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Figure S1 SUPPLEMENTARY

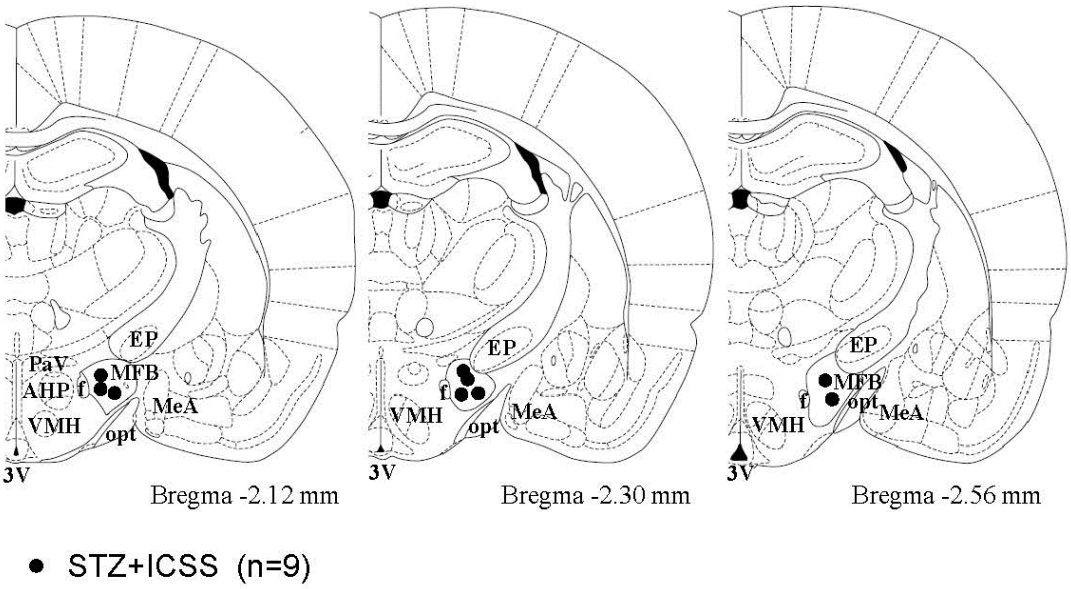

Figure S1. Verification of the location of the ICSS electrodes in the MFB. Location of the terminal tip of the ICSS stimulation electrodes in the subjects of the STZ+ICSS group, superimposed on the figures of the Paxinos and Watson atlas at coordinates -2.12 mm to -2.56 mm posterior to Bregma. Abbreviations: AHP: anterior hypothalamic area; EP: entopeduncular nucleus; f: fornix; MeA: medial amygdaloid nucleus; MFB: medial forebrain bundle-lateral hypothalamus; PaV: paraventricular hypothalamic nucleus; opt: optic tract; VMH: ventromedial hypothalamic nucleus; 3V: 3rd ventricle.

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Figure S2 SUPPLEMENTARY

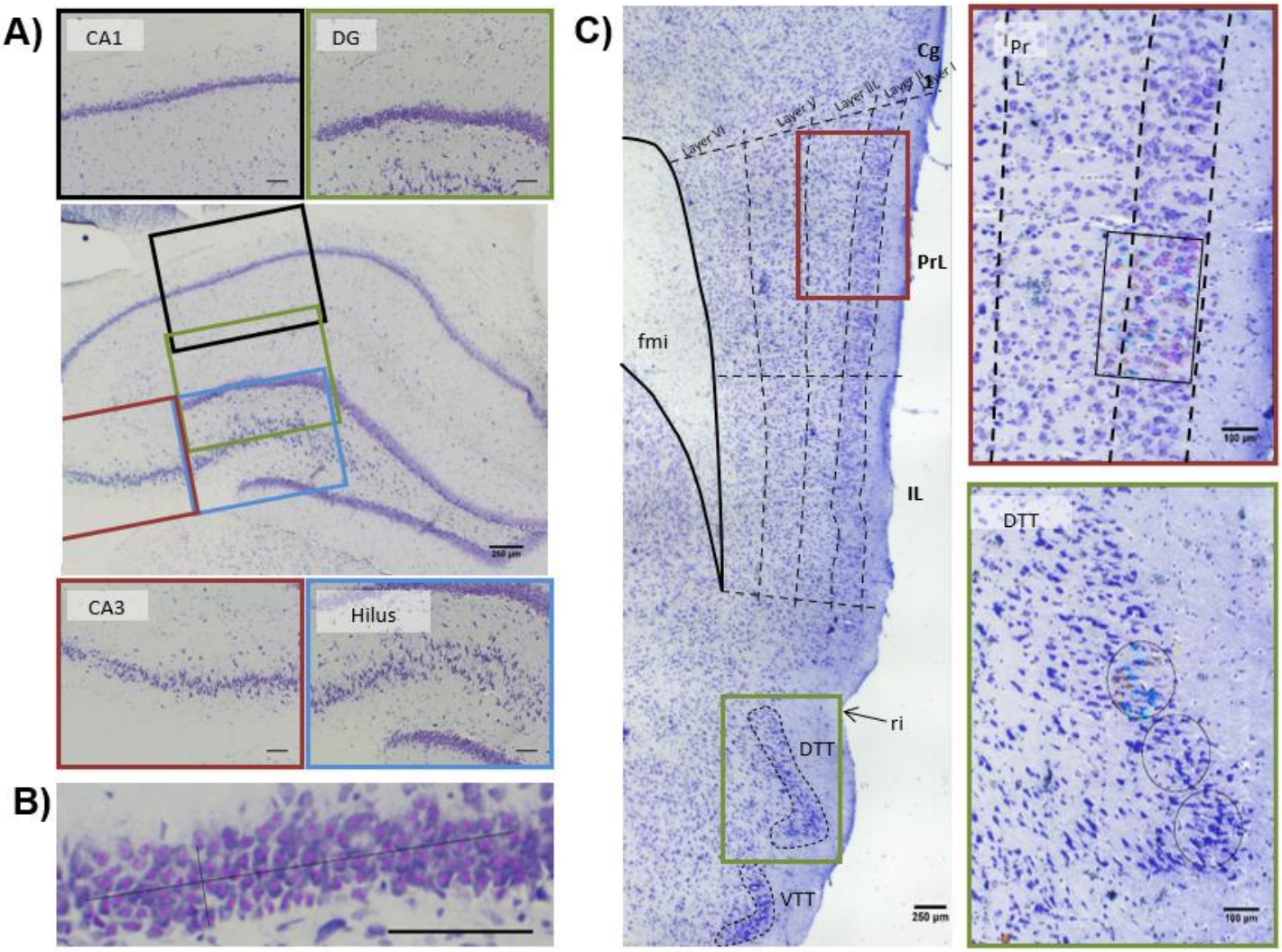

Figure S2. Nissl staining photomicrography and analysis of hippocampal and prefrontal regions. A) Location of photomicrographs for each analysed subregion in the hippocampus of a Nissl-stained parietal-temporal section (-3.30 mm from Bregma, according to Paxinos and Watson's atlas (Paxinos and Watson, 2006). Scale bar=100 µm when not specified. **B)** Representation of cell count in layer-shaped hippocampal

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subregions. Black segments show the length and width in which neurons, labelled with a pink marker, are counted. Abbreviations: DG: dentate gyrus; hil: hilus.

ImageJ was used to manually count the number of neurons in each region. Total counts were normalized by 250 µm length. Neuronal density was determined as cells per mm^2.

C) Location of photomicrographs for PrL layer II-III and DTT in the medial prefrontal cortex of a Nissl-stained frontal section (+3.00 mm from Bregma). In PrL and DTT photomicrographs, rectangular or circular regions of interest (ROIs), respectively, are shown superimposed. Abbreviations: Cg: cingulate cortex area; DTT: dorsal tenia tecta; fmi: forceps minor of the corpus callosum; IL: infralimbic cortex; PrL: prelimbic cortex; ri: rhinal incisure; VTT: ventral tenia tecta. Neurons were counted in each ROI, classifying according to their shape in normal or degenerating neurons. Shrunken, deformed, indistinct borders between the nucleus and cytoplasm, pyknotic and hyperchromatic neurons were counted as degenerating neurons.

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FIGURE S3 SUPPLEMENTARY

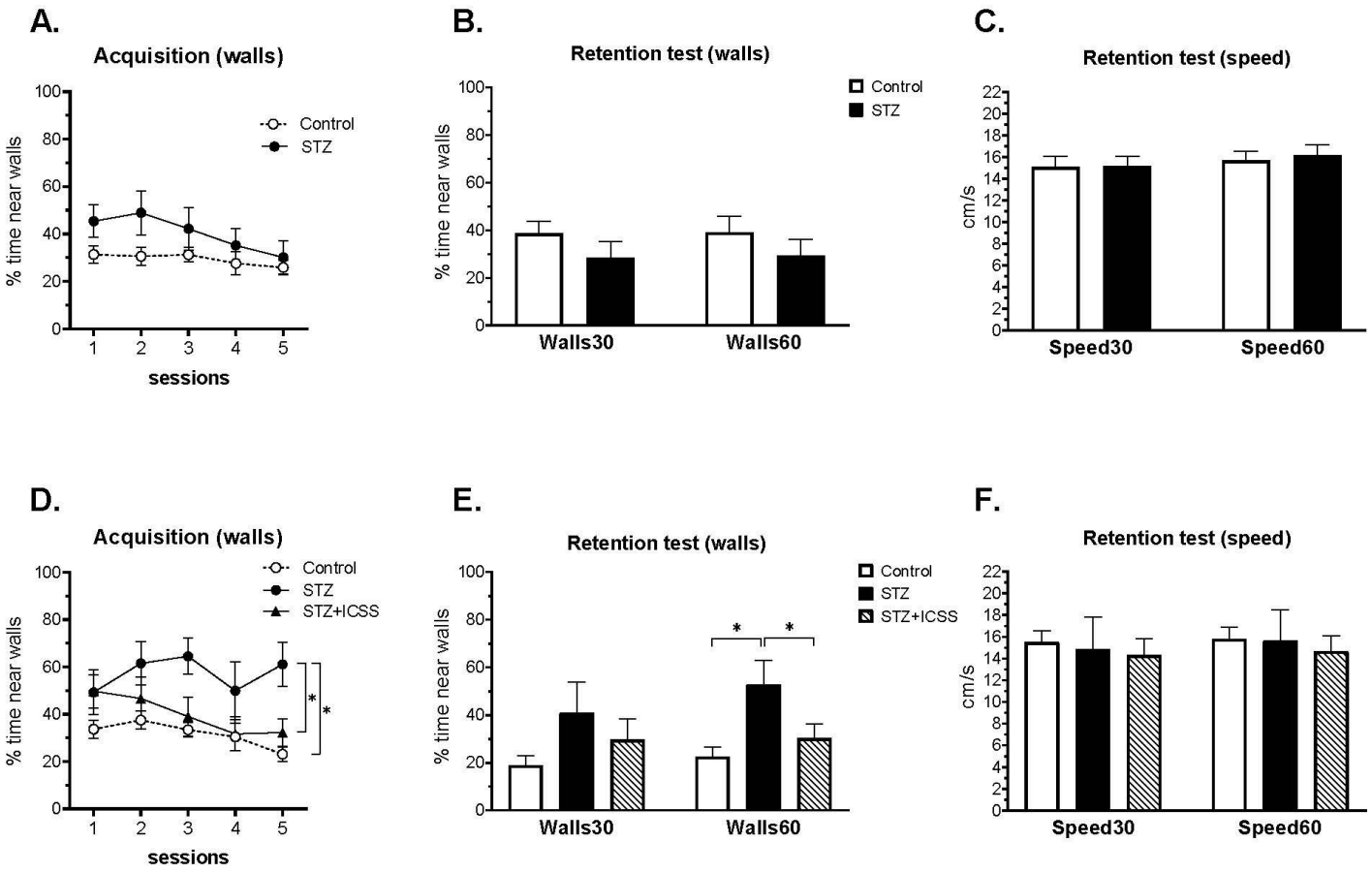

Figure S3. Control variables in the spatial MWM test: Thigmotaxic behaviour and swimming speed. Effects of the STZ (experiment 1) on the percentage of time near the walls in the acquisition **(A)** and retention **(B)** sessions, and swimming speed in the retention **(C)**. In **D**, **E**, **F**, the same variables are represented correlatively for experiment 2, in which the effect of ICSS treatment in STZ animals can also be observed. Data are represented as mean ± SEM. Group factor significance is depicted as *p<.05.

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FIGURE S4 SUPPLEMENTARY

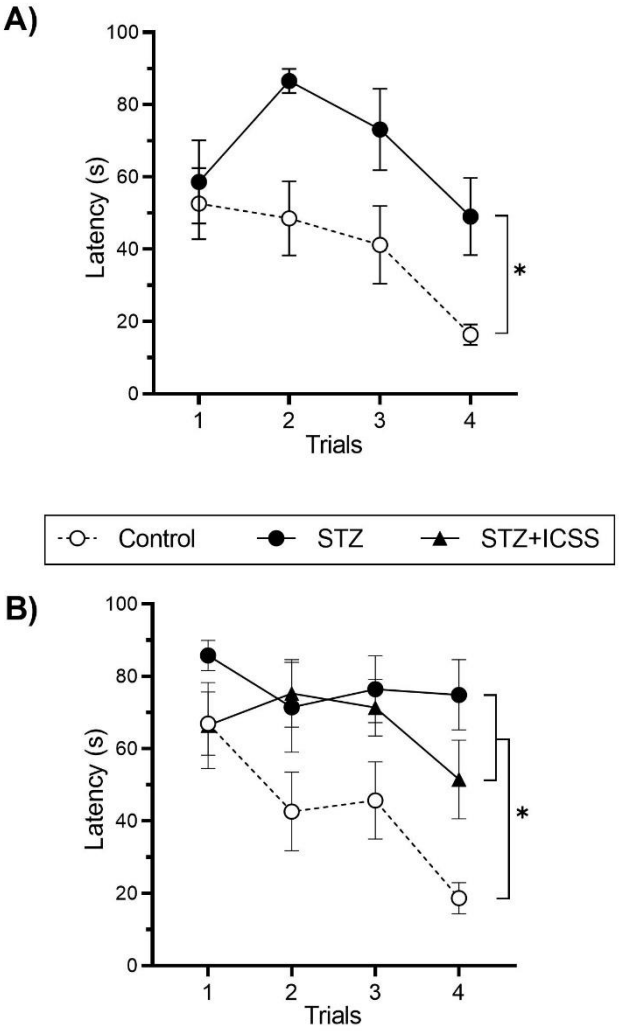

Figure S4. Effects of STZ on the performance of cued Morris Water Maze test. Escape latencies for the four trials of Cued learning, guided by a stimulus attached to the platform, corresponding to experiment 1 **(A)** and 2 **(B)**. Cued learning test in experiment 2 was performed before the administration of ICSS. Data are represented as mean ± SEM. Group factor significance is depicted as *p<.05.

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FIGURE S5 SUPPLEMENTARY

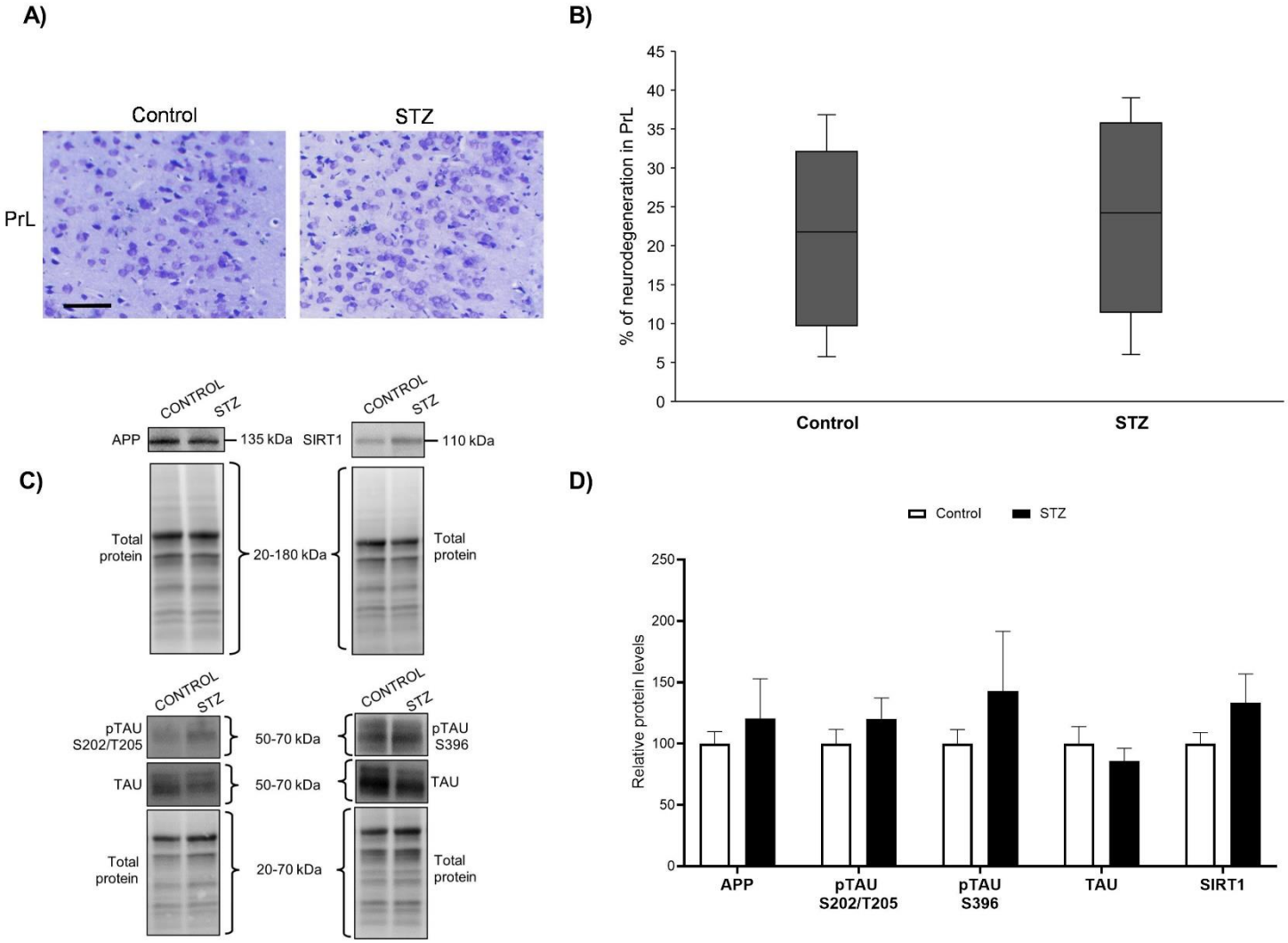

Figure S5. Effects of STZ on neurodegeneration in PrL region. A) Representative photomicrographs of Nissl-stained sections including PrL layers II-III for Control (a) and STZ (b) groups (scale bar =100 μm); **B)** Percentage of neurodegeneration for Control and STZ groups. **C)** Representative Western Blot for APP, pTAU S202/T205, pTAU S396, TAU and SIRT1 proteins with total protein band patterns in each case, in Control and STZ

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groups and **D)** APP, pTAU S202/T205, pTAU Ser396, TAU and SIRT1 protein levels of DG for STZ and Control rats. Data are represented as mean ± SEM.

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FIGURE S6 SUPPLEMENTARY

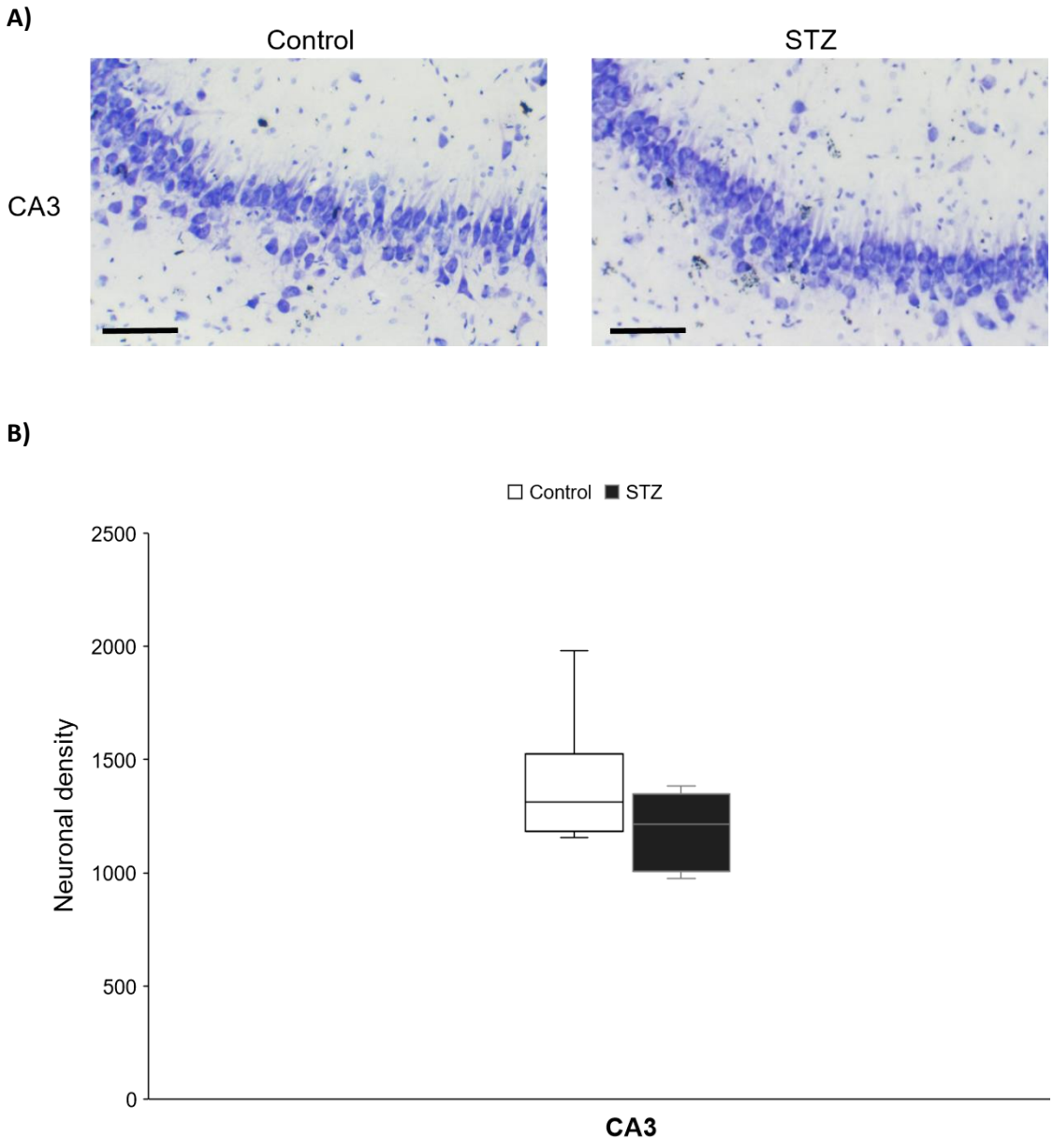

Figure S6. Effects of STZ on neurodegeneration in CA3 region. A) Representative photomicrographs of Nissl-stained sections of CA3 for Control and STZ groups (scale bar=100

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µm) and **B)** Neuronal density in CA3 for Control and STZ groups. Data are represented as mean ± SEM.

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FIGURE S7 SUPPLEMENTARY

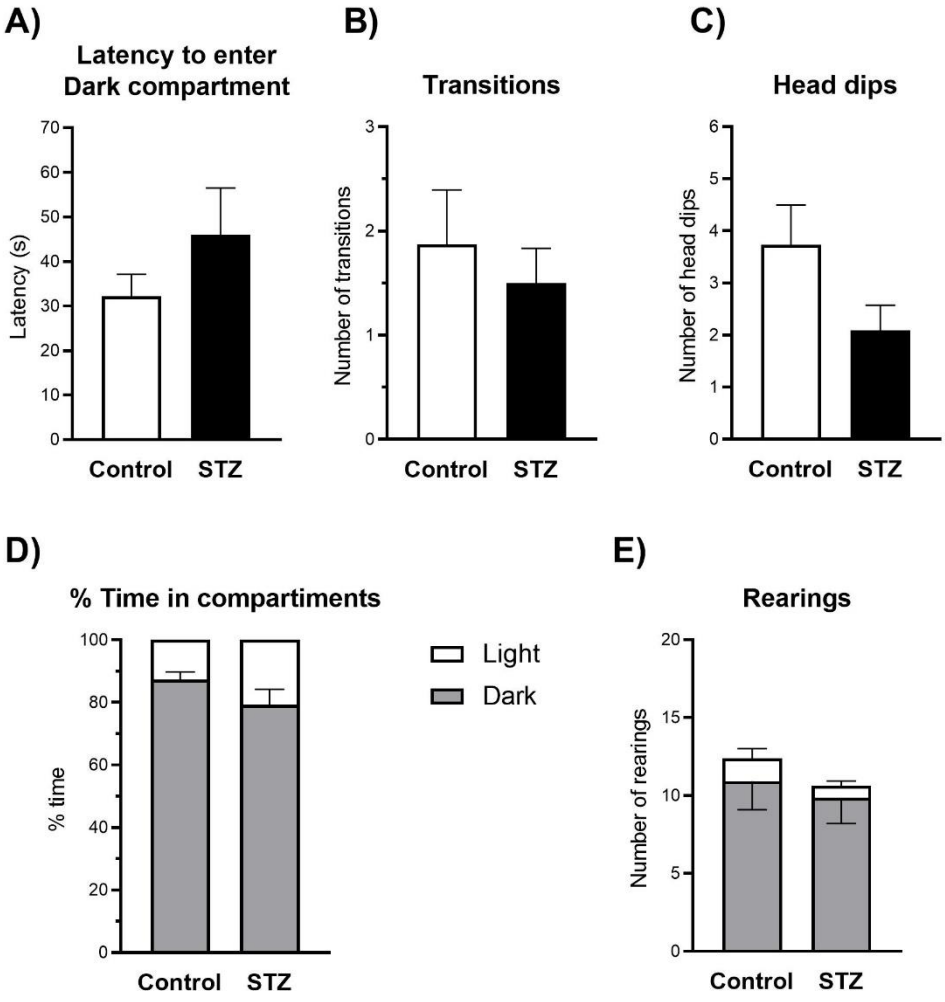

Figure S7. Effects of STZ on the performance of Light/Dark Transition test. No differences between STZ and Control groups were observed in the latency to enter the Dark compartment **(A)**, the number of transitions between compartments (**B)**, the number of head deps **(C)**, the percentage of time spent in each compartment **(D)** or in the number of rears (total or in each of the compartments) **(E)**. Data are represented as mean ± SEM.

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		pTAU DG	SIRT1 DG	A1	A2	A3	A4	A5	Dmt 60	TQ 60
Control Group										
pTAU DG	Correlation Coefficient	1	-0.095	**0.714***	-0.071	-0.429	0.286	-0.190	0.143	-0.299
	Sig. (2-tailed)		0.823	**0.047**	0.867	0.289	0.493	0.651	0.736	0.471
	N	8	8	8	8	8	8	8	8	8
SIRT1 DG	Correlation Coefficient	-0.095	1.000	-0.333	**0.833***	0.476	-0.619	-0.024	-0.381	0.287
	Sig. (2-tailed)	0.823		0.420	**0.010**	0.233	0.102	0.955	0.352	0.490
	N	8	8	8	8	8	8	8	8	8
STZ Group										
pTAU DG	Correlation Coefficient	1	-0.107	0.630	**0.852***	-0.185	0.036	-0.107	0.036	-0.393
	Sig. (2-tailed)		0.819	0.129	**0.015**	0.691	0.939	0.819	0.939	0.383
	N	7	7	7	7	7	7	7	7	7
SIRT1 DG	Correlation Coefficient	-0.107	1.000	0.185	-0.185	0.556	0.643	**0.786***	**0.929****	-0.643
	Sig. (2-tailed)	0.819		0.691	0.691	0.195	0.119	**0.036**	**0.003**	0.119
	N	7	7	7	7	7	7	7	7	7

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table S1. Correlation analyses between pTAU S202/T205 and SIRT1 DG levels and behavioral variables. Table include all the correlations found for Control and STZ groups (Exp. 1) according to Spearman's correlation test (p<.05, highlighted in the table).

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		miR-let-7b	miR-181a	miR-181c	A1	A2	A3	A4	A5	TQ 30	Ann 30	Dmt 30	TQ 60	Ann 60	Dmt 60	CA1 neuronal density	CA3 neuronal density	DG neuronal density	% PrL neuro degeneration	% DTT neuro degeneration
Control Group																				
miR-let-7b	Correlation Coefficient	1.000	-0.400	**1.000****	-0.738	0.800	-0.800	-0.400	-0.400	0.400	0.800	-0.200	0.800	0.800	0.200	0.800	-0.800	-0.400	1.000	-0.400
	Sig. (2-tailed)		0.600		0.262	0.200	0.200	0.600	0.600	0.600	0.200	0.800	0.200	0.200	0.800	0.200	0.200	0.600		0.600
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	2	4
miR-181a	Correlation Coefficient		1.000	-0.400	-0.105	-0.200	0.200	0.600	**1.000****	-0.400	-0.200	0.800	-0.200	-0.200	0.000	-0.800	0.200	0.400	-1.000	0.600
	Sig. (2-tailed)			0.600	0.895	0.800	0.800	0.400		0.600	0.800	0.200	0.800	0.800	1.000	0.200	0.800	0.600		0.400
	N			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	2	4
miR-181c	Correlation Coefficient			1.000	-0.738	0.800	-0.800	-0.400	-0.400	0.400	0.800	-0.200	0.800	0.800	0.200	0.800	-0.800	-0.400	1.000	-0.400
	Sig. (2-tailed)				0.262	0.200	0.200	0.600	0.600	0.600	0.200	0.800	0.200	0.200	0.800	0.200	0.200	0.600		0.600
	N			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	2	4
STZ Group																				
miR-let-7b	Correlation Coefficient	1.000	0.257	-0.600	-0.131	-0.152	0.393	-0.395	-0.131	0.143	0.429	-0.257	0.429	0.429	-0.257	0.200	-0.500	0.400	0.543	-0.714
	Sig. (2-tailed)		0.623	0.208	0.805	0.774	0.441	0.439	0.805	0.787	0.397	0.623	0.397	0.397	0.623	0.747	0.391	0.505	0.266	0.111
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	6	6
miR-181a	Correlation Coefficient		1.000	**-0.886***	-0.655	-0.395	0.393	-0.334	-0.655	0.314	0.314	-0.143	0.314	0.314	-0.143	**-0.900**	**-0.900**	-0.200	-0.200	-0.257
	Sig. (2-tailed)			**0.019**	0.158	0.439	0.441	0.518	0.158	0.544	0.544	0.787	0.544	0.544	0.878	**0.037**	**0.037**	0.747	0.704	0.623
	N			6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	6	6
miR-181c	Correlation Coefficient			1.000	0.655	0.213	-0.655	0.395	0.655	-0.086	0.200	0.029	-0.257	-0.200	0.029	0.600	**0.900**	0.200	-0.257	0.314
	Sig. (2-tailed)				0.158	0.686	0.158	0.439	0.158	0.872	0.704	0.957	0.623	0.704	0.957	0.285	**0.037**	0.747	0.623	0.544
	N			6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	6	6
STZ + ICSS Group																				
miR-let-7b	Correlation Coefficient	1.000	0.233	-0.333	-0.136	-0.419	0.690	-0.333	0.122	-0.683	-0.407	0.643	**-0.714***	-0.619	0.524	-0.214	-0.048	-0.333	0.667	-0.117
	Sig. (2-tailed)		0.546	0.381	0.747	0.302	0.058	0.420	0.774	0.062	0.317	0.086	**0.047**	0.102	0.183	0.610	0.911	0.420	0.071	0.765
	N	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	9
miR-181a	Correlation Coefficient		1.000	-0.350	0.409	-0.165	-0.190	-0.429	-0.220	-0.204	-0.536	0.214	-0.286	-0.452	0.310	0.310	0.238	0.333	-0.357	0.600
	Sig. (2-tailed)			0.356	0.314	0.696	0.651	0.289	0.601	0.629	0.168	0.610	0.493	0.260	0.456	0.456	0.570	0.420	0.385	0.088
	N			9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	9
miR-181c	Correlation Coefficient			1	0.109	0.000	-0.167	-0.143	-0.342	0.503	0.563	-0.619	0.619	**0.833***	**-0.786***	0.000	-0.476	0.143	-0.214	-0.533
	Sig. (2-tailed)				0.797	1.000	0.693	0.736	0.408	0.204	0.146	0.102	0.102	**0.010**	**0.021**	1.000	0.233	0.736	0.610	0.139
	N			9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	9

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

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Table S2. Correlation analyses between miR-let-7b, miR-181c and miR-181a serum levels and behavioural variables and neurodegeneration hallmarks. Table include all the correlations found for Control, STZ and STZ+ICSS groups (Exp. 2) according to Spearman's correlation test ($p<.05$, highlighted in the table).