky gut", which contributes to systemic inflammation, impacting cognitive function through interconnected pathways such as insulin resistance (IR) and lipotoxicity. ACTH – adrenocorticotropic hormone; CRH – corticotropin-releasing hormone, DAMPS – damage-associated molecular patterns; MAFLD – metabolic-associated fatty liver disease; MASLD – metabolic-associated steatotic liver disease. *Created using Biorender.*

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binding to glucocorticoid receptors (GR) located in the hippocampus, amygdala, and prefrontal cortex [84].The proposed mechanism within the gut–brain axis suggests that gut microbes trigger stress circuits in the CNS via the vagus nerve and sensory neurons of the ENS [85,86].

Immune Pathways

Immune pathways are another integral dimension of the complex interconnections within the gut–brain axis. The gut, the main interface with the external environment, is endowed with a robust immune system, including an intricate network of immune cells, mucosal surfaces, and immunomodulatory molecules [87]. Communication between the intestinal immune system and the CNS involves both direct and indirect mechanisms [88]. Gut-associated lymphoid tissue (GALT) communicates with the CNS through release of signaling molecules, such as cytokines and chemokines, which influence neuroimmune responses [89-91]. Additionally, microbiome-derived products, such as short-chain fatty acids and various metabolites, can influence immune cell function and modulate inflammation both locally in the gut and systemically [92-94].

Liver and Cognitive Impairment

In the overall framework of the brain–gut–liver axis, the liver emerges as a central player in the orchestration of physiological responses, especially regarding MAFLD/MASLD and its effects on cognitive function. The liver, intimately connected to the gut via the portal vein, receives signals from gut-derived microbial molecules and products, creating a direct link between liver health and the gut–brain axis [95]. Disruptions of this axis, as occurs in MAFLD/MASLD, can increase intestinal permeability and allow translocation of harmful substances into the bloodstream. This phenomenon, known as „leaky gut", can contribute to systemic inflammation and affect cognitive processes through the previously discussed pathways [96,97].

Neurological Manifestations

Multiple neurological manifestations of MAFLD/MASLD have been described, including decreased brain volume, subclinical or clinical cerebrovascular disease, and cognitive impairment [20,46,98]. These findings underscore the existence of brain signatures, which are distinct patterns or indicators within the brain that reflect the impact of MAFLD/MASLD on neurological health.

Brain Volume

The Framingham Study measured brain volume by brain MRI in patients with MAFLD/MASLD and found that this disease is associated with lower total brain volume, corresponding to brain aging in the overall sample at 7.3 years, in patients younger than 60 years, independent of visceral adipose tissue and cardiovascular risk factors [98].

Vascular Disease

Furthermore, a brain magnetic resonance spectroscopy study employing perfusion techniques was conducted to identify subclinical vascular damage in individuals with non-alcoholic fatty liver disease (NAFLD) who did not exhibit overt cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia, and obesity. The findings indicated that NAFLD patients have diminished cerebral perfusion (CBFr) in the semioval center and posterior cingulate cortex, but when the NAFLD cohort was categorized into subgroups based on factors like NAS score, presence/absence of NASH/fibrosis, and degree of steatosis, no statistically significant differences in CBFr values were observed [99]. Additionally, patients with stroke displayed a heightened prevalence of MAFLD/MASLD, characterized by greater severity according to the National Institutes of Health Stroke Scale, and poorer outcomes in terms of functionality at discharge as per the modified Ranking scale [100]. Exploring the relationship between MASLD and stroke with respect to its location, it was noted that patients with brainstem damage exhibited worsening of the initial NIHSS, along with a higher incidence of stroke progression and severity [101].

White Matter Lesions

Examining white matter lesions in MAFLD/MASLD patients, it was found that while the prevalence of these lesions was comparable between patients with and without MAFLD/MASLD, it was higher in those with MASH compared to non-MASLD individuals. Moreover, a direct correlation emerged between the number of white matter lesions and the degree of liver fibrosis in MASLD patients. However, multivariate analysis suggested that the presence of white matter lesions was closely linked to metabolic diseases in general [46].

Challenges and Treatment

As we have discussed throughout the review, currently there is not a single phenotype of cognitive impairment in individuals with MAFLD/MASLD [10,13,20]. The existing psychometric and neuropsychological test batteries, while valuable, may fall short in capturing the extensive spectrum of cognitive dysfunction implied by the complex interplay of metabolic and liver factors [51]. The multifactorial nature of cognitive impairment in the context of MAFLD/MASLD underscores the need for specialized assessment tools that can provide a more nuanced understanding of the diverse cognitive challenges faced by affected individuals.

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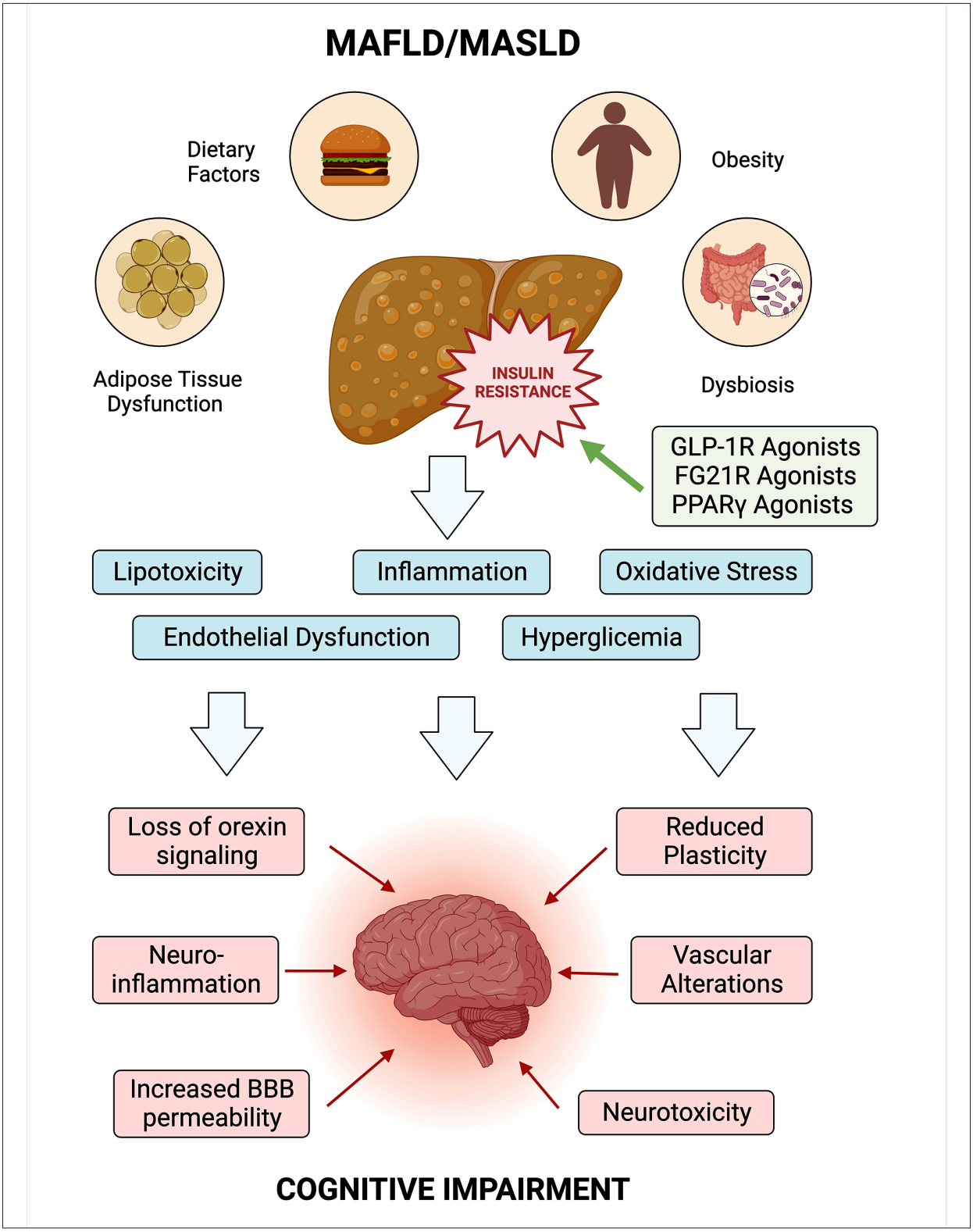

Figure 2. Exploring the link between MAFLD/MASLD, insulin resistance, and cognitive impairment. Insulin resistance serves as a central node linking MAFLD/MASLD to systemic effects, influencing both metabolic and cognitive health. The figure shows potential pathways and shared risk factors. Understanding these intricate relationships is vital for advancing holistic approaches to health and potential interventions. BBB – blood–brain barrier. *Created using Biorender.*

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Furthermore, the cognitive and functional challenges observed carry significant consequences for both healthcare systems and society. The increased demand for medical services, diagnostic procedures, and therapeutic interventions places a substantial burden on healthcare infrastructure. Additionally, the societal implications are profound, encompassing aspects such as reduced quality of life, diminished work productivity, and an increased need for caregiving suport [102].

Potential Treatments

Various treatments for MAFLD/MASLD have been explored, and some may influence cognitive function. Glucagon-like peptide (GLP-1) exhibits neuroprotective and anti-inflammatory properties, potentially reducing neuroinflammation in neurodegenerative diseases [103-105]. Insulin and liraglutide can improve brain damage through the Wnt/β-catenin signaling pathway, offering therapeutic potential for T2DM patients with cognitive impairment in [106]. A clinical trial with liraglutide in AD patients increased glucose transport in the blood–brain barrier, increasing the cerebral glucose metabolic rate [107]. Long-term liraglutide treatment in diabetic mice protected against impaired motor function and dopaminergic neuron loss [108]. Neuroprotective effects of liraglutide on diabetes-induced cognitive impairments were associated with enhanced hippocampal synapses and reduced neuronal apoptosis [109]. Repurposing FDA-approved GLP-1R agonists for neuroinflammation and neurodegeneration treatment requires human clinical trials to assess safety, tolerability, and efficacy [110].

In rats, FGF21 and vildagliptin attenuated IR, brain mitochondrial dysfunction, apoptosis, and cognitive impairment [111]. A study in HFD-fed rats with vildagliptin and dapagliflozin demonstrated improved peripheral insulin sensitivity, reduced weight gain, and prevention of cognitive impairment [112]. Empagliflozin protected cognitive functions in obese mice [12]. PPARγ agonists exhibited protective activity against oxidative damage, mitochondrial dysfunction, and apoptosis in various animal models [113].

Microinjection of synthetic CUR improved spatial memory in rats with multiple sclerosis [114]. Alpha linoleic acid (ALA) showed promise in inhibiting neuroinflammation, apoptotic cell loss, amyloidogenesis, and memory dysfunction [115]. Omega-3 supplementation in controlled clinical trials demonstrated positive outcomes in cognitive function [116]. A study with high-dose omega-3 and omega-6 fatty acid supplementation, combined with antioxidant vitamins, showed favorable improvements in cognitive function, functional capacity, fatigue, physical health, and daily sleepiness in elderly individuals with mild cognitive impairment [117].

Future Directions

The intricate interconnection between MAFLD/MASLD and cognitive impairment underscores the complexity of their impact on both metabolic and neurological well-being. The convergence of insulin resistance with NAFLD appears to exert systemic effects, possibly mediated through chronic inflammation, oxidative stress, and adipokine imbalance. This systemic perturbation may extend its influence to the brain, where the intricate crosstalk between metabolic health and cognitive function becomes apparent (**Figure 2**). Ongoing exploration of the complicated mechanisms linking MAFLD/MASLD with cognitive impairment is imperative. Anticipated advancements in diagnostic tools, treatment strategies, and preventive measures are poised to improve clinical outcomes and enrich the lives of individuals navigating these health challenges. Beyond mere acknowledgment of their coexistence, comprehending the relationship between MAFLD/MASLD and cognitive impairment necessitates a transformative approach to integrated care. This holistic perspective addresses the nuanced interplay between metabolic and cognitive health, holding significant potential to enhance patient outcomes, improve quality of life, and pave the way for future breakthroughs in managing these intertwined conditions.

Conclusions

In conclusion, the intricate relationship between MAFLD/MASLD and cognitive impairment involves a multifaceted interplay of metabolic and neurological factors. The prevalence of MAFLD/MASLD globally, driven by epidemics of T2DM and obesity, highlights the urgent need for a comprehensive understanding of its systemic implications. Beyond its primary impact on liver function, MAFLD/MASLD is associated with a spectrum of extrahepatic manifestations, including cognitive impairment.

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Declaration of figures' authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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