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Time-Restricted Feeding Improves High-Fat Diet-Induced Cognitive Dysfunction

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Abstract

Objective: Obesity is an important modifiable risk factor for cognitive impairment. This study aimed to investigate whether time-restricted feeding can improve obesity-related cognitive decline and to preliminarily explore its underlying mechanisms in mice on a high-fat diet.

Methods: A total of thirty male C57BL/6 mice were randomly assigned to three groups: Normal Chow Diet (NCD), High-Fat Diet (HFD), and Time-Restricted Feeding (TRF). The NCD group received standard chow ad libitum, while the HFD group was provided a 60% high-fat diet ad libitum. The TRF group was provided with ad libitum access to the high-fat diet within an 8-hour window during the early active phase (00:00 AM to 08:00 AM), corresponding to the definition of early-time restricted feeding (eTRF). After 24 weeks of intervention, spatial learning and memory were assessed using the Morris water maze. Inflammatory markers (TNFα, IL1β, IL6), lipid metabolism profiles, and circadian rhythm gene expression were analyzed. Liver, epididymal, and subcutaneous adipose tissues were collected for histological analysis.

Results: After 24 weeks of intervention, the TRF group exhibited significantly lower body weight compared to the HFD group (-10.20 ± 3.65 g, $p < 0.05$), despite comparable food intake. TRF effectively reversed HFD-induced cognitive deficits, as evidenced by significantly shortened escape latency and increased time spent in the target quadrant during the probe trial. At the molecular level, TRF attenuated HFD-elevated hippocampal levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). Furthermore, TRF restored the expression of hepatic circadian clock genes (Bmal1, Clock, Per1) and down regulated lipogenic genes (SREBP1c, SCD1, FASN), which were disrupted by HFD. Histological analysis confirmed that TRF alleviated HFD-induced hepatic steatosis and adipose tissue hypertrophy.

Conclusion: Early-time TRF attenuates HFD-induced cognitive impairment *via* mitigating neuroinflammation, restoring circadian rhythms, and improving lipid metabolism in mice. These findings support TRF as a promising non-pharmacological intervention against obesity-related cognitive decline.

Keywords: Time-restricted feeding; High-fat diet; Cognitive dysfunction; Neuroinflammation; Circadian Rhythm

Introduction

Obesity is a significant and modifiable risk factor for various cognitive impairments and dementia, including Alzheimer's disease [1-3]. This association is particularly prominent in middle-aged and elderly populations, though early-life obesity also adversely affects long-term cognitive health [4-8]. Compared to those with normal weight, individuals with early-onset obesity exhibited an average reduction of 3.2% in hippocampal volume and a decrease of 0.06 mm in prefrontal cortex thickness [9]. A cross-sectional study [10] of 180 individuals with severe obesity found that 41% of participants met the criteria for "cognitive impairment" on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scale; 8% showed abnormalities only in basic tests, with the most pronounced deficits observed in executive function and short-term memory. In a longitudinal cohort study [11] of 1,823 middle-aged and elderly obese adults, verbal memory Z-scores declined by an additional 0.05 per year and executive function by 0.04 per year compared to normal-weight individuals.

Studies have shown that cognitive impairment can occur within 3-14 days after on a high-fat diet (HFD) [12-14]. Adipose tissue, particularly visceral fat, functions as an endocrine organ that secretes pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [15]. These cytokines traverse the blood-brain barrier, activate microglia, and induce chronic neuroinflammation, ultimately impairing synaptic plasticity and promoting neurodegeneration. Furthermore, Central Nervous System (CNS) insulin receptor signaling plays a crucial role in synaptic plasticity, neuronal survival, and learning and memory [16]. Diet-induced obesity, particularly visceral fat accumulation, promotes peripheral insulin resistance and hyperinsulinemia, and is associated with disrupted insulin signaling in the CNS [17,18].

Over the past decade, lifestyle modifications have become a promising alternative strategy for reducing the risk of cognitive impairment [19]. Compared to traditional caloric restriction, Time-Restricted Feeding (TRF) may offer unique advantages in mitigating obesity-related cognitive decline [20]. By consolidating food intake within a consistent daily window (e.g., 8-10 hours) during the early active phase - known as early time-restricted feeding (eTRF) - this approach reinforces circadian rhythms [21,22], improves glycolipid metabolism [23,24], and promotes autophagy [25]. It also facilitates spontaneous calorie reduction without active counting, improving long-term adherence [26].

Therefore, in this study, we implemented an 8-hour eTRF regimen in high-fat diet-fed mice to evaluate its effectiveness in counteracting HFD-related cognitive decline. We further explored its potential mechanisms from the perspectives of neuroinflammation, hepatic circadian rhythm resetting, and lipid metabolism.

Materials and Methods

Animals

Thirty healthy male C57BL/6 mice (13-14 weeks old, 25-30 g) were obtained from the Laboratory Animal Centre of Sun Yat-sen University (Guangzhou, China). They were housed under controlled conditions (24-26°C, 45-55% humidity, 12-hour light/dark cycle) with ad libitum access to food and water. The experimental protocol was approved by the Laboratory Animal Management and Ethics Committee of Top Biotechnology Co., Ltd., Shenzhen (TOP-IACUC-2021-0061), and complied with National Institutes of Health guidelines.

Animal experimental procedure

After one week of adaptive feeding, the mice were randomly divided into normal chow diet (NCD) group, high-fat diet (HFD) group, and time-restricted feeding (TRF) group, with 10 mice in each group. The NCD group was fed a standard chow diet (LAD2001, 3.8 kcal/g, 4% fat content, TROPHIC Animal Feed High-tech Co., Ltd., China) ad libitum. The HFD group received a high-fat diet (TP24200, 5.5 kcal/g, 60% fat content, TROPHIC Animal Feed High-tech Co., Ltd., China) ad libitum. The TRF group was also provided with the high-fat diet, but their daily food access was restricted to an 8-hour window during the early active phase (from 00:00 AM to 08:00 AM), consistent with early-time restricted feeding (eTRF). The intervention lasted for 24 weeks, with body weight and food intake recorded weekly. Cognitive function in each group of mice was assessed using the Morris water maze test prior to sacrifice. Mice were then euthanized with pentobarbital sodium (45 mg/kg, i.p.). Brain, liver, subcutaneous adipose tissue (SAT), and epididymal white adipose tissue (eWAT) were subsequently collected for further analysis.

For hippocampal tissue dissection, the mouse brain was carefully extracted from the cranial cavity and immediately placed in a petri dish on ice following decapitation. The cerebellum and brainstem were removed gently. Using a sterile scalpel, the cerebral hemispheres were separated along the midline fissure. The hippocampus, located medially and inferiorly to the lateral ventricle, was then delicately dissected away from the overlying cortex using fine forceps. All procedures were performed on a chilled surface to minimize RNA and protein degradation. The isolated hippocampal tissues were immediately snap-frozen in liquid nitrogen and stored at -80°C until further processing.

Morris water maze (MWM) test

Spatial learning and memory were assessed using the MWM system (Top Biotechnology Co., Ltd., Shenzhen), following established protocols [27]. The apparatus consisted of a white circular pool (120 cm in diameter, 50 cm in height) filled with water (22 ± 1°C) to a depth of 35 cm. The pool was conceptually divided into four quadrants (I-IV) by two perpendicular lines intersecting at the center. A hidden platform (10 cm in diameter) was placed 2 cm below the water surface in the center of quadrant III.

Each mouse underwent two hidden-platform trials per day for five consecutive days. Before the first trial each day, the animals were placed on the platform for 30 s for spatial orientation. On the sixth day, a probe trial was conducted with the platform removed. Escape latency, defined as the time taken to locate the hidden platform, was recorded to evaluate learning and memory performance. During the probe trial, the time spent in the target quadrant (quadrant III) was measured to assess spatial memory retention. All behavioral assessments were performed by an experimenter blinded to the group assignments.

Hematoxylin and Eosin staining

Liver, subcutaneous adipose tissue and epididymal white adipose tissue were rapidly collected, rinsed in normal saline, and fixed in 4% formaldehyde followed by paraffin embedding. Sections of 2 μm thickness were prepared from the paraffin blocks and stained with hematoxylin and Eosin (H&E). Histological examination was performed under a light microscope at 200× magnification.

Oil red O staining

Liver tissues were embedded in optimal cutting temperature compound and frozen for cryosectioning. Sections of 8 μm thickness were fixed in 10% neutral buffered formalin for 10 minutes, rinsed gently, and then stained with filtered Oil Red O working solution for 15 minutes at room temperature. After differentiation in 60% isopropanol, the sections were counterstained with hematoxylin to visualize nuclei. Finally, the slides were mounted with glycerin gelatin and observed under a light microscope at 200× magnification. Lipid droplets appeared bright red against a blue nuclear background.

qPCR

Total RNA was extracted from liver and hippocampal tissues using TRIzol reagent [28]. cDNA was synthesized following the instructions provided with the Prime Script RT reverse transcription kit. Quantitative real-time PCR (qPCR) was performed using the primer sequences listed in table 1. Gene expression levels were quantified using the comparative 2^(-ΔΔCt) method.

Statistical analysis

Data are expressed as mean ± SD. One-way ANOVA with Tukey's post hoc test was used for group comparisons (SPSS 26.0). A p-value < 0.05 was considered statistically significant.

Results

TRF ameliorates obesity and cognitive deficits induced by a high-fat diet

At the end of the intervention, the TRF group exhibited significantly lower body weight compared to the HFD group (–10.20 ± 3.65 g; $p < 0.05$; figure 1A), despite no significant difference in average food intake between the two groups ($p > 0.05$; figure 1B). Furthermore, compared to baseline, the TRF group showed no significant change in body weight (1.24 ± 2.38; $p > 0.05$; figure 1A), whereas the HFD

group demonstrated a significant increase (12.02 ± 4.894; $p < 0.05$; figure 1A).

Figures 1A-1C illustrates the swimming paths and trajectories of mice from the three groups during the acquisition training phase. Escape latencies to locate the hidden platform were significantly longer in HFD-fed mice compared to NCD mice (95.58 ± 16.504 vs. 54.03 ± 14.01; $p < 0.05$; figure 1D). Notably, the TRF group exhibited a pronounced decrease in escape latency over the testing period. By the final trial, no significant difference was detected between the NCD and TRF groups (−1.569 ± 10.61; $p > 0.05$; figure 1D), whereas a substantial difference remained between the NCD and HFD groups (−66.40 ± 10.61; $p < 0.001$; figure 1D).

In the probe trial initiated on day 6 (with the platform removed), swimming time in the target quadrant (Q3) was significantly reduced in HFD-fed mice compared to the NCD-fed mice (−14.27 ± 1.483; $p < 0.0001$; figure 1E). This impairment was markedly ameliorated by TRF intervention (−1.360 ± 1.483; $p > 0.05$; figure 1E). C57BL/6 mice were fed either a normal chow diet (NCD group) or a high-fat diet (HFD

Table 1: Primer Gene Sequences.

Gene	Forward	Reverse
SREBP-1c	GGTTTTGAACGACATCGAAGA	CGGGAAGTCACTGTCTTGGT
SCD1	TTCCCTCCTGCAAGCTCTAC	CAGAGCGCTGGTCATGTAGT
FASN	GCTGCTGTTGGAAGTCAGC	AGTGTTCGTTCCTCGGAGTG
Clock	CAGCCAGTGATGTCTCAAGC	ATGCGTGTCCGTTGTTCC
Bmal1	TGCCACCAATCCATACACAG	TTCCCTCGGTCACATCCTAC
Per1	CTGCTACAGGCACGTTCAAG	CTCAGGGACCAAGGCTAGTG
TNF-α	ACTCCAGGCGGTATGT	GTGAGGGTCTGGGCGATAGAA
IL-1β	TTCCTGAAACTGATGC	TGTTGATGGCTGCGAG
IL-6	CCACTTCACAAGTCGGAGGCTTA	CCAGTTTGGTAGCATCCATCATTTC
36B4	ACTGGTCTAGGACCCGAGAAG	CTCCCACCTTGTCTCCAGTC

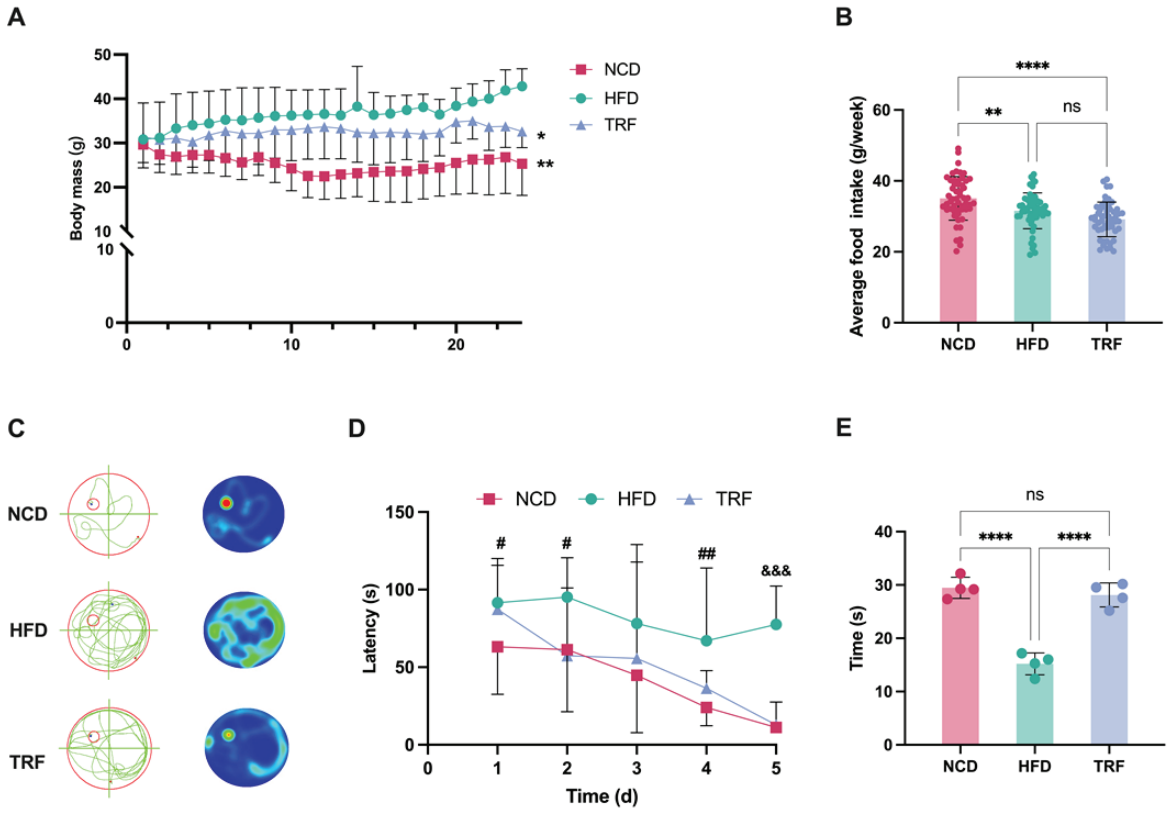

Figure 1: Scatter plot: the graph illustrates the distribution of the percentages of reduction in the thickness of the cSDH after the treatment. It indicates that in approximately a third of cases, there was a 100% resolution by three months.

group) for 24 weeks. The TRF group received the same HFD but was subjected to 8-hour time-restricted feeding (00:00 AM to 08:00 AM). N=10 for each group. (A) Body weight changes; (B) Average weekly food intake;(C) Representative swimming paths of mice from each group during the Morris water maze acquisition training phase. (D) Escape latency during hidden platform training. N=4 for each group. (E) Time spent in the target quadrant (Q3) during the probe trial on day 6. N=4 for each group. Data are presented as mean ± S.D. *p < 0.05, ***p < 0.001, ****p < 0.0001 vs. HFD group; #p < 0.05, ##p < 0.01 vs. NCD group; &&&p < 0.001 vs. NCD or TRF group (or as appropriate based on actual statistical comparisons). ns: not significant (p > 0.05).

TRF decreases the levels of inflammatory factors in hippocampal tissue

The high-fat diet significantly elevated the concentrations of pro-inflammatory cytokines in hippocampal tissue, with increases of 1.337 ± 0.329 for TNF-α, 0.401 ± 0.111 for IL-1β, and 0.870 ± 0.131 for IL-6 compared to the control group (p < 0.05, figures 2A-2C). Notably, TRF intervention effectively attenuated the HFD-induced neuroinflammatory response, reducing the elevations of pro-inflammatory cytokines by 1.297 ± 0.329 for TNF-α, 0.333 ± 0.111 for IL-1β, and 0.645 ± 0.131 for IL-6 compared to the HFD group (p < 0.05, figures 2A-2C).

C57BL/6 mice were fed either a normal chow diet (NCD group) or a high-fat diet (HFD group) for 24 weeks. The TRF group received the same HFD but was subjected to 8-hour time-restricted feeding (00:00 AM to 08:00 AM). Levels of pro-inflammatory cytokines (A) TNF-α, (B) IL-1β, and (C) IL-6 in hippocampal tissue. Gene expression was analyzed and normalized to 36B4 expression in the same sample. "A.U." stands for "arbitrary units." N=4 for each group. Data are presented as mean ± S.D.; *p < 0.05, **p < 0.01, ***p < 0.001; ns: not significant (p > 0.05).

TRF favorably regulates hepatic circadian rhythms and the expression of genes related to lipid metabolism

The expression levels of core circadian clock genes in the liver were significantly decreased in the HFD group compared to the NCD group, with reductions of 0.592 ± 0.061 for Bmal1, 0.530 ± 0.160 for Clock, and 0.583 ± 0.123 for Per1 (p < 0.05, figures 3D-3F). Time-restricted feeding effectively counteracted this HFD-induced decline and restored the expression of hepatic circadian rhythm genes, increasing their levels by 0.822 ± 0.061 for Bmal1, 1.493 ± 0.160 for Clock, and 0.373 ± 0.131 for Per1 compared to the HFD group (p < 0.05; figures 3D-3F). Meanwhile, the mRNA levels of key lipogenic genes (SREBP1c, SCD1, FASN) were markedly up-regulated by HFD, with increases of 0.602 ± 0.122 for SREBP1c, 0.771 ± 0.158 for SCD1, and 0.803 ± 0.127 for FASN compared to the NCD group (p < 0.01; figures 3A-3C). TRF intervention significantly attenuated this HFD-induced increase, reducing the expression levels by 0.346 ± 0.122 for SREBP1c, 0.469 ± 0.158 for SCD1, and 0.501 ± 0.127 for FASN compared to the HFD group (p < 0.05; figures 3A-3C).

C57BL/6 mice were fed either a normal chow diet (NCD group) or a high-fat diet (HFD group) for 24 weeks. The TRF group received the same HFD but was subjected to 8-hour time-restricted feeding (00:00 AM to 08:00 AM). mRNA levels of key lipogenic genes (A) SREBP1c, (B) SCD1, (C) FASN and core circadian clock genes (D) Bmal1, (E) Clock, (F) Per1 in liver. Gene expression was analyzed and normalized to 36B4 expression in the same sample. "a.u." stands for "arbitrary units." N=4 for each group. Data are presented as mean ± S.D.; *p < 0.05, **p < 0.01, ***p < 0.001; ****p < 0.0001; ns: not significant (p > 0.05).

TRF ameliorates hepatic steatosis and adipose tissue morphology

Compared to the NCD group, HFD feeding induced pronounced hepatic steatosis, characterized by substantial lipid droplet accumulation in hepatocytes, as well as adipose tissue abnormalities exemplified by adipocyte hypertrophy and disrupted tissue architecture in both epididymal (eWAT) and subcutaneous (SAT) fat depots. Time-restricted feeding intervention significantly alleviated these HFD-induced pathological alterations: lipid deposition in the liver was reduced, and adipocyte size and tissue morphology in white adipose tissues were restored to a state comparable to the NCD group. These results demonstrate that TRF effectively counteracts HFD-induced lipid deposition.

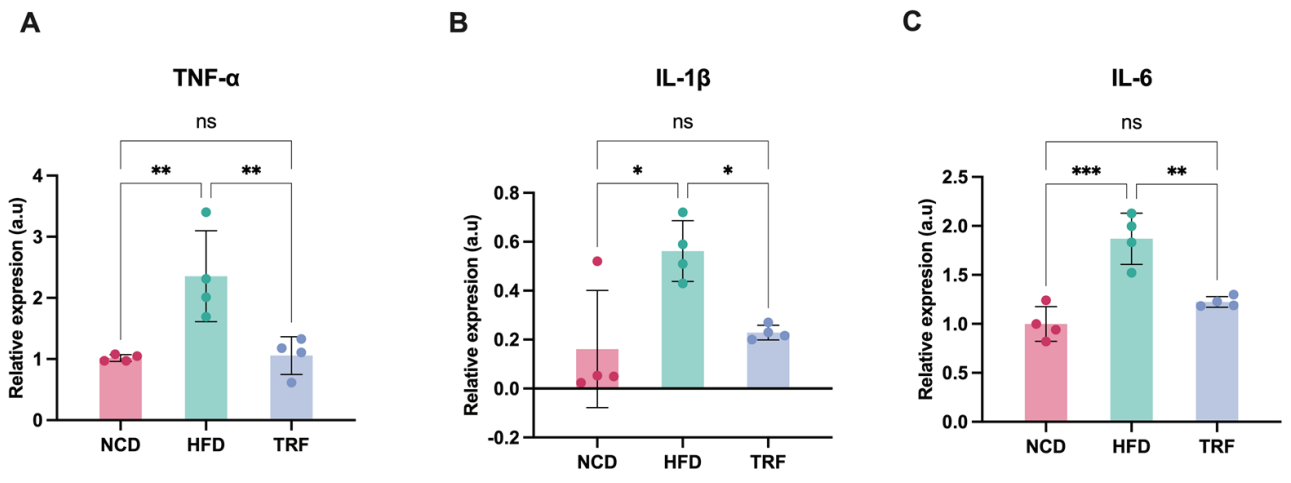

Figure 2: Time-restricted feeding reduces hippocampal inflammation induced by high-fat diet.

Discussion

Our study provides comprehensive evidence that 8-hour time TRF effectively ameliorates HFD induced cognitive impairment through multi-system mechanisms involving metabolic, inflammatory, and circadian pathways. While the ability of TRF to ameliorate HFD-induced weight gain is consistent with previous reports, our findings significantly extend current knowledge by demonstrating that its cognitive benefits occur independently of caloric reduction, suggesting a fundamental role of feeding-fasting cycles in brain health (Figure 4).

C57BL/6 mice were fed either a normal chow diet (NCD group) or a high-fat diet (HFD group) for 24 weeks. The TRF group received the same HFD but was subjected to 8-hour time-restricted feeding (00:00 AM to 08:00 AM). Representative images of liver tissue sections stained with Oil Red O (for lipids, red) and hematoxylin (for nuclei, blue). Representative hematoxylin and eosin (H&E)-stained sections of liver, epididymal white adipose tissue (eWAT) and subcutaneous adipose tissue (SAT). N=4 for each group. Images were observed though a light microscope at 200× magnification.

Time-restricted feeding is operationally defined as the voluntary limitation of all daily caloric intake to a predefined window of 4-12 h, followed by a prolonged fasting period of 12-20 h without overt caloric reduction [29]. Based on the alignment of this window with the master circadian clock, TRF protocols are conventionally classified into early (eTRF; first meal before 9:00 a.m.) and late TRF (lTRF; first meal after 11:30 a.m.; thus, typically excluding breakfast) [30]. Accumulating evidence indicates that the metabolic and chronobiological outcomes of these two variants diverge markedly. In humans, eTRF (08:00-14:00) for 5 weeks improved 24-h glucose homeostasis, increased nocturnal autophagy flux markers, and synchronized peripheral clock gene expression, despite isocaloric conditions [25]. Conversely, lTRF (12:00-20:00) failed to enhance insulin sensitivity or advance the phase of core-body-temperature rhythm in overweight adults [23]. Similarly, another study [21] demonstrated that restricting high-fat feeding to the active phase (eTRF) preserved circadian amplitude of clock genes and attenuated metabolic dysfunction in middle-aged mice, whereas late TRF failed to do so. Collectively, these data support the hypothesis that the physiological response to TRF is gated by circadian timing, with eTRF conferring superior metabolic protection and more robust reinforcement of circadian rhythms. Guided by this framework, the present study adopted a 8-h eTRF protocol (00:00 AM-08:00 AM) in mice to maximize the potential for both metabolic improvement and clock realignment. Nevertheless, we propose that future studies should include both eTRF and lTRF protocols in parallel to compare their differential effects on high-fat-diet-induced cognitive impairment.

The rescue of hippocampal-dependent memory by TRF may be attributed to several interconnected mechanisms. First, the observed reduction in hippocampal pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) indicates suppression of neuroinflammation-a known driver of synaptic dysfunction and cognitive decline [31-35]. This anti-inflammatory effect likely originates from multiple sources: the reduction in visceral adipose tissue mass decreases systemic inflammation, while the daily fasting window may promote ketogenesis, and ketone bodies like β-hydroxybutyrate have demonstrated potent anti-inflammatory properties through inhibition of NLRP3 inflammasome activation [36-38]. Additionally, TRF has been shown to enhance autophagy, a cellular clearance process that removes damaged organelles and protein aggregates, thereby reducing neuronal stress and inflammation [39,40].

Notably, our study reveals that TRF restores the expression of core circadian clock genes (Bmal1, Clock, Per1) in the liver. This finding is particularly significant in light of emerging research on the gut-brain-liver axis and its role in cognitive function. Circadian disruption has been increasingly implicated in blood-brain barrier leakage, impaired glymphatic clearance, and neuroinflammation [41-43]. By realigning peripheral circadian rhythms, TRF may help restore optimal temporal organization of metabolic processes, such as lipid handling and glucose metabolism, thereby reducing the systemic metabolic stress that contributes to neural impairment.

Furthermore, the downregulation of lipogenic genes (SREBP1c, SCD1, FASN) and reduction in hepatic steatosis indicate that TRF promotes a metabolic shift toward lipid utilization and oxidative metabolism. This is consistent with studies showing that TRF enhances mitochondrial biogenesis and function, particularly in peripheral tissues like the liver and muscle [44-46]. Improved metabolic health not only reduces ectopic lipid deposition but may also enhance brain energy substrate availability and insulin sensitivity-both critical for cognitive processes.

The integration of these findings supports a model in which TRF acts as a system-level intervention that synchronizes metabolic, inflammatory, and circadian processes. Rather than targeting a single pathway, TRF leverages the inherent coupling of these systems, resulting in synergistic benefits that are difficult to achieve with pharmaceutical or dietary composition interventions alone. Our work reinforces the growing recognition that when we eat may be as critical as what we eat, particularly in the context of circadian biology and brain health.

This study has several limitations: First, the sample size in behavioral and molecular assays (n=4) may limit the generalizability of some findings. Second, although TRF restored circadian gene expression and reduced neuroinflammation, the exact causal links between these pathways and cognitive improvement remain to be fully elucidated through targeted mechanistic studies. Besides, the study was conducted in a male mouse model; future research should include female subjects to examine potential sex differences in TRF response. Finally, physical activity is a key factor affecting body weight but was not assessed in this study. This limitation should be addressed in future research.

Conclusions

In conclusion, our findings demonstrate that early time TRF is an effective non-pharmacological strategy to counteract high-fat diet-induced cognitive impairment in mice. Early time TRF not only ameliorate HFD-induced weight gain but also significantly improved spatial learning and memory, likely through multi-level mechanisms involving the suppression of neuroinflammation, restoration of circadian rhythm gene expression, and regulation of lipid metabolism. These results highlight the critical role of feeding timing in metabolic and brain health, and support early time TRF as a promising lifestyle intervention for preventing obesity-related cognitive decline.

Conflict of Interest

None.

Acknowledgement

None.

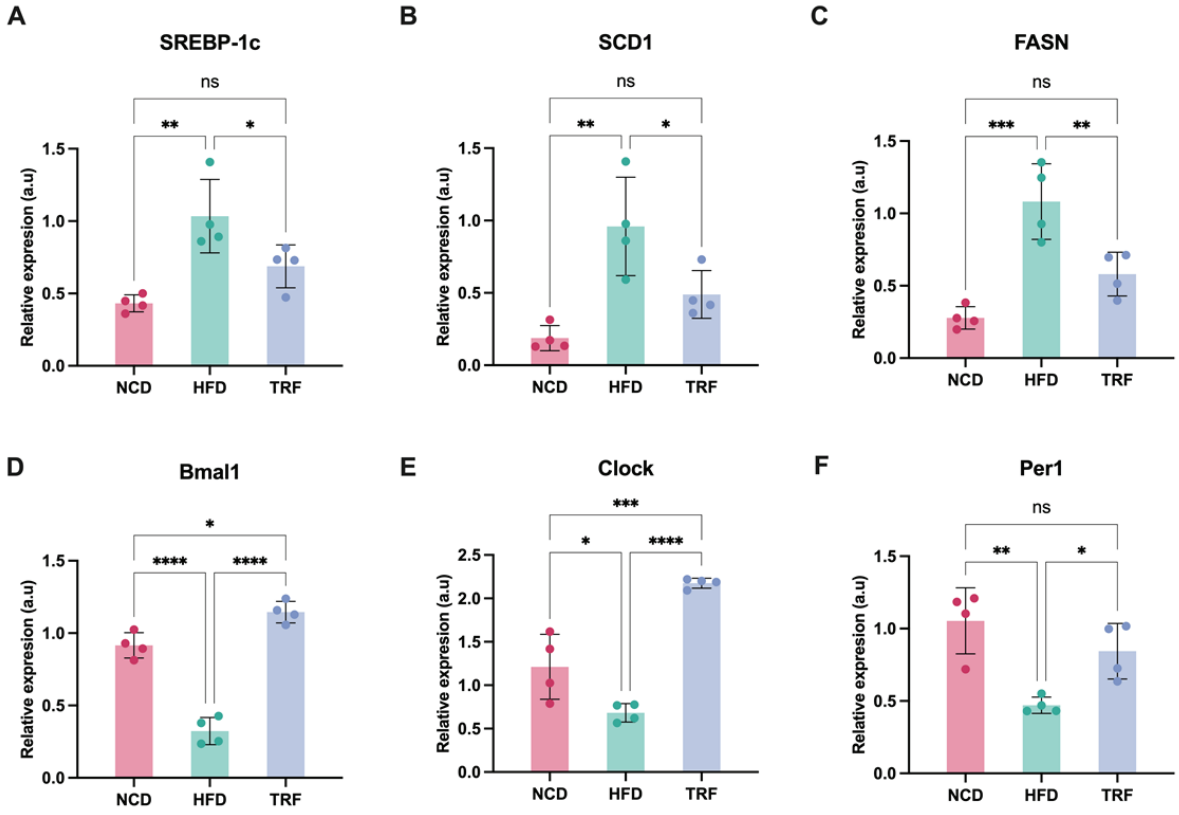

Figure 3: Time-restricted feeding favorably regulates hepatic circadian rhythms and the expression of genes related to lipid metabolism.

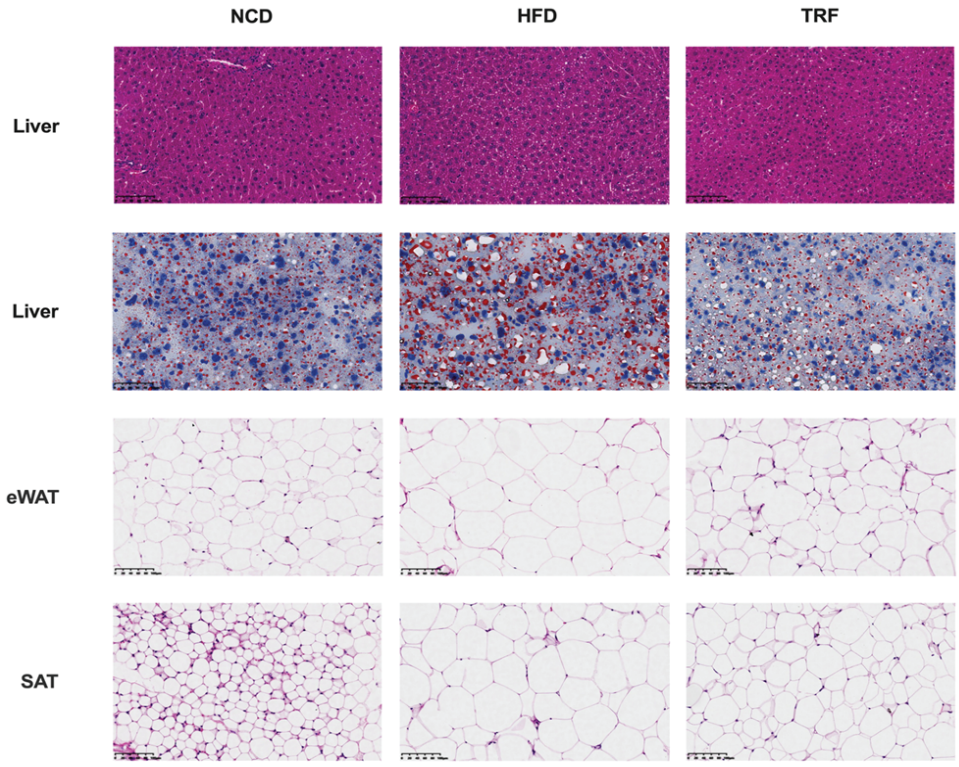

Figure 4: Time-restricted feeding ameliorates hepatic steatosis and adipose tissue morphology in high-fat diet (HFD)-fed mice.

Author Contributions

Taoli Liu: Conceptualization, Methodology, Validation, Writing - Original Draft Preparation, Writing - Review & Editing. Tingying Zhang: Methodology, Validation, Data Curation, Writing - Original Draft Preparation, Writing - Review & Editing. Jiapan Sun: Methodology, Validation. Li Zhang: Conceptualization, Data Curation, Supervision.

References

1. Hildreth KL, Van Pelt RE, Schwartz RS (2012) Obesity, Insulin Resistance, and Alzheimer's Disease. Obesity (Silver Spring) 20: 1549-1557.
2. Koriath CAM, Perneczky R (2025) Obesity and Obesity and Alzheimer's disease dementia: Examining inflammatory links to cognitive decline and neuropsychiatric symptoms. J Alzheimers Dis 106: 51-53.
3. Rajput M, Malik IA, Methi A, Silva JAC, Fey D, et al. (2025) Cognitive decline and neuroinflammation in a mouse model of obesity: An accelerating role of ageing. Brain Behav Immun 125: 226-239.
4. Ceolin B, Prinelli F, Trevisan C, Ravelli A, Conti S, et al. (2025) Body weight trajectories from midlife are associated with cognitive decline in advanced age. Sci Rep 15: 24128.
5. Wang C, Chan JSY, Ren L, Yan JH (2016) Obesity Reduces Cognitive and Motor Functions across the Lifespan. Neural Plast 2016: 2473081.
6. Dahl AK, Hassing LB, Fransson EI, Gatz M, Reynolds CA, et al. (2013) Body mass index across midlife and cognitive change in late life. Int J Obes (Lond) 37: 296-302.
7. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry Jr CP, Yaffe K (2005) Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 330: 1360.
8. Al Hazzouri AZ, Vittinghoff E, Hoang T, Golden SH, Fitzpatrick AL, et al. (2021) Body mass index in early adulthood and dementia in late life: Findings from a pooled cohort. Alzheimers Dement 17: 1798-1807.
9. Li L, Yu H, Zhong M, Liu S, Wei W, et al. (2022) Gray matter volume alterations in subjects with overweight and obesity: Evidence from a voxel-based meta-analysis. Front Psychiatry 13: 955741.
10. Wernberg CW, Grønkjær LL, Jacobsen BG, Chandran VI, Krag A, et al. (2023) The prevalence and risk factors for cognitive impairment in obesity and NAFLD. Hepatol Commun 7: e00203.
11. Deckers K, Boxtel MPJV, Verhey FRJ, Köhler S (2017) Obesity and Cognitive Decline in Adults: Effect of Methodological Choices and Confounding by Age in a Longitudinal Study. J Nutr Health Aging 21: 546-553.
12. McLean FH, Grant C, Morris AC, Horgan GW, Polanski AJ (2018) Rapid and reversible impairment of episodic memory by a high-fat diet in mice. Sci Rep 8: 11976.
13. Murray AJ, Knight NS, Cochlin LE, McAleese S, Deacon RMJ, et al. (2009) Deterioration of physical performance and cognitive function in rats with short-term high-fat feeding. FASEB J 23: 4353-4360.
14. Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, et al. (2012) Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest 122: 153-162.
15. Buie JJ, Watson LS, Smith CJ, Sims-Robinson C (2019) Obesity-related cognitive impairment: The role of endothelial dysfunction. Neurobiol Dis 132: 104580.
16. Chiu SL, Cline HT (2010) Insulin receptor signaling in the development of neuronal structure and function. Neural Dev 5: 7.
17. Hussain Y, Jain SK, Samaiya PK (2019) Short-term westernized (HFFD) diet fed in adolescent rats: Effect on glucose homeostasis, hippocampal insulin signaling, apoptosis and related cognitive and recognition memory function. Behav Brain Res 361: 113-121.
18. Sims-Robinson C, Bakeman A, Bruno E, Jackson S, Glasser R, et al. (2016) Dietary Reversal Ameliorates Short- and Long-Term Memory Deficits Induced by High-fat Diet Early in Life. PLoS One 11: e0163883.
19. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly Jr ES, et al. (2010) NIH state-of-the-science conference statement: Preventing Alzheimer's disease and cognitive decline. NIH Consens State Sci Statements 27: 1-30.
20. Ezpeleta M, Cienfuegos S, Lin S, Pavlou V, Gabel K, et al. (2024) Time-restricted eating: Watching the clock to treat obesity. Cell Metab 36: 301-314.
21. Duncan MJ, Smith JT, Narbaiza J, Mueez F, Bustle LB, et al. (2016) Restricting feeding to the active phase in middle-aged mice attenuates adverse metabolic effects of a high-fat diet. Physiol Behav 167: 1-9.
22. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, et al. (2018) Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab 27: 1212-1221.e3.
23. Hutchison AT, Regmi P, Manoogian ENC, Fleischer JG, Wittert GA, et al. (2019) Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. Obesity (Silver Spring) 27: 724-732.
24. Jones R, Pabla P, Mallinson J, Nixon A, Taylor T, et al. (2020) Two weeks of early time-restricted feeding (eTRF) improves skeletal muscle insulin and anabolic sensitivity in healthy men. Am J Clin Nutr 112: 1015-1028.
25. Jamshed H, Beyl RA, Manna DLD, Yang ES, Ravussin E (2019) Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. Nutrients 30 11: 1234.
26. Kibret KT, Peeters A, Tegegne TK, Mesfin YM, Nichols M (2025) Intermittent Fasting for the Prevention of Cardiovascular Disease Risks: Systematic Review and Network Meta-Analysis. Curr Nutr Rep 14: 93.
27. Huang YJ, Zhang L, Shi LY, Wang YY, Yang YB (2018) Caloric restriction ameliorates acrolein-induced neurotoxicity in rats. Neurotoxicology 65: 44-51.
28. Zhang L, Wang B, Pan L, Peng J (2013) Recycling isolation of plant DNA, a novel method. J Genet Genomics 40: 45-54.
29. Manoogian ENC, Laferrère B (2023) Time-restricted eating: What we know and where the field is going. Obesity 31 Suppl 1: 7-8.
30. Petridi F, Geurts JMW, Nyakayiru J, Schaafsma A, Schaafsma D, et al. (2024) Effects of Early and Late Time-Restricted Feeding on Parameters of Metabolic Health: An Explorative Literature Assessment. Nutrients 16: 1721.
31. Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. Science 302: 1760-1765.
32. Poluektova L, Meyer V, Walters L, Paez X, Gendelman HE (2005) Macrophage-induced inflammation affects hippocampal plasticity and neuronal development in a murine model of HIV-1 encephalitis. Glia 52: 344-353.

33. Lampe L, Zhang R, Beyer F, Huhn S, Masouleh SK, et al. (2019) Visceral obesity relates to deep white matter hyperintensities *via* inflammation. Ann Neurol 85: 194-203.

34. Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Keun Ha BK, et al. (2002) Control of synaptic strength by glial TNFalpha. Science 295: 2282-2285.

35. Ma YL, Xia JL, Gao X (2018) Suppressing Irf2bp2 expressions accelerates metabolic syndrome-associated brain injury and hepatic dyslipidemia. Biochem Biophys Res Commun 503: 1651-1658.

36. Shippy DC, Wilhelm C, Viharkumar PA, Raife TJ, Ulland TK (2020) β-Hydroxybutyrate inhibits inflammasome activation to attenuate Alzheimer's disease pathology. J Neuroinflammation 17: 280.

37. Şahin E, Aykanat NEB, Kacar S, Bagci R, Sahinturk V (2021) β-Hydroxybutyrate, One of the Three Main Ketone Bodies, Ameliorates Acute Pancreatitis in Rats by Suppressing the NLRP3 Inflammasome Pathway. Turk J Gastroenterol 32: 702-711.

38. Youm YH, Nguyen KN, Grant RW, Goldberg EL, Bodogai M, et al. (2015) The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med 21: 263-269.

39. Jeong S, Davis CK, Vemuganti R (2025) Mechanisms of time-restricted feeding-induced neuroprotection and neuronal plasticity in ischemic stroke as a function of circadian rhythm. Exp Neurol 383: 115045.

40. Ulgherait M, Midoun AM, Park SJ, Gatto JA, Tener SJ, et al. (2021) Circadian autophagy drives iTRF-mediated longevity. Nature 598: 353-358.

41. Nakazato R, Kawabe K, Yamada D, Ikeno S, Mieda M, et al. (2017) Disruption of Bmal1 Impairs Blood-Brain Barrier Integrity *via* Pericyte Dysfunction. J Neurosci 37:10052-10062.

42. Hablitz LM, Plá V, Giannetto M, Vinitsky HS, Stæger HF, et al. (2020) Circadian control of brain glymphatic and lymphatic fluid flow. Nat Commun 11: 4411.

43. Hurtado-Alvarado G, Domínguez-Salazar E, Pavon L, Velázquez-Moctezuma J, Gómez-González B (2016) Blood-Brain Barrier Disruption Induced by Chronic Sleep Loss: Low-Grade Inflammation May Be the Link. J Immunol Res 2016: 4576012.

44. Milan M, Brown J, O'Reilly CL, Bubak MP, Negri S, et al. (2024) Time-restricted feeding improves aortic endothelial relaxation by enhancing mitochondrial function and attenuating oxidative stress in aged mice. Redox Biol 73: 103189.

45. Smith JG, Molendijk J, Blazev R, Chen WH, Zhang Q, et al. (2023) Impact of Bmal1 Rescue and Time-Restricted Feeding on Liver and Muscle Proteomes During the Active Phase in Mice. Mol Cell Proteomics 22: 100655.

46. Rodrigues LGF, de Araujo LD, Roa SLR, Bueno AC, Uchoa ET, et al. (2021) Restricted feeding modulates peripheral clocks and nutrient sensing pathways in rats. Arch Endocrinol Metab 65: 549-561.