Supplementary Figure 1. Behavioral profile of female NZB/W-F1 lupus mice at the pre-nephritic and nephritic stages of the disease. (A) Acoustic startle reactivity revealed that 6 month-old WT exhibit defective hearing and thus, (B) prepulse inhibition at 6 month-old mice is not reliable (n=7-8/group). (C-H) Comparison of behavioral phenotype between 3 month-old and 6 month-old female Lupus mice; (C) Novel object recognition evaluates visual recognition memory; expressed as discrimination index (time spent sniffing novel object-time spent sniffing familiar object/total time spent sniffing) and (D) novel object location evaluates spatial recognition memory; expressed as discrimination index (time spent sniffing object in novel location-time spent sniffing object in familiar location/total time spent sniffing). (E) Elevated plus maze evaluates anxiety-like phenotype; expressed as time spent (%) in the open arms. (F) Tail suspension test and (G) Sucrose preference test evaluate depressive-like behavior. (H) Rotarod assesses motor performance/coordination. n=10-13/group, Lupus; NZB/W-F1 stain, WT; wild-type, C57BL/6. Data were analyzed: A: two-way ANOVA, Bonferroni post hoc test; B-H: Student's t-test, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Supplementary Figure 2. Hippocampal neurogenesis in NZB/W-F1 lupus. (A) Representative images of immunohistochemical detection of DCX+ neuronal progenitors in the ventral hippocampus of 3 month-old mice; Scale bar: 100mm. (B) Quantification of DCX+ cells in the ventral hippocampus of WT and Lupus mice at 3 and 6 months of age (n=5/group). (C-F) Quantification of (C) late DCX+ neuronal progenitors (D) Quiescent GFAP+/Sox2- RGL neuronal precursors (E) proliferating GFAP+/Sox2+ RGL neuronal precursors and (F) fast proliferating GFAP-/Sox2+ neural progenitors in the DG of WT and Lupus mice at 3 and 6 months of age (n=5/group). (G) Representative FACS plots of gating strategy, representative histogram and (H) MFI of cleaved caspase-3 in CD11b-CD45- neuronal cells. (I-K) Quantification of (I) DCX+ cells, (J) Sox2+ fast proliferating neural progenitors and (K) the proliferation rate of RGL neuronal precursors; expressed as the percentage of Sox2+/GFAP+ activated RGL of total RGL neuronal precursors in the DG of WT and Lupus mice at 3 and 6 months of age (n=5/group). Lupus, NZB/W-F1 stain; WT (Wild-type), C57BL/6; Bars, mean±SD. Data were analyzed with Student's t test; $*P < 0.05$,$**P < 0.01$,$***P < 0.001$.

Supplementary Figure 3. Transcriptomic signature in hippocampal tissue of NZB/W-F1 lupus. (A-B) Heatmap of DEGs ($|FC|>1.5$, p-value<0.05) in hippocampal tissue between WT and Lupus at (A) 3 and (B) 6 months of age (n=4-5/group). (C-D) GO enrichment analysis; enriched terms in Lupus versus WT mice at (C) 3 and (D) 6 months of age. (E) DEGs ($|FC|>1.5$, FDR<0.05) in hippocampal tissue between 3 month-old and 6 month-old lupus mice. (F) GSEA plots showing enriched terms of 6 month-old versus 3 month-old lupus mice comparison. Lupus, NZB/W-F1 stain; WT (Wild-type), C57BL/6; DEG, differentially expressed gene; FC, fold change; FDR, false discovery rate; GO, gene ontology; GSEA, gene set enrichment analysis.

Supplementary Figure 4. Blood brain barrier permeability and immune cells populations in the NZB/W-F1 lupus hippocampus. (A) Evans blue dye were intravenously injected in WT and Lupus mice at 3 and 6 months of age (n=4/group) following quantification of Evans blue in whole brain. (B) Flow cytometry gating strategy. (C) Flow cytometry analysis; frequency of CD11b+CD45+ cells in total cells. (D) Flow cytometry analysis; frequency of CD11b+CD45+Ly6G-Ly6C+ infiltrating monocytes in total cells. (E) Flow cytometry analysis; representative FACS plots and frequency of granulocytes (Ly6G+) in myeloid (CD11b+CD45+) cells. (F) Flow cytometry analysis; representative FACS plots and frequency of MHC-II+ cells in CD11b+CD45+Ly6G- myeloid cells. (G) Flow cytometry analysis; frequency of B-cells (B220+) in total cells. (H) Flow cytometry analysis; representative FACS plots and frequency of CD4+ T-cells in lymphocytes and the frequency of CD4+ and CD8+ T-cells in total cells. All experiments were performed in Lupus and WT mice at 3 and 6 months of age (n=4-6/group) and obtained from 2

independent experiments. Lupus, NZB/W-F1 stain; WT, C57BL/6; Bars, mean±SD. Data were analyzed with Student's t-test, *P < 0.05, **P < 0.01, ***P < 0.001.

Supplementary Figure 5. Cytokine expression in lupus hippocampus. (A) Quantification of IL-12p70, IL-1b, TNF-a, IL-10, TGF-b1 and G-CSF in hippocampal tissue. All experiments were performed in Lupus and WT mice at 3 and 6 months of age (n=4-5/group) and obtained from 2 independent experiments. Lupus, NZB/W-F1 stain; WT, C57BL/6; Bars, mean±SD. Data were analyzed with Student's t-test, *P < 0.05.

Supplementary Figure 6. Increased CD45 expression in myeloid population in lupus hippocampus. (A) Representative FACS plots of gating strategy for myeloid cells in hippocampal tissue. (B) Flow cytometry analysis; representative histogram and mean fluorescence intensity (MFI) of CD45 in myeloid cells (CD11b+). (C) Representative FACS plots of gating strategy for myeloid cells in hippocampal tissue. All experiments were performed in Lupus and WT mice at 3 and 6 months of age (n= 5-6/group) and obtained from 3 independent experiments. Lupus, NZB/W-F1 stain; WT, C57BL/6; Bars, mean±SD. Data were analyzed with Student's t-test, *P < 0.05.

Supplementary Figure 7. Microglia are activated in distinct regions in lupus hippocampus. (A) Representative images of immunohistochemical detection of IBA1+ microglia cells in the DG, CA1 and CA3 of 3 month-old mice; Scale bar: 50mm. (B) Quantification of mean fluorescence intensity (MFI) of IBA1+ in the DG, CA1 and CA3 of WT and Lupus mice at 3 and 6 months of age (n=5/group). All experiments were performed in Lupus and WT mice at 3 and 6 months of age (n=5/group) and obtained from 3 independent experiments. Lupus, NZB/W-F1 stain; WT, C57BL/6; Bars, mean±SD. Data were analyzed with Student's t-test, *P < 0.05.

Supplementary Figure 8. Lupus microglia secrete increased levels of chemokines in hippocampus. (A) Quantification of CCL17, CCL22 and CXCL1 in hippocampal tissue. (B) Quantification of CCL17, CCL22 and CXCL1 mRNA levels of sorted microglia with real time RT-qPCR in 6 month-old mice. All experiments were performed in Lupus and WT mice at 3 and 6 months of age (n=4-6/group) and obtained from 2 independent experiments. Lupus, NZB/W-F1 stain; WT, C57BL/6; Bars, mean±SD. Data were analyzed with Student's t-test, *P < 0.05,**P < 0.01,***P < 0.001.