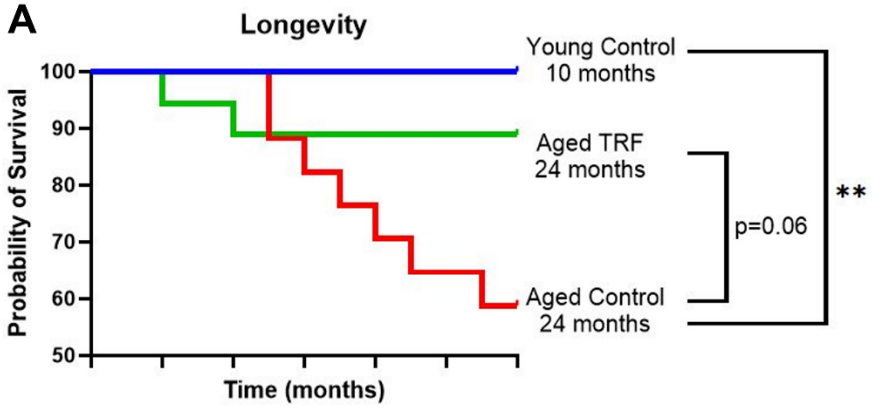
A



B

Survival Rates (%)			
Months	Young	Aged	Aged TRF
0	100	100	100
1	100	100	94
2	100	100	89
3	100	82	89
4	100	71	89
5	100	65	89
6	100	59	89

Extended Figure 1. Time-restricted feeding promotes survival in aging.

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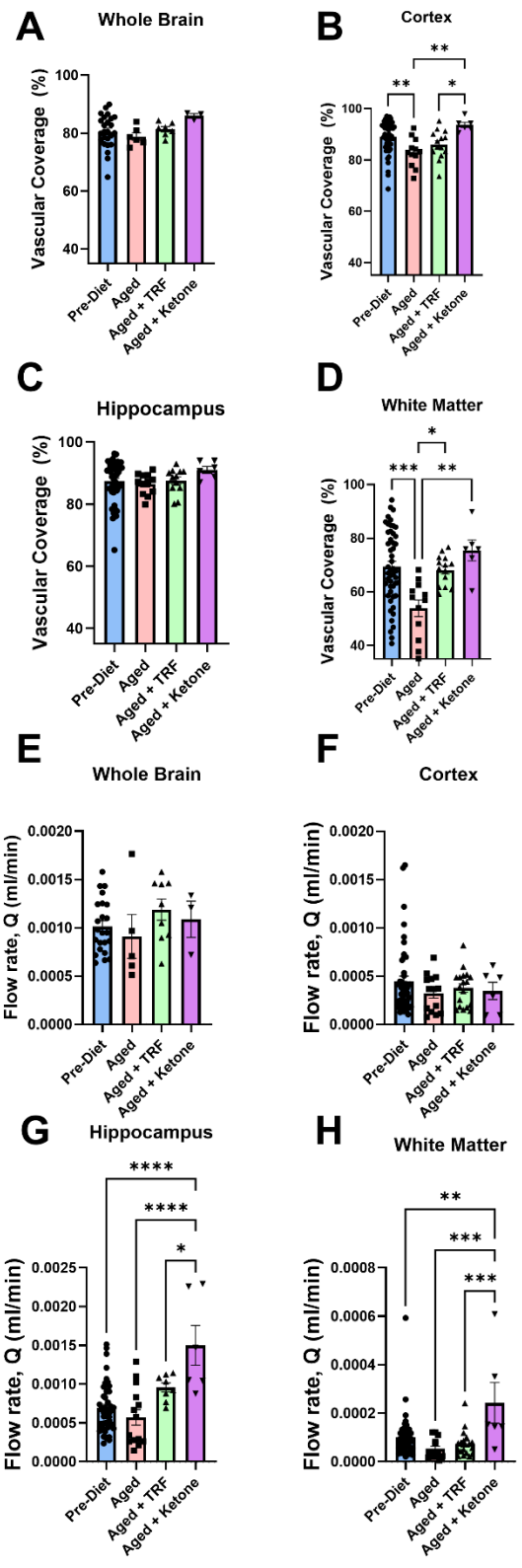
(A-B) Survival of mice from each group over time. Month 0 indicates the beginning of the study, where young control mice are 4-months, and aged control and aged TRF mice are 18-months. Statistical significance was determined using log-rank (Mantel-Cox) test to compare survival curves. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.



Extended Figure 2. Vascular coverage and resting flow rate among all groups.

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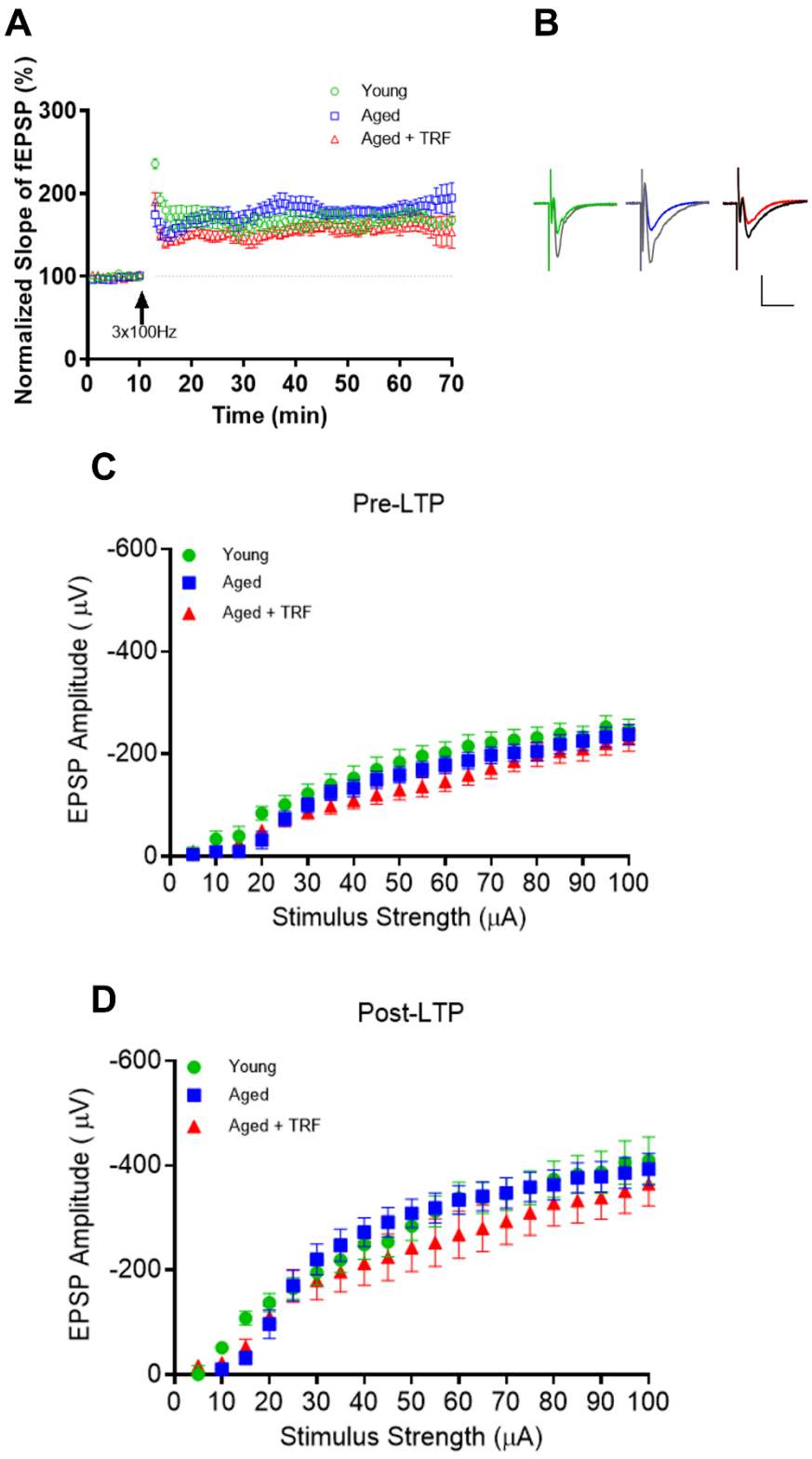
(A-D) Vascular coverage measured by fUS in whole brain, cortex, hippocampus, and white matter, comparing pre-diet to aged control, aged TRF, and aged ketone mice. (E-H) Resting flow rate in whole brain, cortex, hippocampus and white matter, comparing pre-diet to aged control, aged TRF, and aged ketone mice. All data are shown as mean ± SEM. Statistical significance was calculated using one-way ANOVA with Tukey's post hoc test to determine differences among groups. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.



Extended Figure 3. Long-term potentiation at Schaffer collateral-CA1 synapses in the hippocampus is not altered in aged TRF mice.

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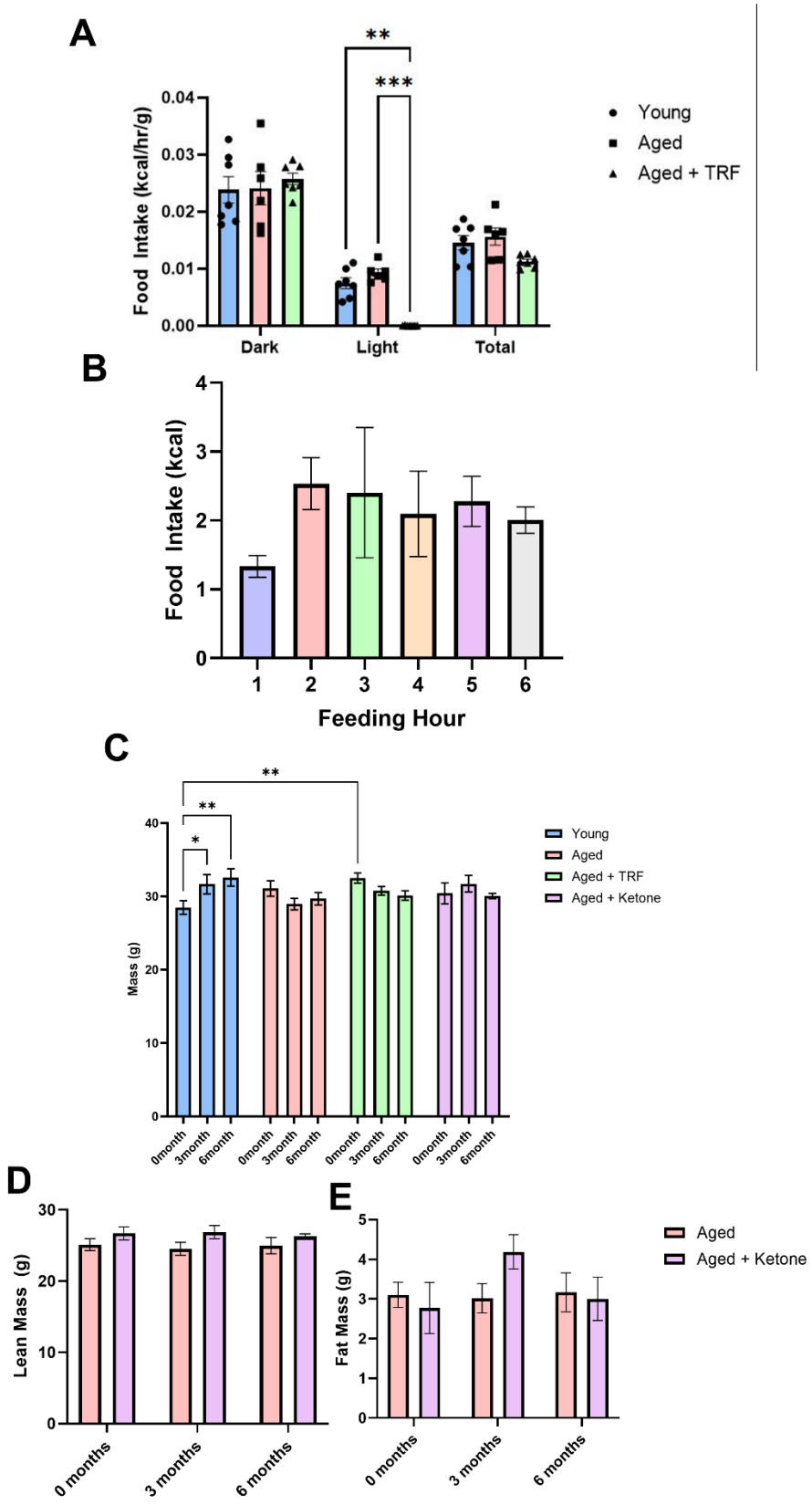
(A) Time-course graph of normalized fEPSP slope showing induction of LTP by 3x100 Hz stimulation (arrow) in aged TRF mice compared to young and aged control mice. n = 8 recordings, 4 slices per group. (B) Representative traces show averaged fEPSP before (color line) and 1 h after (black line) LTP induction (young control-green, aged control-blue and aged TRF-red). Each data point on the graph represents the average of two successive responses. Scale bars y= 200 μV, x = 20 ms. (C, D) Input-output (I/O) curves of fEPSP amplitude, evoked before (C) and 1 h after LTP induction (D) in the three groups by stepwise increase in the stimulus from 5 to 100 μA. All groups show comparable I/O before LTP and similar increase in the fEPSP amplitudes after 1 h of LTP induction. Data are shown as mean ± SEM.



Extended Figure 4. Food intake, body mass, and body composition in each group.

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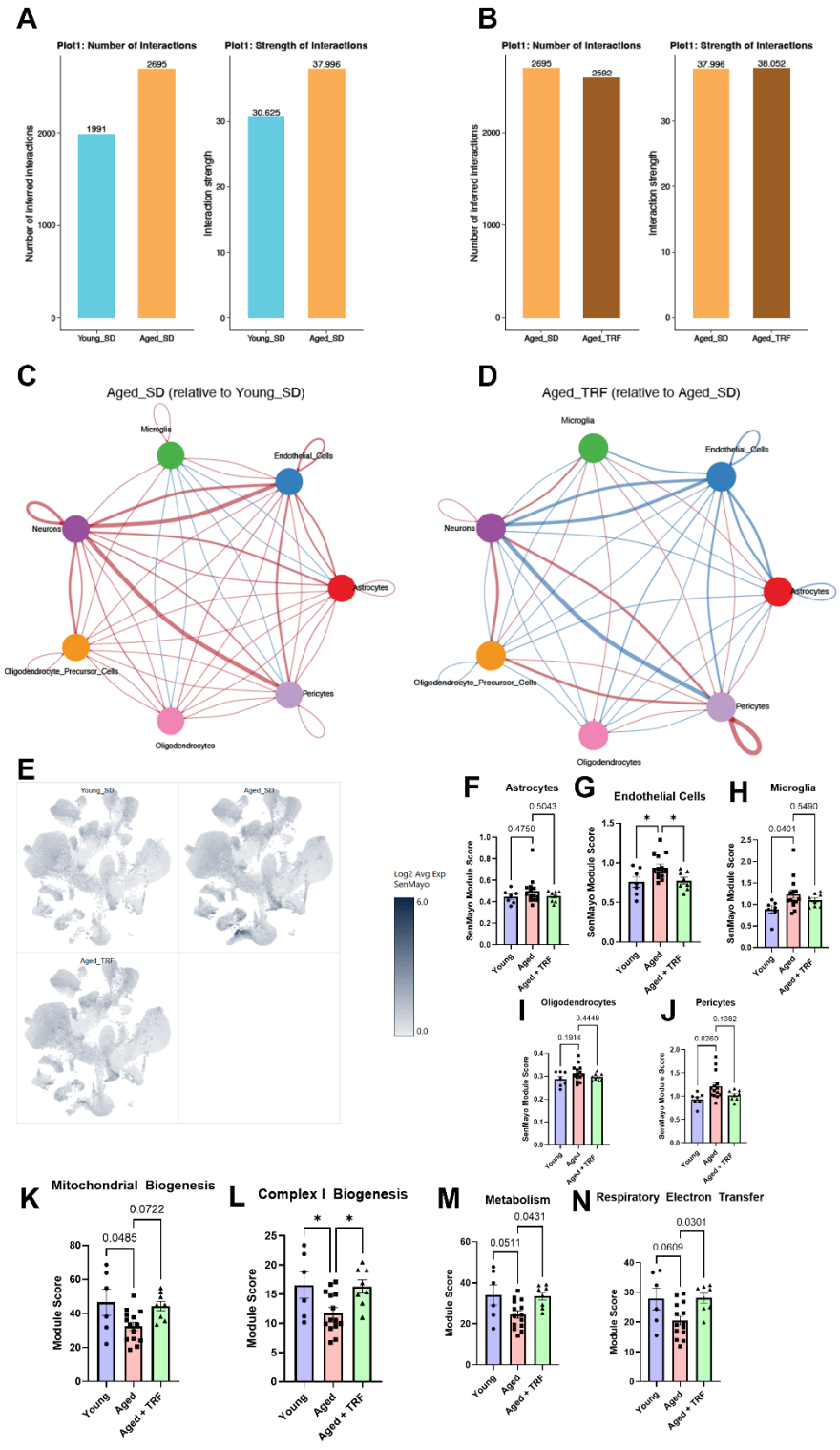
(A) Hourly food intake of young control, aged control, and aged TRF mice during the dark and light cycles. (B) Food intake of aged TRF mice during each hour of the feeding period. (C-E) Body mass, lean mass, and fat mass of mice in each group at the beginning of the study, where young mice were 4 months and aged, aged TRF, and aged ketone mice were 18 months. The weights were compared after 3 and 6 months of intervention. All data are shown as mean ± SEM. Statistical significance was calculated using one-way ANOVA and two-way ANOVA with Tukey's post hoc test to determine differences among groups. *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.



Extended Figure 5. Transcriptomic signature of time-restricted feeding in the brain cortex.

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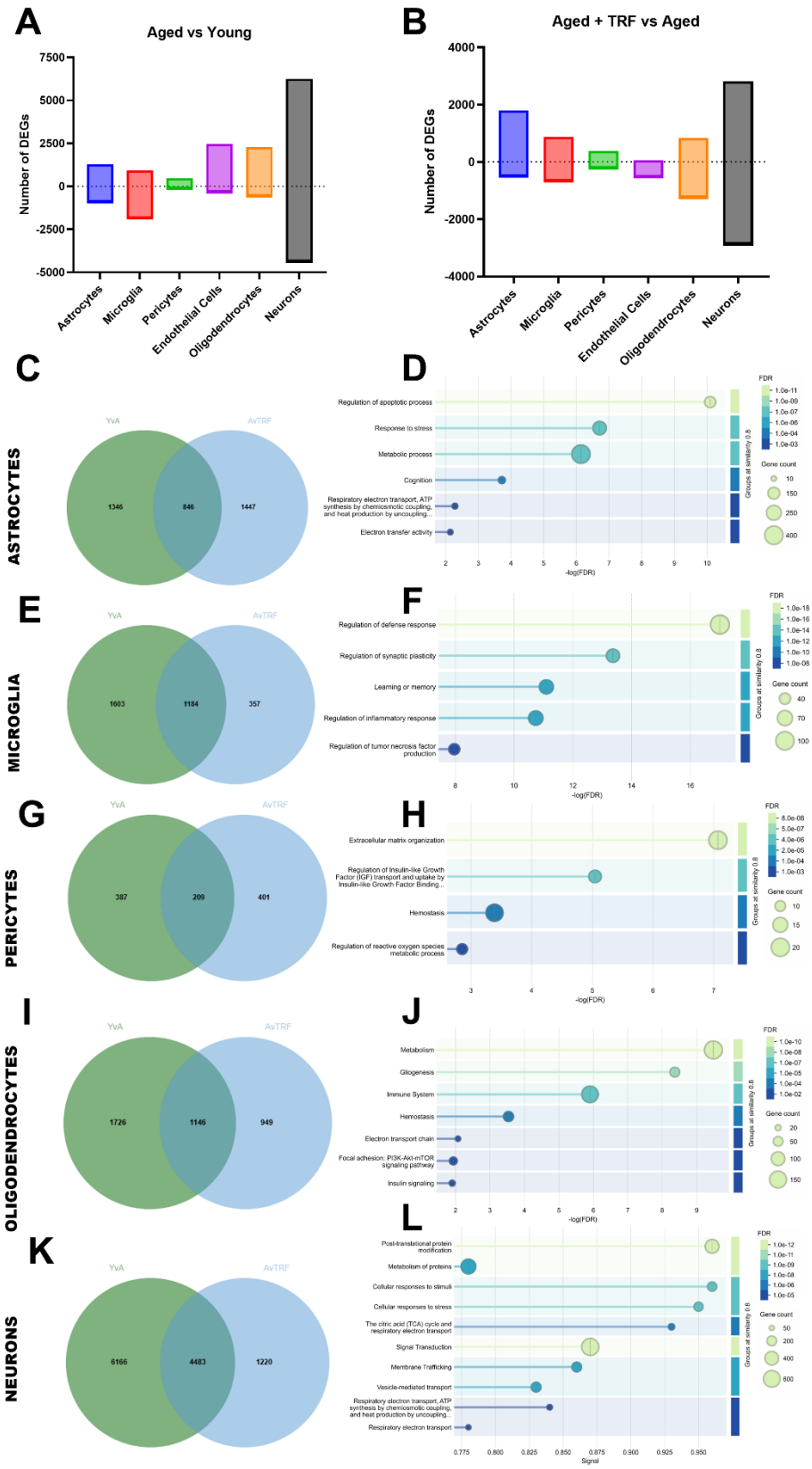
A-D) Number and strength of interactions among cell types in young compared to aged, and aged compared to aged TRF, respectively. E) UMAP of gene expression from the SenMayo gene set, separated by group. F-J) Module score of expression from the SenMayo gene set in each cell type, where individual data points represent the mean score of all cells from one mouse. K-N) Module score of expression of enriched pathways in the capillary sub-cluster of endothelial cells, where individual data points represent the mean score of all cells from one mouse.



Extended Figure 6. Differentially expressed genes in aged TRF mice.

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A-B) Number of differentially expressed genes (DEGs) which were upregulated (positive) and downregulated (negative) in each cell type, when comparing aged to young, or aged TRF to aged control, respectively. C-L) Venn diagrams of genes which were DEGs in both aged vs young and aged TRF vs aged, divided by cell type (left column). Enriched pathways from genes that were part of both DEG sets, divided by cell type (right column).