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A narrative review about cognitive impairment in Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD): Another matter to face through a holistic approach

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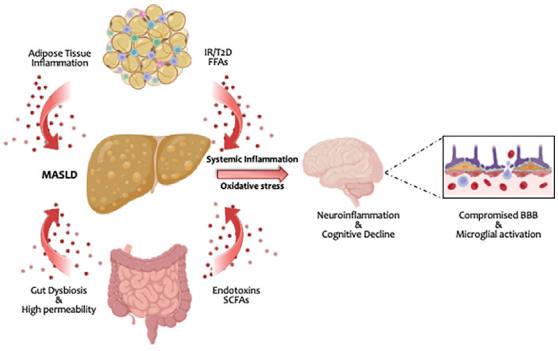
HIGHLIGHTS

- Metabolic disorders are frequently associated with a cognitive decline.
- Inflammation and oxidative stress may contribute to blood brain barrier disruption.
- Dyslipidemia, inflammation and mental disorders share genetic predictors.
- Gut microbiota impacts on mental performance by enhancing inflammation.
- Nutritional and lifestyle interventions may counteract the cognitive decline.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic hepatic disorder worldwide in both adults and children. It is well established that MASLD represents the hepatic manifestation of the metabolic syndrome whose definition includes the presence of obesity, type 2 diabetes (T2D), dyslipidemia, hypertension and hypercoagulability. All these conditions contribute to a chronic inflammatory status which may impact on blood brain barrier (BBB) integrity leading to an impaired function of central nervous system (CNS).

Aim of review: Since the mechanisms underlying the brain-liver-gut axis derangement are still inconclusive, the present narrative review aims to make a roundup of the most recent studies regarding the cognitive decline in MASLD also highlighting possible therapeutic strategies to reach a holistic advantage for the patients.

Key Scientific Concepts of Review: Due to its ever-growing prevalence, the MASLD-related mental dysfunction represents an enormous socio-economic burden since it largely impacts on the quality of life of patients as well as on their working productivity. Indeed, cognitive decline in MASLD translates in low concentration and processing speed, reduced memory, sleepiness but also anxiety and depression. Chronic systemic inflammation, hyperammonemia, genetic background and intestinal dysbiosis possibly contribute to the cognitive decline in MASLD patients. However, its diagnosis is still underestimated since

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; T2D, type 2 diabetes; NO, nitric oxide; RHI, reactive hyperemia index; BBB, blood brain barrier; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; IR, insulin resistance; BMI, body mass index; GGT, gamma-glutamyltransferase; FFAs, free fatty acids; LTD, long term depression; ROS, reactive oxidative species; APOE, apolipoprotein E; AD, Alzheimer's disease; SNP, single nucleotide polymorphism; PDE7A, phosphodiesterase 7A; MTFR1, mitochondrial fission regulator 1; GWAS, genome wide association studies; CRP, C-reactive protein; CNS, central nervous system; HFHC, high fat high cholesterol; SCFAs, short chain fatty acids; GABA, gamma-aminobutyric acid; LGG, Lactobacillus rhamnosus; HSCs, hepatic stellate cells; BCAA, branched-chain amino acids.

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the leading mechanisms are multi-faceted and unexplained and do not exist standardized diagnostic tools or cognitive test strategies. In this scenario, nutritional and lifestyle interventions as well as intestinal microbiota manipulation (probiotics, fecal transplantation) may represent new approaches to counteract mental impairment in these subjects.

In sum, to face the "mental aspect" of this multifactorial disease which is almost unexplored, cognitive tools should be introduced in the management of MASLD patients.

Contents

Background

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is ramped up in the past three decades thus representing a health and socio-economic burden in about one fourth of the world population, including both adults and children [1]. MASLD ranges over a spectrum of liver conditions starting from simple steatosis which is defined by triglyceride accumulation in > 5 % of hepatocytes, in the absence of other causes of lipid overload (i.e., alcohol abuse). Steatosis may remain uncomplicated or progress to metabolic dysfunction-associated steatohepatitis (MASH) related to lobular inflammation, hepatocellular degeneration and fibrosis, finally leading to cirrhosis and hepatocellular carcinoma (HCC) [2].

MASLD is highly intertwined with obesity, type 2 diabetes (T2D) and other clinical conditions as dyslipidemia and hypertension which contribute to its extra-hepatic complications including cardiovascular and kidney diseases, vascular dysfunction, arterial remodeling, atherosclerosis and cognitive decline [3]. Insulin resistance (IR) is the shared pathogenic mechanism between obesity and T2D, whose co-presence reaches almost 100 % of prevalence in MASLD. Both conditions which are featured by chronic inflammation due to cytokines release from adipocytes, impaired glycemic control and enhanced oxidative stress have been largely associated with mental illness, psychiatric and neurodegenerative disorders [4]. In addition, nutritional risk factors and lifestyle habits through a vicious cycle further potentiate the inflammatory milieu thus amplifying the cognitive decay.

In line with the aforementioned, it has been reported that up to 70 % of MASLD patients show depression, problems with the memory, confusion and low concentration which largely impact on their quality of life [5]. In a cross-sectional study of 4,472 adults aged 20–59 years who participated in the Third National Health and Nutritional Examination Survey, a lower cognitive performance has been demonstrated in patients with MASLD independently of cardiovascular disease and other risk factors [6]. In the Framingham study, MASLD patients with higher risk to develop fibrosis exhibited signs of impaired function reasoning compared to those with low risk although overall MASLD was not associated with cognitive dysfunction [7]. By using NHANES data from 2011 to 2014, Weinstein and colleagues found that individuals with both MASLD and T2D showed lower cognitive performance in terms of processing speed, sustained attention and working memory than individuals with neither [8].

Youssef and colleagues examined the association of depression and anxiety with the severity of MASLD in 567 biopsied patients. They found that the former was related to more severe hepatic ballooning at logistic regression models [9]. An inverse correlation between ballooning degree and reactive hyperemia index (RHI) and a lower mini-mental state examination have been found in a study which enrolled 80 patients with biopsy-proven MASLD and 83 controls without fatty liver disease. RHI score reflects nitric oxide (NO) bioavailability thus indicating a measurement of endothelial vasodilator function thus possibly predicting cardiovascular outcomes. The authors suggested a reduced cognitive performance in MASLD patients with higher arterial stiffness [10]. Furthermore, another study reported that MASLD is associated with a smaller total cerebral brain volume, indicating a possible link between hepatic steatosis and brain aging [11].

However, the association between MASLD and cognitive impairment is still controversial, mainly due to different types of diagnostic tools or cognitive test strategies exploited and the underlying mechanisms are only conceivable. Moreover, limited time of follow-up and small sample size further mislead data interpretation. Finally, since MASLD is closely entangled with obesity and IR, it is challenging to dissect the contribution of liver damage *per se* in precipitating cognitive function.

Therefore, the present narrative review aims to provide a roundup of the literature concerning the connection between metabolic disturbances and cognitive function which is emerging as a further note to face in the management of MASLD patients.

The metabolic importance of adipose tissue depots in determining cognitive decline

Given the worldwide spreading of overweight among all-age groups, cognitive impairment linked to obesity and its comorbidities, including MASLD, may represent a serious health concern. This notion gains even more value if we consider the aging of the global population and the lack of available preventive strategies for the cognitive deterioration.

Although it has been largely described that increased body fat depots may contribute to several metabolic alterations, thus fostering the risks of metabolic syndrome, T2D, cardiovascular diseases and so on, less is known regarding their impact on the cognitive sphere.

Depending on the location of fat storages, adipose tissue is mainly subdivided into subcutaneous and visceral adipose tissues (SAT and VAT). The latter is primarily connected to a higher pro-inflammatory milieu, oxidative stress, unfavorable metabolic and vascular outcomes, compared to SAT. Accordingly, it has been established that the low-grade systemic inflammation, IR and endothelial dysfunctions contribute to trigger a more prone neuroinflammatory environment in obese individuals in which VAT expansion occurs.

Previous studies reported that adiposity and body mass index (BMI) inversely correlated with lower executive performance [12], working memory, learning [13] and verbal fluency [14] in both adults and children [15]. More in deeply, Moh and colleagues demonstrated that the expanded VAT (>100 cm^2) influenced the delayed memory, cognitive and language scores, in 677 Asian patients affected by T2D, thus pointing out that visceral adiposity may participate in the pathogenesis of cognitive dysfunctions [16]. Similarly, a cross-sectional study conducted in 9,189 adults between 30 and 75 years of age demonstrated that excessive VAT increased was a risk factor for reduced cognitive scores, independently of educational levels, cardiovascular risk factors and vascular brain injuries [17].

In keeping with these observations, it has been reported that the presence of ectopic fat correlated with an increased risk of developing a cognitive impairment, whereas SAT might exert a protective role [18]. Indeed, specific regional lipid depots lead to abnormal adipokine secretion penetrating the blood–brain barrier (BBB) and driving brain injuries thus leading to different neurobiological modifications and ultimately to various cognitive-related outcomes and dementia [19]. Moreover, sex differences in regional fat distribution should be considered and the evaluation of BMI alone does not account for this discrepancy. In particular, women are characterized by high SAT storages compared to men, thus less affecting cognition [19].

Notably, given that MASLD often occurs in the co-presence of other metabolic risk factors, it is difficult to dissect the impact of liver steatosis and steatohepatitis from that of other components of the metabolic syndrome, which are associated with declines in mental skills [20,21]. For instance, IR has been outlined as causative of poor function in multiple cognitive domains and global brain atrophy [21], while in elderly, T2D 2.4-fold increases the risk of developing dementia [22], neuropathy and retinopathy, due to vascular abnormalities, oxidative damage and synaptic failure.

Intriguingly, Xu and colleagues pointed out the tempo-occipital cortex, cerebellum and regions involved in sensorimotor and reward systems, as vulnerable targets for cognitive failure also in lean patients with liver disease [23]. However, the differences between non-obese and obese MASLD need to be further investigated.

Cognitive deterioration in MASLD: A matter that remains to be debated

The available evidence on non-cirrhotic MASLD related to cognitive anomalies are often conflicting. A very recent cross-sectional study among 180 patients who underwent bariatric surgery defined that nearly half of them exhibited measurable cognitive impairments, regarding short-time memory and executive functions [24]. However, the authors concluded that these abnormalities were not associated with the presence of MASLD or MASH. Similarly, a cross-sectional analysis within the Rotterdam Study revealed that non-invasively assessed MASLD and fibrosis were not associated with the increased risk of dementia and cognitive impairment [25]. Conversely, a Swedish population-based study on a total of 2,898 patients with MASLD and 28,357 matched controls showed a modest trend for association of MASLD with the rate of dementia [26]. Hence, larger studies conducted in biopsy-proven MASLD patients, in which neuroimaging data are available are required.

A cross-sectional study conducted in 320 biopsied patients demonstrated that severe steatosis and ballooning were related to higher memory defects, due to volume loss in left hippocampus [27]. Likewise, elevated gamma-glutamyltransferase (GGT) levels were associated with structural changes of total brain and grey matter volumes and with hemodynamic cerebral markers within the population-based Rotterdam Study across 3,493 patients, [28], thus sustaining the previously described pro-oxidant and pro-inflammatory nature of GGT. In line with these findings, also Filipović and coworker observed a total tissue volume reduction involving both white and gray matter in MASLD patients [29]. In addition, it has demonstrated that patients with biopsy-proven MASLD have a blunted cerebral perfusion in left semioval center and posterior cingulate cortex which may contribute to cerebral atherosclerosis [30].

A *meta*-analysis across 7 studies, including 891,562 individuals from 6 countries, proved that the presence of MASLD increases the risk of cognitive impairment [31]. Similarly, Yu and colleagues corroborated the relationship between MASLD, and cognitive functions based on the database of NHANES III, including 5,662 participants. This correlation is even stronger in those individuals with a significant liver stiffness, moderate-severe steatosis, or hyperglycemia mainly due to adipokine and cytokine imbalances [32]. The association between liver damage, brain subcortical changes and all causes of incident dementia, including vascular and neurodegenerative ones, has been further corroborated by a very recent prospective cohort study among 431,699 adults with MASLD [33].

In particular, Younossi and collaborators demonstrated that MASH significantly impact on the quality of life of patients, whereby inducing fatigue and a considerable physical and mental health deterioration [2]. In this context, skeletal-muscle disorders (i.e., myosteatosis and sarcopenia) as well as severe hypovitaminosis could also be important contributing factors to induce a state of mental clouding and sickness [34,35].

Conversely, a sustained physical activity, a balanced diet and adherence to Mediterranean diet seem to ameliorate memory, attention, quality of life, depression and anxiety and prevent several brain disorders including ischemic stroke, mild cognitive impairment, dementia and Alzheimer's disease (AD) [36]. The relationship between physical exercise and fine motor skills has been further confirmed also by Weinstein and collaborators in subjects with MASLD, suggesting that it may constitute not only a preventive option for MASLD, but also for cognitive deterioration [37].

Alongside, Mediterranean diet, vitamins, flavonoids and long chain ω-3 fatty acids supplementation were associated with an improvement of fatigue symptoms and with beneficial effects on cognitive functions [38,39].

How genetics links metabolic alterations and cognitive impairment

The association between lipid levels, inflammation, and cognitive impairment is complex. Lipid metabolism is related to inflammatory markers and apolipoprotein E (APOE) is a component of circulating lipoproteins and a ligand for cholesterol transport [52]. APOE protein is emerged as the almost exclusive lipid transporter in the CNS, but it participates in several biological processes including lipoprotein metabolism, inflammation, cell growth and neuroprotection. *ApoE* knock out mice are characterized by synaptic loss, cognitive dysfunction and elevated plasma lipid levels that can affect brain function. In addition, changes in cholesterol metabolism occur simultaneously in the liver and brain and may be considered possible biomarkers of the both tissues aging [53].

It has been demonstrated that *APOE* ε4 allele carriers have a higher risk to develop both vascular dementia and AD compared to noncarriers [54]. A possible explanation may be linked to cholesterol distribution throughout the tissues. Indeed, preclinical studies indicated that during aging, cholesterol is primarily accumulated into the liver, while it decreases in brain. In addition, APOE plays a pivotal role in cholesterol trafficking from astrocytes to neurons [53]. Moreover, it has been demonstrated that gut microbiota modulation improves the cardio-metabolic profile in *ApoE*-deficient mice and it has been shown an association between *APOE4* genotype and gut microbiome profiles in both humans and mice models. Overall, the authors concluded that gut microbiome should be addressed as a potential target to mitigate the deleterious impact of the *APOE4* allele on cognitive decline [55].

Genome-wide association studies (GWAS) demonstrated a strong association between variants affecting the rate of age-related cognitive decline and *APOE*. Moreover, it has emerged that the rs10808746 variant in the *APOE* gene affects the expression of phosphodiesterase 7A (*PDE7A*) and mitochondrial fission regulator 1 (*MTFR1*) which are adjacent genes and potential regulators of inflammation and oxidative stress [56,57].

Lutz et al. examined pleiotropic genetic effects on cognitive impairment conditioned on genetic variants associated with systemic inflammation and with plasma lipids by exploiting data obtained from the Health and Retirement Study which is a representative sample of older Americans. They showed that single nucleotide polymorphisms (SNPs) related to cognitive impairment were also associated with C-reactive protein (CRP), low-density lipoproteins and total cholesterol, and they were located in genes or in the proximity of genes involved in multiple pathological processes including cholesterol metabolism, inflammation and mitochondrial transport [58].

In the attempt to define whether genetic loci associated with metabolic traits also impact on cognitive impairment, Hebebrand and colleagues performed a lookup analysis of variations which reached a significance in GWAS related to metabolism in those focused on cognitive defects. The authors found that about 5 %-10 % of the 216 regions which were relevant for the regulation of blood/urine metabolites possibly played a role also in mental disorders [59].

Finally, a Mendelian randomization analysis revealed that genetic traits related to insomnia were associated with MASLD, ALT levels and percent of liver fat whereas those which are linked to snoring and dozing were associated with steatosis grade thus suggesting a relation between the steatotic phenotype and sleep traits [60]. Therefore, not only obstructive sleep apnea is associated with MASLD but also sleep duration and state (i.e., insomnia) should be considered in the management of the disease.

The liver – Brain axis: The hepatic homeostasis may influence mental performances

Brain cognitive functions include a series of processes which allow to receive, integrate, elaborate and store external information. All these processes require a high amount of energy and ATP production in brain mitochondria [21]. Mounting evidence supports the notion that MASLD may foster low cognitive functions along with brain structural changes. Nonetheless, the mechanisms underlying these associations remain to be fully clarified and they may possibly encompass several processes including inflammation and oxidative stress, due to Kupffer cells and macrophages activation in the liver with the consequent release of pro-inflammatory cytokines, which may bypass BBB [40]. All these events together with obstructive sleep apnea, glycemic, hemodynamic and coagulation disturbances trigger microglial cells activation, brain mitochondrial disorders, neuronal degeneration and cognitive impairment [41]. Chronic microglial cells activation amplifies neuroinflammatory conditions by recruiting activated monocytes into the brain, driving the impairment of axons and myelin sheaths and neurotoxic effects [42].

Several preclinical and clinical studies supported the evidence of cognitive dysfunctions and neuroinflammation during the MASH outbreak. Accordingly, Balzano and collaborators detected an elevated activation of microglia and astrocytes, lymphocyte infiltration, loss of Purkinje and granular neurons and microangiopathy in patients affected by MASH, compared to controls by analyzing post-mortem biopsies of hippocampus [43]. Furthermore, a two-sample Mendelian Randomization analysis, across 33,992 participants, supported a causal relationship between MASLD and alterations in cortical structures, particularly in the pars orbitalis gyrus. More in details, genetically predisposed patients with MASLD displayed a thinning of cortical thickness in this region [44].

Specifically, cognitive declines observed in patients with MASLD include defects in psychomotor and processing speed, sustained attention, and visuospatial functions [8], together with low memory performances [6], reduced executive functions, abstract reasoning [7] and depression-like behavior [5]. Likewise, evidence gathered from 11 studies determined that MASLD patients have approximately four times higher risk of developing cognitive detriments [45].

In addition, obesity and MASLD contribute to peripheral IR on one hand, thus impairing insulin signaling and insulin-induced long-term depression (LTD) in brain [41] and participate in neuro-toxic ceramide overproduction, on the other [46]. Even more, hyperglycemia drives the abnormal replication and death of vascular endothelial cells and compromises BBB permeability by altering the distribution of tight junction proteins and nutrients transporters [47]. Hence, increased BBB permeability, vascular injuries and hypoperfusion have been described in patients with T2D [48].

Interestingly, functional and structural changes in brain mitochondria occurred during obesity, mainly as a consequence of reactive oxygen species (ROS) overproduction, lower mitochondrial biogenesis, mitochondrial depolarization and swelling [49]. Moreover, sustained or long-term changes in brain regional oxidative metabolic capacity may affect neuronal communication. Hyperammonemia due to urea cycle impairment [50], severe deficit in antioxidant vitamins and hyperhomocysteinemia induced worse neuropsychological outcomes [35]. In addition, low-grade brain inflammation triggers cerebral hypoxia, due to reduced oxygen

delivery and/or utilization and the latter predisposes to neurodegenerative conditions [51].

Urea cycle impairment from pre-cirrhotic to cirrhotic MASLD driving hepatic encephalopathy

In patients with cirrhosis, it has been largely described that ammonia clearance through the conversion into urea is completely burned out, as a consequence of the massive loss of functional hepatic tissue. High systemic levels of ammonia due to the impaired urea cycle facilitate the pass of inflammatory molecules through the BBB [86] and induce neuro-toxic effects, cerebral edema, brain herniation, and seizures [87]. In particular, hyperammonemia induces neuronal damage, astrocyte swelling, and poor synaptic plasticity, leading to memory loss [88]. Indeed, astrocytes are widely sensitive to the effects of ammonia, and in attempt to detoxify themselves from hyperammonemia, a severe osmotic stress is generated, altering their morphology and function.

However, an inefficacious ammonia disposal is observed early in pre-cirrhotic MASLD. Indeed, it has been reported that the compromised activity of the urea cycle in MASH patients may likely result from mitochondrial dysfunction and epigenetic alterations in genes coding the urea cycle enzymes and from hepatocyte senescence [86,89]. The fine-tuned urea synthetic processes are required to regulate body nitrogen homeostasis and to retain low ammonia at both cellular and systemic levels. Fatty liver *per se* initiates the intracellular accumulation of ammonia, next priming the transition from simple steatosis to MASH, fibrosis and up to cirrhosis [90]. Specifically, hyperammonemia activates the hepatic stellate cells (HSCs), determining the induction of fibrogenesis and fostering portal hypertension.

Interestingly, ammonia derangement may link MASLD also to sarcopenia, chronic fatigue and reduced physical fitness, to the point that its levels play a detrimental effect on muscle mass and function [91]. Since ammonia passively diffuses through the plasma membranes, its exacerbated uptake in muscle hesitates into glutamine synthesis from branched-chain amino acids (BCAA) determining their exhaustion. For this reason, in cirrhotic patients with hepatic encephalopathy, BCAA supplementation is required to rescue the amount of substrate for ammonia detoxification.

As aforementioned, high ammonia levels strongly affect mitochondrial ATP synthase activity, whereby enhancing ROS production and oxidative damage in brain and muscle [50]. Furthermore, it compromises the immunity response, opening the way to tumor immune escape mechanisms and increasing the risk to develop hepatocellular carcinoma [92].

Nutrition and lifestyle interventions to improve cognitive performance in MASLD patients

A preclinical study demonstrated that a long-term consumption of high fat diets predisposed to cognitive disruptions mainly affecting hippocampus, even in the absence of obesity, further corroborating the importance of nutritional choices on brain heath [93]. Conversely, alternate-day fasting provided advantages on cognitive domains including working memory and synaptic structure in obese mice, by softening oxidative stress, systemic inflammation and microglial activation [94].

Although it is well recognized that lifestyle and physical activity severely influenced the muscle strength and adiposity, less is known regarding their impact on mental homeostasis preservation. A study across 2,377 overweight adults (age = 69.3 ± 6.7 years; BMI = 29.1 ± 6.3 Kg/m^2) from the NHANES 2011–2014 determined that a sustained physical activity may ameliorate the executive function and processing speed domains of cognition [95]. Accordingly, 8-week supervised aerobic training in sedentary adult obese individuals (BMI, Kg/m^2 ranging from 27.5 to 45.5) improved brain insulin sensitivity and strengthened hippocampal functional connectivity [96]. Similarly, it has been described that a significant weight loss following 18 months of lifestyle intervention might have a neuroprotective effect on brain aging in adults (age > 30 years) with abdominal obesity (waist circumference for men > 102 cm, for women > 88 cm) [97]. The effect of physical activity and dietary interventions have been investigated also in a 2-year nonrandomized controlled trial in 504 overweight children (aged 6–9 years), showing that a more balanced diet, characterized by high low-fat milk consumption and an increased time spent in organized sports and reading overall supported cognitive development [98].

Together with BMI also severe hypovitaminosis due to unbalanced diets may reduce mental performances. Therefore, it seems conceivable that the preventive strategies aimed at hampering the adiposity and at ameliorating the skeletal muscle tone may possibly be useful to preserve cognitive function among adults. Alongside a correct nutritional intake may be helpful to counteract mental decline and memory loss. A systematic *meta*-analysis reported beneficial effects of essential EPA/DHA and multimicronutrient supplementation on specific cognitive domains including attention and orientation, perception, verbal functions and language skills in older individuals with physical frailty [99]. Indeed, EPA/DHA are fundamental structural components of neuronal cells' membranes, influencing their composition and fluidity. Therefore, their accumulation is required for synaptic plasticity, hippocampal neurogenesis, learning, vision and memory [100]. Likewise, vitamins and flavonoids may exert benefits on mental decline. In particular, Vitamin D, B, E, carotenoids, antioxidants and ω-3 fatty acids were associated with lower risk of dementia or AD, and memory loss [101]. For instance, flavonoids supplementation exerts benefits for hippocampal neurogenesis whereby potentiating spatial working memory, whereas vitamins and minerals participates to neuronal communication, fiber myelination and neuronal survival [100].

In addition, berberin-enriched extract administration attenuated hippocampal IR, ameliorated locomotor activity and coordination, reduced anxiety-like behavior and increased muscle strength, by softening oxidative stress and neuroinflammation in rodent models of cognitive dysfunction [102–104] and mitigating cognitive deficits in patients with schizophrenia [105]. A similar effect has been reported for *Syzygium aromaticum* consumption that refines brain mitochondria homeostasis in rat with AD [106].

MASLD patients have been widely established to be characterized by a poor quality of life, sometimes from the childhood, thus constituting excellent targets for early cognitive decline preventive strategies. It is frequent that children whose parents have low education levels or live in not industrialized areas develop overweight or obesity compared to kids from higher-educated families [107]. Few studies focused on the identification of a specific dietary path to enhance cognitive performances in patients with MASLD, regardless the presence of obesity. For instance, it has been determined that in mice fed HFD, a 4-week treatment with Quercetin, a flavonoid with anti-inflammatory and antioxidant properties, protected against the diet-induced learning and memory impairments, by enhancing synaptic plasticity [108]. Superimposable findings have been observed also after a 4-week administration of another polyphenolic compound, Resveratrol, which mitigated glucolipid profile, behavioral and cognitive derangements in a rat model of MASLD [109].

Similarly, moderate nut intake (15.1–30.0 g/d) has been associated with an overall improvement of immediate and delayed memory in 1,848 older adults (≥60 years) with MASLD [110]. Another study demonstrated that low lutein and zeaxanthin intake, that are two different carotenoids with anti-inflammatory

and antioxidant capacities, is responsible for the reduced cognitive performances observed in geriatric MASLD patients (mean age 68. 11 ± 0.32 years), whereas their moderate consumption preserves meningeal stability and defends the structure and the integrity of axons [111].

Notably, nutritional status played a pivotal role in modulating intestinal flora homeostasis. Indeed, it has been widely described that HFHC diet induced an unbalance in bacterial species, favoring *Bacteroidetes* and *Proteobacteria,* at the expense of the *Lactobacillaceae* family [112]. Therefore, the rescue of intestinal eubiosis by using untargeted procedures (diet, probiotics, prebiotics i.e., fibers boosting SCFAs, antibiotics i.e., Rifaximin or fecal microbiota transplantation) or microbiota-targeted therapy directed against a specific microbial species and host metabolites may represent good opportunities to safely and effectively restrain brain-associated liver disease dysfunctions [113]. However, further studies dealing with this purpose are needed to better understand how and when intervene on MASLD patients to prevent/revert cognitive alterations (Fig. 1).

Gut microbiota, cognitive impairment and intestinal microflora manipulation

Growing body of evidence indicates that MASLD and other components of metabolic syndrome are responsible for substantial modifications in quantity and quality of intestinal flora taxa (unbalances referred to as dysbiosis), mucosal alterations and enhanced gut permeability, resulting in endotoxemia, ethanolemia, inflammation and oxidative injuries [61]. Alongside, gut-liver axis plays a key role in MASLD development and progression to MASH, as testified by preclinical models of MASH, obtained by human fecal microbiota transplantation [62]. However, less is known regarding the impact of gut microbiota and its metabolites on BBB function and on behavioral aspects.

In details, it has been reported that an enhanced gut permeability due to intestinal dysbiosis has been associated with the escape of pathogenic microorganisms and endotoxemia, thereby fostering intestinal mucosal inflammation and a chronic low-grade immune system activation. Intriguingly, circulating endotoxin concentrations have been significantly correlated with higher scores of depression, anxiety and decreased social interactions and the '*leaky gut*' influenced CNS homeostasis fostering different psychiatric and non-psychiatric disorders [63]. Thus, cognitive impairment and altered gut microbiota seem to be tightly correlated in patients with MASLD and gut-liver-brain network seems to be functionally connected.

In deeply, Aljumaah et al. reported a significant association between gut microflora composition and cognitive impairment [64]. A similar effect may be exerted by microbial harmful by-products, which strongly induce systemic inflammation and affect BBB integrity. Higarza and colleagues demonstrated that a high-fat, high-cholesterol (HFHC) diet induced gut dysbiosis as well as hyperammonemia and reduced short chain fatty acids (SCFAs) production in rats. These findings suggest that gut-derived microbiota metabolites, along with pathogen-associated molecular patterns (PAMPs), ammonia and bacterial DNA, may propagate systemic inflammation thus leading to a neurotoxic environment that could be reflected in functional brain deficits [65,66].

Notably, other possible mechanisms encompass microbial fermentative processes of fibers which release SCFAs with neuroactive properties (i.e., butyric acid) along with bacterial synthesis of different neurotransmitters (i.e., gamma-aminobutyric acid (GABA), dopamine, serotonin and acetylcholine) [67]. Alterations in these neurotransmitters driven by Western diet administration in mice compromise cognitive performance and induce astrogliosis and microgliosis of hippocampus due to neuroinflammation or to a disruption of neurovascular unit [68]. Furthermore, dysbiosis contributes also to dysregulate bile acid synthesis, thus affecting neuroplasticity [69]. On the contrary, Indolepropionic acid (IPA), a tryptophan-derived metabolite produced by gut microbiota seems to be able to attenuate systemic inflammation, MASLD and cognitive impairment [70].

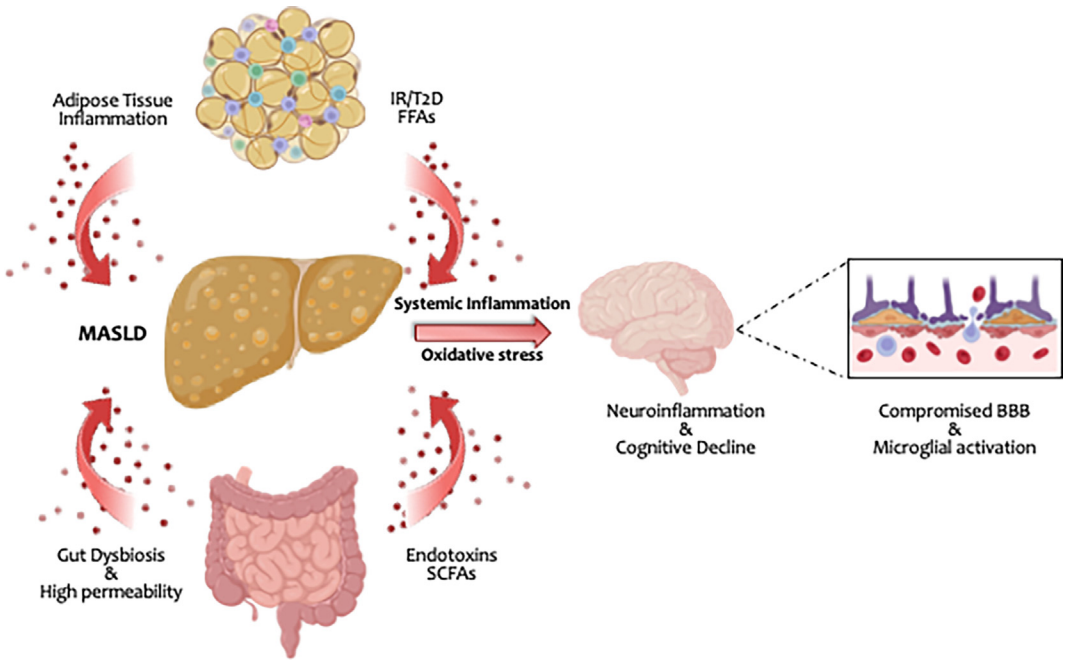

Fig. 1. How chronic inflammation affects the brain-liver-gut axis in MASLD patients. MASLD is characterized by a systemic chronic inflammation mainly due to adipose tissue insulin resistance (IR) driving the release of free fatty acids (FFAs), proinflammatory cytokines and hormones in the circulation. Another component of MASLD is represented by intestinal dysbiosis which fosters enhanced gut permeability and the secretion of endotoxins and microbial metabolites as short chain free fatty acids (SCFAs). All these soluble mediators pass the blood brain barrier (BBB) triggering microglial cells activation, neuronal degeneration, brain mitochondrial disorders and ultimately cognitive impairment.

Thus, dietary habits, probiotics and antimicrobials may positively influence the health of the brain, ameliorating memory and cognition [71] and it could be hypothesized that gut microbiota manipulation may be an effective strategy to rescue cognitive deficiencies related to MASH. As proof of this concept, dietary supplementation with *Akkermansia muciniphila* CIP107961 may reverse the HFHC-induced cognitive dysfunctions in mice [65], whereas *Lactobacillus rhamnosus GG* (LGG) administration may exert benefits in middle-aged and older adults with cognitive impairment [72]. Furthermore, *Lactobacillus Plantarum* EMCC-1039 supplementation rescued dysbiosis-induced MASH in rodents [73] and multistrain probiotics ameliorated cognitive functions even in patients affected by cirrhosis, thus reducing inflammatory response [74]. Similarly, patients affected by overweight/obesity are characterized by defects in the quantity of *Clostridium butyricum* combined with a predominance of the phylum Proteobacteria. Conversely, oral supplementation of probiotics containing *Clostridium butyricum* attenuates the obesity-induced cognitive impairment, improves hippocampal functions and attenuates endotoxemia in mice fed HFD. These favorable outcomes could be transmitted to germ free mice through fecal transplants [75].

Gut dysbiosis has been observed also in T2D patients, showing an enrichment of *Blautia*, *Fusobacterium*, and *Ruminococcus*, which affect gut permeability, inflammation and glucose metabolism [76]. More in deeply, the co-presence of MASLD and T2D determines a shift towards a more severe abundance of *Enterobacter*, *Romboutsia,* and *Clostridium* [77]. Conversely, physical exercise positively impacts on gut microbiota diversity, ameliorating synaptic function and cellular plasticity changes [78].

Other possible interventions to restore microflora composition encompass the treatment with Rifaximin and fecal microbiota transplantation. The former is a gut-selected antibiotic, particularly indicated to counteract mental decline and endotoxemia in cirrhotic patients with mild hepatic encephalopathy, and to ameliorate motor coordination, T cells and macrophages infiltration in cerebellum, and spatial learning and memory in rodent models of severe fibrosis [79–81].

The latter, instead, is becoming attractive in the management of chronic liver diseases as MASLD, although several concerns about its safety and potential infectivity still remain. Bajaj and collaborators addressed this point in a randomized clinical trial, showing that this practice ameliorate cognitive functions in patients with cirrhosis and advanced hepatic encephalopathy, characterized by progressive neuropsychiatric and motor dysfunctions [82]. In another clinical trial, the same authors attributed this favorable effects on the gut-brain axis to the significant reduction of systemic inflammation, testified by the decrease in serum IL-6 and LPS-binding protein [83]. Accordingly, the fecal microbial colonization from patients with cirrhosis hesitated into neuroinflammation and neuronal activation in germ free mice [84]. Next, another open-label trial corroborated the positive impact of fecal microflora transplantation in cirrhotic patients with hepatic encephalopathy [85].

Conclusions

Cognitive decline is a physiological process, which occurs during aging in healthy individuals throughout the adult lifespan. However, this event is further accelerated by various triggers, among which MASLD, obesity, IR and T2D. Indeed, MASLD is frequently associated with a cognitive decline which includes fatigue, low concentration, reduced attention, loss of memory together with more severe conditions as depression and anxiety. It seems established that inflammation represent the common denominator of MASLD progression and mental disorders although the mechanisms through which cognitive impairment in these patients occur are scantly understood. The diagnosis of mental decline in MASLD patients is underestimated possibly due to different types of diagnostic tools or cognitive test strategies exploited. Nevertheless, mental dysfunction in MASLD patients represent an enormous socio-economic burden since it largely impacts on the quality of life of these patients, on their ability of social networking and on their working productivity, which are representative of around a third of the global population.

In this scenario, nutritional and lifestyle interventions may represent a new avenue to counteract cognitive failure in patients with MASLD. Indeed, several preclinical models indicated that different nutrients and in particular the Mediterranean diet may be helpful in maintaining mental health, and preventing the risk of developing AD, dementia and memory loss [114]. However, a whole comprehensive dietary and physical approach would be preferable in these subjects in order to achieve widespread benefits on different aspects. Even more, forefront intestinal microbiota manipulation including fecal microbiota transplantation may represent a novel strategy to deal with the burden of cognitive decline in MASLD patients (Fig. 2).

To sum, by considering the global spreading of MASLD and the progressive aging of the worldwide population, the assessment of cognitive performance in these patients becomes crucial and gains value as further note to face in the management of the disease. A holistic approach will allow the clinicians to tackle the disease from a multi-organ and multi-systemic point of view, thus ameliorating the clinical practice and possibly introducing early interventions to prevent or partially revert cognitive sphere deterioration.

Author Contributions: MM and PD conceptualized and wrote the manuscript; ML and EP prepared the figures and revised the final version of the manuscript.

Ethics approval Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano.

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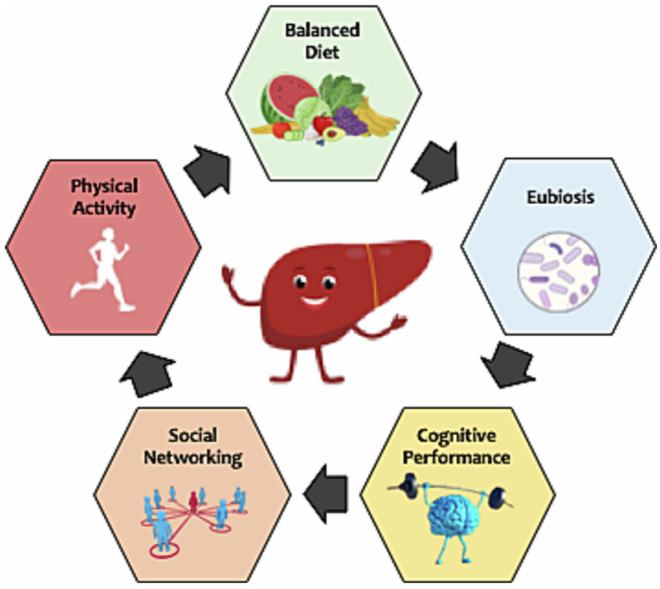

Fig. 2. A holistic approach for the binary treatment of MASLD and cognitive impairment A schematic representation of possible therapeutic strategies and lifestyle changes to ameliorate the quality of life in terms of healthy liver, higher occupational performance, social gathering, reduce fatigue and increased brain sharpness.

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Ethics approval Statement.

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CRediT authorship contribution statement

Marica Meroni: Data curation, Writing – original draft, Funding acquisition. **Miriam Longo:** Writing – review & editing. **Erika Paolini:** Writing – review & editing. **Paola Dongiovanni:** Conceptualization, Data curation, Writing – original draft, Funding acquisition, Supervision.

Declaration of competing interest

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

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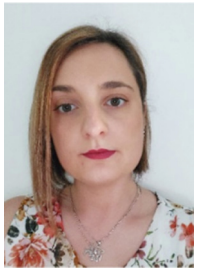

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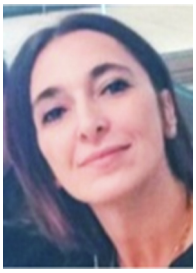

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