**Supporting Information**

# Restoration of Glyoxalase Enzyme Activity Precludes Cognitive Dysfunction in a Mouse Model of Alzheimer's Disease

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**Determination of methylglyoxal concentration in brain tissue.** Excised brain tissue from Wild type and transgenic Alzheimer's mice was homogenized in a Dounce instrument with the aid of phosphate buffer (pH 7.4, 0.1 M). The resulting homogenates were centrifuged and the supernatent fluid was examined for methylglyoxal content upon derivatization with 1,2-diaminobenzene as follows[14]: a mixture consisting of the supernatent from brain homogenate (200 μL), 5 M $HClO_4$ (50 μL), 10 mM aqueous solution of 1,2-diaminobenzene (100 μL) and an internal standard consisting of 5-methylquinoxaline (1 μM, 50 μL) was diluted with water to a final volume of 2 mL. These mixtures were incubated overnight and centrifuged. The supernatent was passed through a C-18 SPE cartridge that had been pretreated by flushing sequentially with 2–4 mL portions of acetonitrile and aqueous $KH_2PO_4$ (10 mM, pH = 2.4). The eluates from this process were examined for their 2-methylquinoxaline content utilizing a Beckman Coulter Gold chromatography system with a Varian® Microsorb-MV® 200-5 C-18 column (20 cm, 4.6 mm I.D. and 5 μM mean particle diameter). The eluant was a 4:1 volume mixture of 10 mM aqueous $KH_2PO_4$ and HPLC grade MeCN, respectively. Chromatography conditions consisted of a detection wavelength of 313 nm, eluant flow rate of 1.0 mL per minute and an average injection volume of 50 μL. Samples were analzyed in duplicate and were standardized by comparison with the 2-methylquinoxaline standard, which had a mean retention time of 6.78 minutes under these conditions.

**Supplementary Figures:**

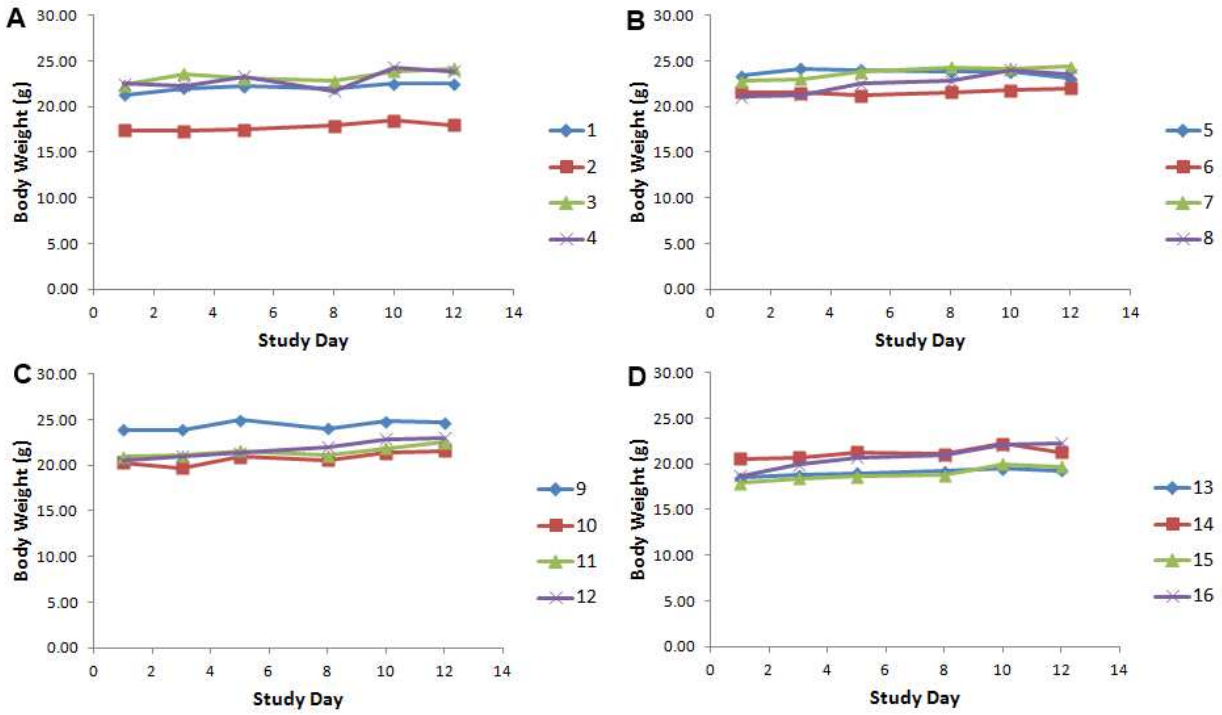


**Figure S1.** Dose determination and short term toxicity study of Ψ-GSH. Changes in body weights of C57BL/6 mice treated with i.p. Ψ-GSH at 0 (**A**), 500 (**B**), 1000 (**C**) and 2000 (**D**) mg/kg doses, 3×/week for two weeks. Administration of Ψ-GSH did not have any effect on body weights of mice. Each graph is represented by individual mouse in each group.

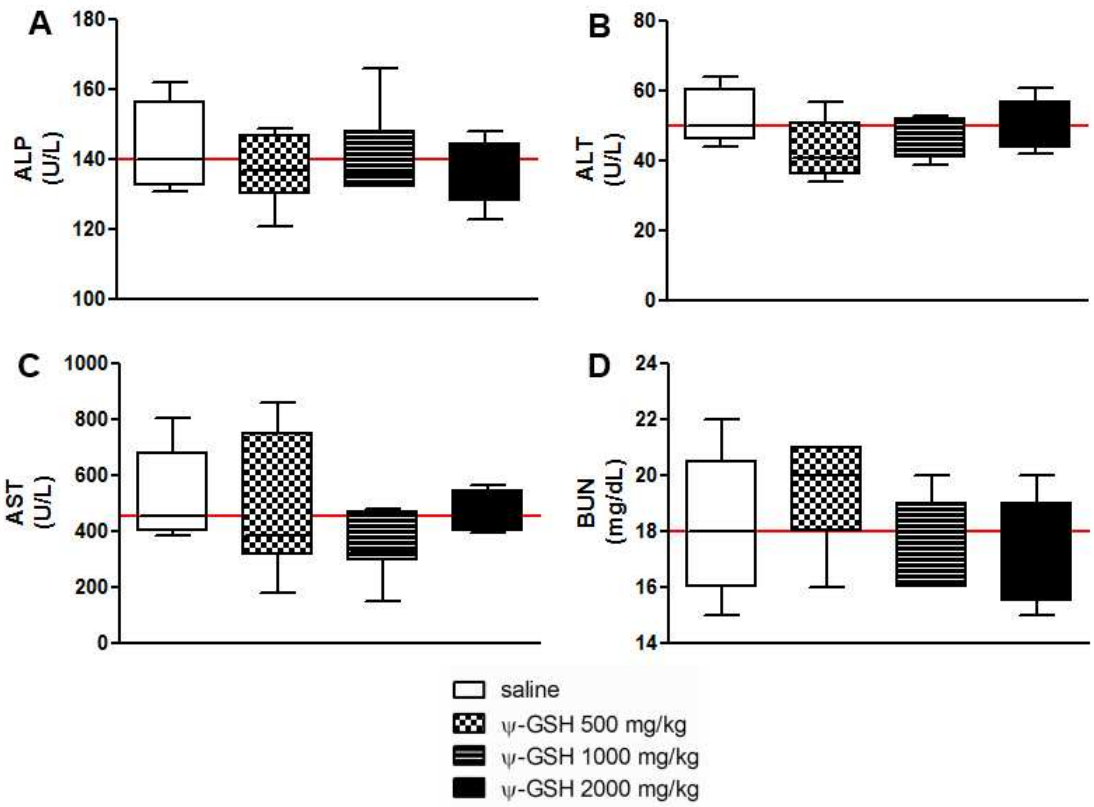


**Figure S2.** Ψ-GSH treatment (3×/week for two weeks) did not affect liver enzyme levels [alkaline phosphatase (ALP, **A**), alanine transaminase (ALT, **B**), and aspartate transaminase (AST, **C**)] and kidney function as represented by blood urea nitrogen (BUN, **D**). Blood creatinine levels in these mice were less than 0.2 mg/dL.

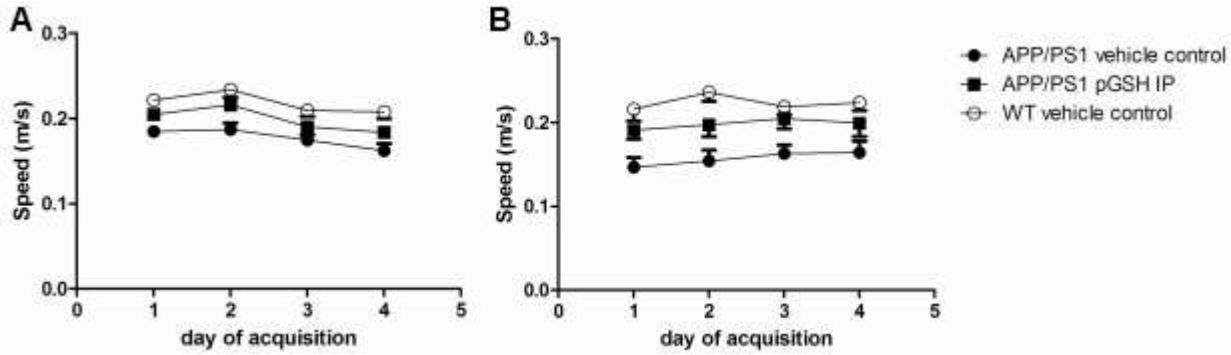


**Figure S3.** There was no effect of Ψ-GSH on the speeds of mice in the hidden platform (**A**) and the visible platform (**B**) training.

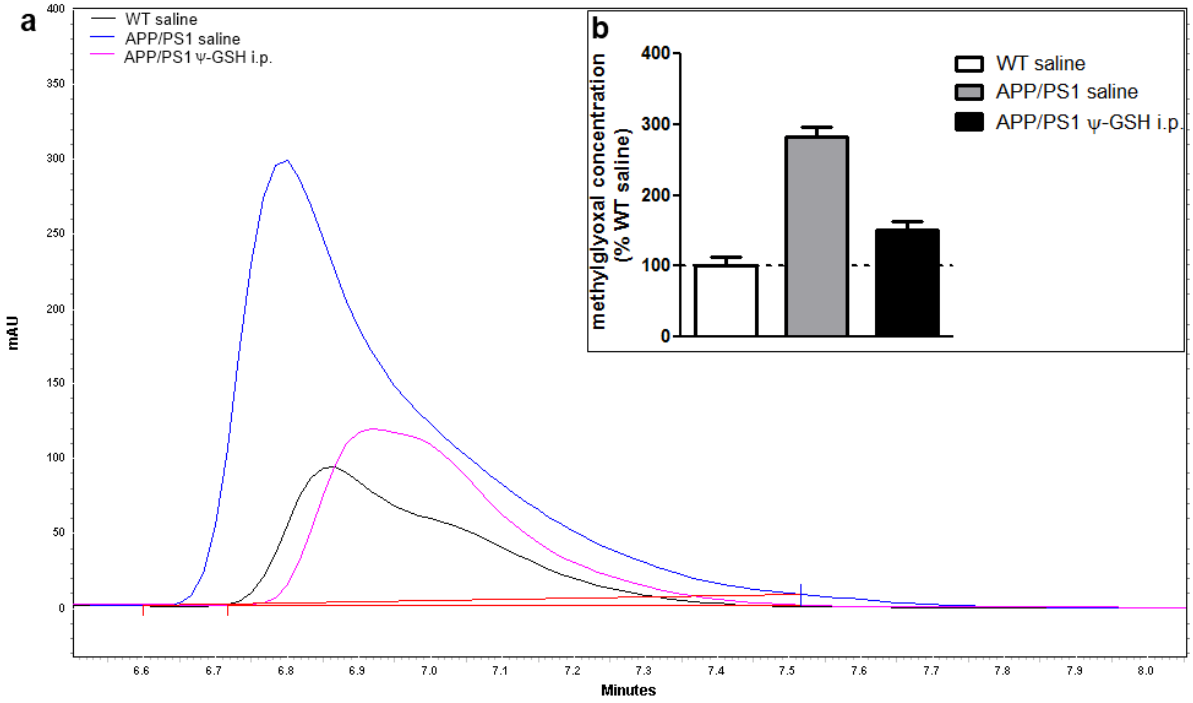


**Figure S4.** Effect of Ψ-GSH treatment on methylglyoxal concentration in mouse brain. Brains of mice treated and untreated with ψ-GSH (WT and APP/PS1 mice) were homogenized in 0.1 M potassium phosphate buffer (pH 7.4). Total concentrations of MG were quantified by HPLC after derivatization with 1,2-diaminobenzene as described in Supporting Materials. The results of this experiment demonstrated that the elevation of MG levels observed in APP/PS1 saline treated mice was diminished by Ψ-GSH treatment to levels comparable to WT saline treated mice. Figure (a) shows representative HPLC traces of the MG derivative, 2-methylquinoxaline from brain homogenates and figure (b) is a bar graph represented by mean ± SEM (n = 4) displaying MG concentrations as percentages of MG concentrations in WT saline treated mouse brain homogenates (n = 4).