Thanks very much for the editor and reviewer's valuable comments that helped make our paper better. We have revised the format and contents following these comments. All the modifications made this manuscript better. The following contents show the detailed responses to the reviewer's comments. The revised/ added contents are highlighted with yellow color in the revised manuscript.

a) Introduction could be centered just in those points related to approach. Other sentences could be moved to discussion section.

RE: Thanks for your valuable comments. We have summarized the introduction briefly, with a greater emphasis on the methodology. These details are in Lines 92-98, Lines 101-103, Lines 116-119 and Lines 128-131.

Lines 92-98：

Immune system abnormalities play a pivotal role in the pathogenesis of T2DM. Dysregulation of inflammation and immune responses is intricately linked to insulin resistance and beta cell dysfunction[3]. Furthermore, alterations in the expression of immune-related genes may also serve as crucial determinants in the development of diabetes-associated cognitive impairment. Therefore, a complete understanding of the involvement of these immune genes in the cognitive impairment of individuals with T2DM is imperative.

Lines 101-103:

Compared to the traditional experimental methods, bioinformatics can explore the hidden molecular mechanisms of diseases, and is regarded as a highly effective research method.

Lines 116-119:

Our study employed advanced bioinformatic methods to conduct a comprehensive analysis of immune-related genes, aiming to elucidate the regulatory mechanisms of these genes on cognitive function in individuals with T2DM and explore their underlying pathogenic pathways.

Lines 128-131:

Through these insights, we aspire to provide valuable information for the development of more efficacious treatment strategies and the enhancement of the quality of life of patients with T2DM-related cognitive impairment.

Several literature reviews on neuroinflammation and microglia have been incorporated into the discussion section. These details are in Lines 469-478, Lines 502-504, and Lines 509-513.

Lines 469-478：

Several mechanisms have been proposed to explain the relationship between T2DM and cognitive impairment, including hyperglycemia, insulin resistance, vascular impairment, oxidative stress, and neuroinflammation[3]. Neuroinflammation is a term used to describe the stimulation of glial cells, specifically microglia and astrocytes, leading to the generation of inflammatory cytokines and chemokines within the central nervous system[38]. A study found that knockout of TLR2 protected against diabetes-induced cognitive impairment[39]. Similarly, suppression of NLRP3 enhances cognitive ability and maintains vascular health following stroke in diabetic animals[40].

Lines 502-504:

Microglia are the main components of the brain's natural defense system, and play a vital role in neuroinflammation, which is strongly linked to cognitive impairment associated with T2DM[41, 42].

Lines 509-513:

A single-cell sequencing study confirmed the opinion that microglia in the hippocampus and immune system play a vital role in diabetes-associated cognitive impairment[45]. Focusing on the immune system and neuroinflammation could offer a promising pathway for creating new treatment approaches to enhance cognitive abilities in T2DM.

b) Discussion section should be enriched. Particularly, the 11 drugs identified as potential to act in the reported gens-proteins should be discussed as they could be acting. As an example: valproic acid is clearly an antiseizure agent, but multiple reports suggest action in neurodegeneration, while some structurally-related compounds are active in metabolism and neurons.

RE: Thanks for your valuable comments. We focused on several drugs such as Cyclosporine, Valproic acid, Choline, Folic acid, and Methionine that have beneficial effects on the nervous system. These drugs have a variety of functions, and when the dosage or duration of application is different, it is possible to have the opposite effects on cognitive function. Several other compounds that are harmful to the nervous system have been briefly discussed. Each compound is accompanied by corresponding references. We have added some highlights to the article references. These details are in Lines 578-605: *Eleven potential drugs were identified in this study. These drugs have a variety of functions, and when the dosage or duration of application is different, it is possible to have the opposite effects on cognitive function. Cyclosporine is an immunosuppressant, mainly used for rejection after organ and tissue transplantation. During surgery under general anesthesia, Cyclosporine treatment can increase ATP levels in the cerebral cortex and improve learning and memory function[69]. Valproic acid is commonly used in the treatment of epilepsy and bipolar affective disorder. It is reported that it improves cognitive function in patients with bipolar affective disorder[70]. However, long-term use of valproic acid can impair cognitive function[71]. Valproic acid exposure can cause autism in prepubertal rats[72]. Choline is a constituent of biological membranes and precursor of acetylcholine in cholinergic neurons. It can promote brain development and improve memory[73]. Lifelong choline supplementation may ameliorate AD by attenuating microglial activation[74]. It is well known that folic acid is closely related to fetal neurodevelopment. The deficiency of folic acid can result in elevated levels of homocysteine, thereby contributing to the development of atherosclerosis, stroke, diabetes, and other related conditions[75]. Folic acid supplementation affects cognition and inflammation in patients with AD[76]. A Methionine-restricted diet can improve cognitive function[77]. Another study of Chinese adults revealed that animal methionine and plant methionine intake were positively and inversely associated with cognition[78]. These drugs, which have beneficial effects on the nervous system, may become therapeutic options for diabetes-related cognitive impairment. However, 11-nor-delta (9)-tetrahydrocannabinol-9-carboxylic acid[79], Cannabinoids[80], Benzo(a)pyrene[81], Bis(4-hydroxyphenyl)s, Bisphenol A[82] and Vinclozolin[83] are neurotoxic and can lead to cognitive impairment. This suggests that patients with diabetic cognitive impairment should avoid exposure to neurotoxic drugs.*

c) Figures caption should be edited to improve readers' understanding without read the entire manuscript. Some of them just describe in a general way that presented in each panel.

RE: Thanks for your valuable comments. To improve readers' understanding without read the entire manuscripte, we have re-edited the figure captions of the Figure 1-4 and Figure 6-9. These details are highlighted with yellow color in the revised manuscript.

d) In table of compounds, the information in the last -on right- column should be checked and supported by specific references. Some compounds have more than one (or contrary) actions supported by recent literature.

RE: Thanks for your valuable comments. We have checked the information and added supporting references to the Column Interaction of the table. We have supplemented the title of the table.

In addition to the reviewer's comments, we also make comprehensive modifications to make sure everything fit the editorial office's and editor-in-chief's comments. We have proofread the abbreviations in the manuscript according the basic rules provided. The revised manuscript has been edited by the professional English language editing company, and the English Language Certificate has been provided. We have provided the filled conflict-of-interest disclosure form. We have provided the figures cited in the original manuscript in the form of PPT. All of them are original images created for the manuscript. We have made corrections to the format of all the legends, and made certain revisions to the title and explanation for each figure. For the representation of p-values, we have changed the * to superscript letters in Figure 7 and Figur 9. We have upload the approved grant application form and funding agency copy of approval document. We have added the "Article Highlights" section at the end of the main text. According to the suggestions of the editor and reviewer, we have supplemented and improved the highlights of the latest cutting-edge research results, and improved the content of the manuscript. We used RCA for literature search and citations according to "Impact Index Per Article". We have checked the authors names and institutions to meet the requirements of the journal. We have checked the manuscript carefully.

Editor-in-Chief: It is acceptable although there was only one reviewer. In addition, if the authors have chance （1） to add the diabetic model information, it will be great; (2） For figures 7 and 10, labels of Y and X axis are better to be a little bigger and readable.

RESPONSE: Thanks for your valuable comments. We have added the diabetic model information we used for validation in the "Experimental animals and ethics" of MATERIALS AND METHODS. "Male BKS.Cg-Dock7m +/+ Leprdb/J homozygous Leprdb/db mice were diabetic, and heterozygous Leprdb/m mice were used as controls (denoted as db/db and db/m in the text) in this study. As a diabetic model, the mice we used were consistent with the dataset GSE125387." We have previously described in detail the use of PA as an in vitro model of type 2 diabetes in the "Cell line culture and treatment" of MATERIALS AND METHODS. "Palmitic acid (PA) is a common saturated fatty acid. It is the main component of HFD and it has been found increased in the circulation of obese and diabetic people. PA has been studied in various biological contexts including inflammation, metabolic disorders, and cell signaling. In the central nervous system, PA has been associated with inflammatory responses. PA is recognized as a T2DM model in vitro, such as in BV2 cells[34], β cells[35], and skeletal muscle cells[36]. Changes in the cerebral gene expression profiles seemed to be specific in the T2DM model, as no such alterations were found in the type 1 diabetes mellitus model[37]. So we chose the high-fat model instead of the high-glucose model."