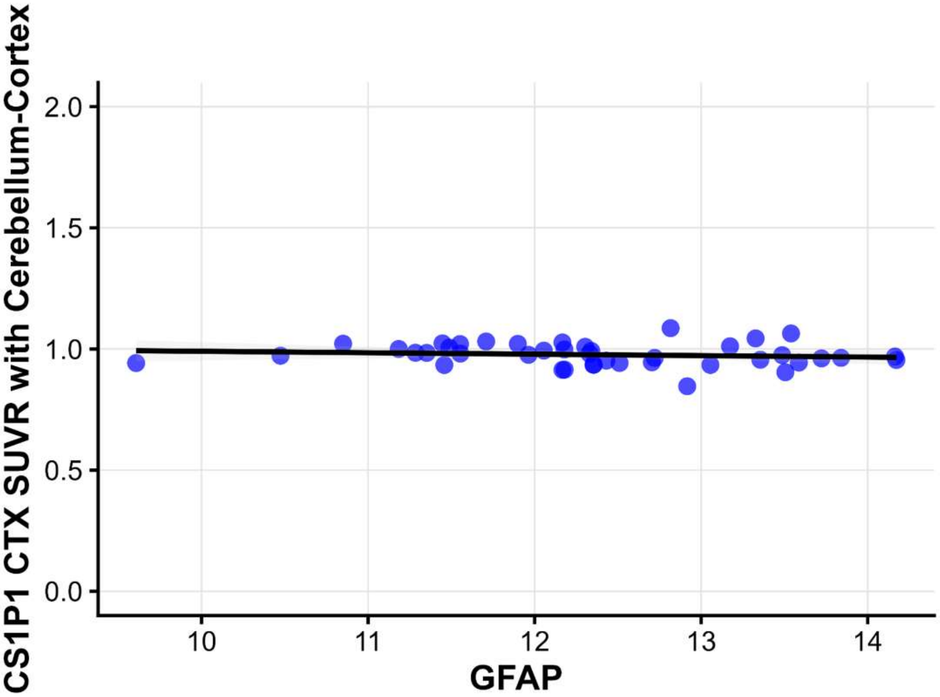
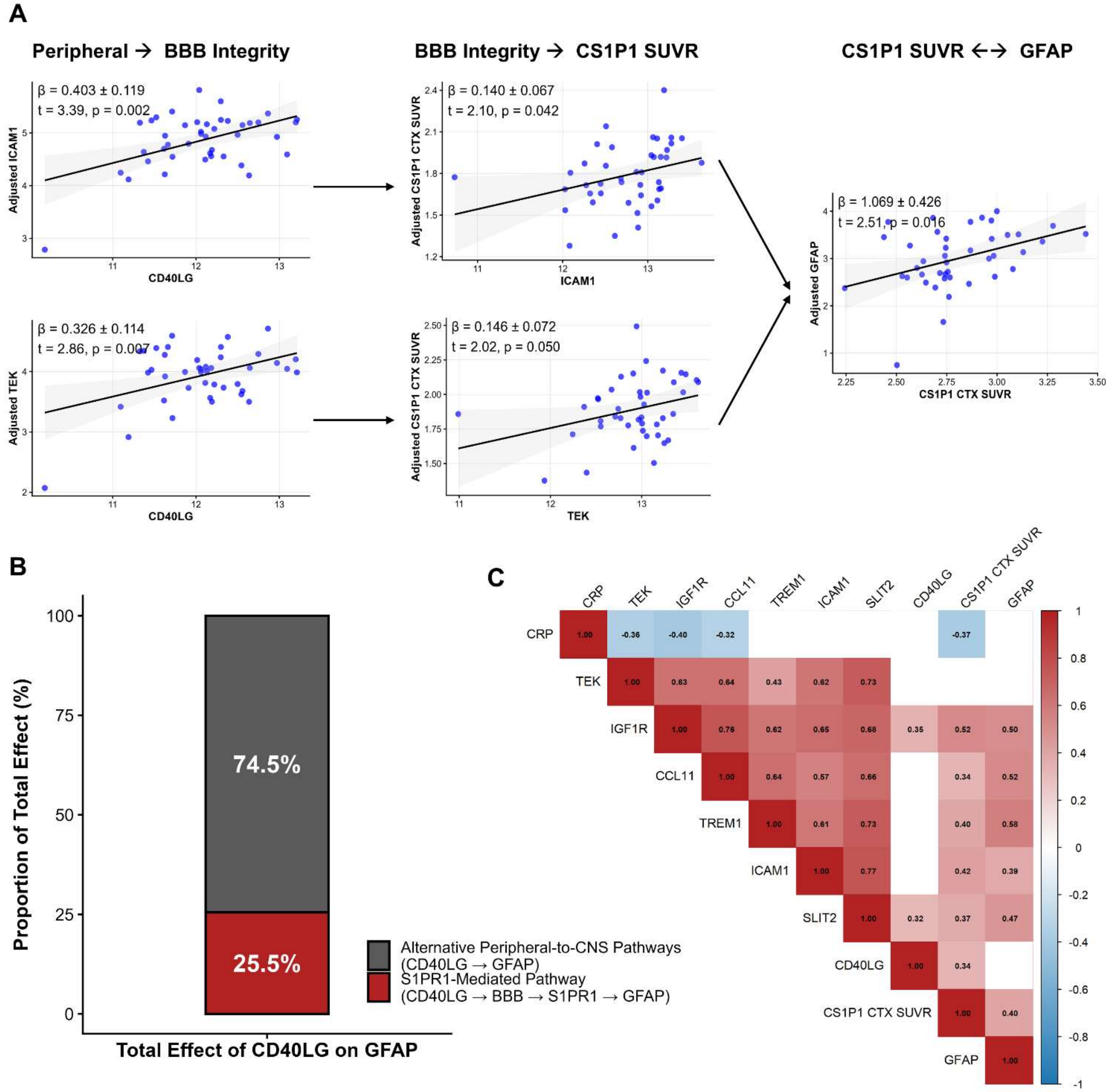
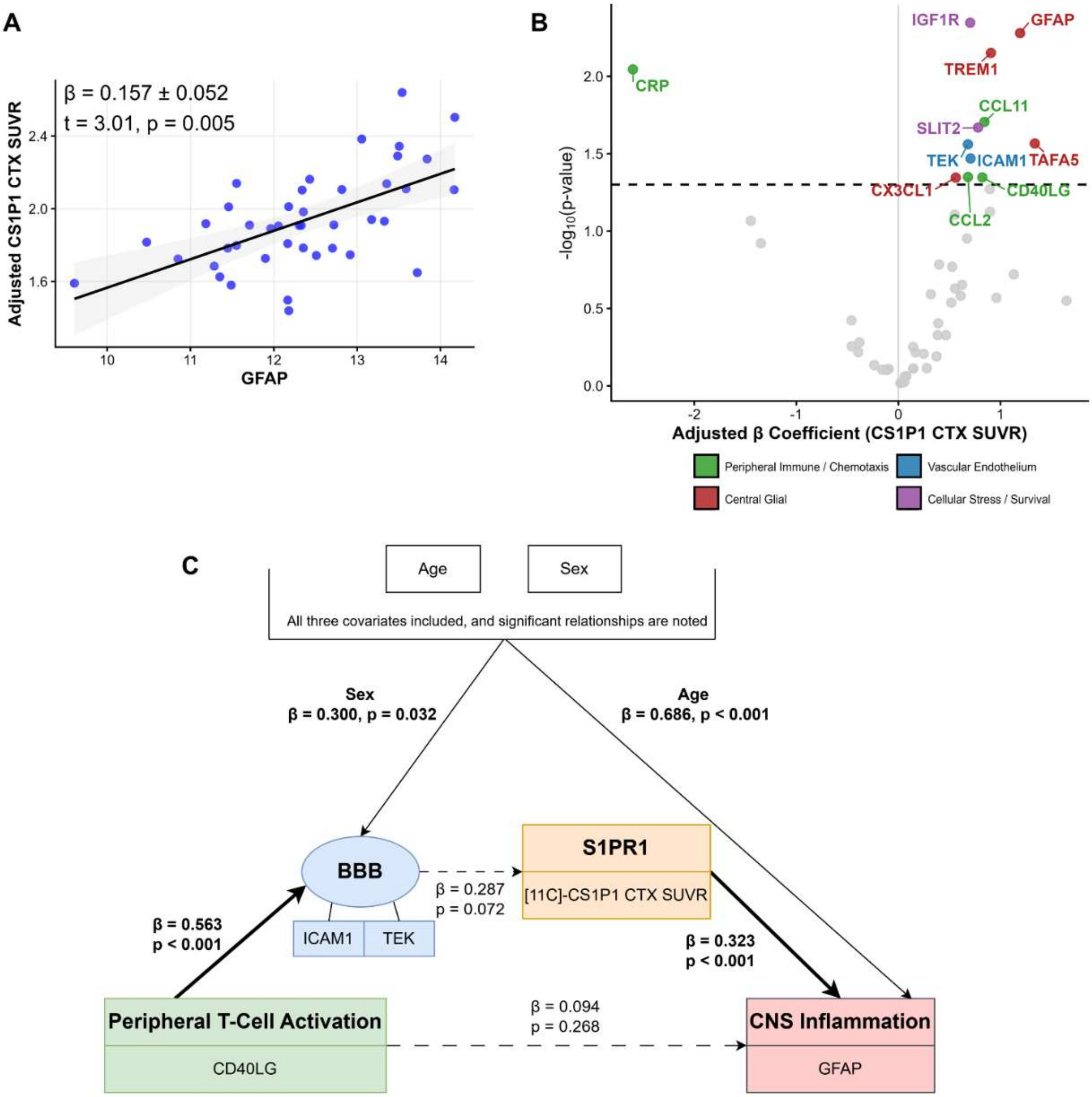
SUPPLEMENTARY INFORMATION



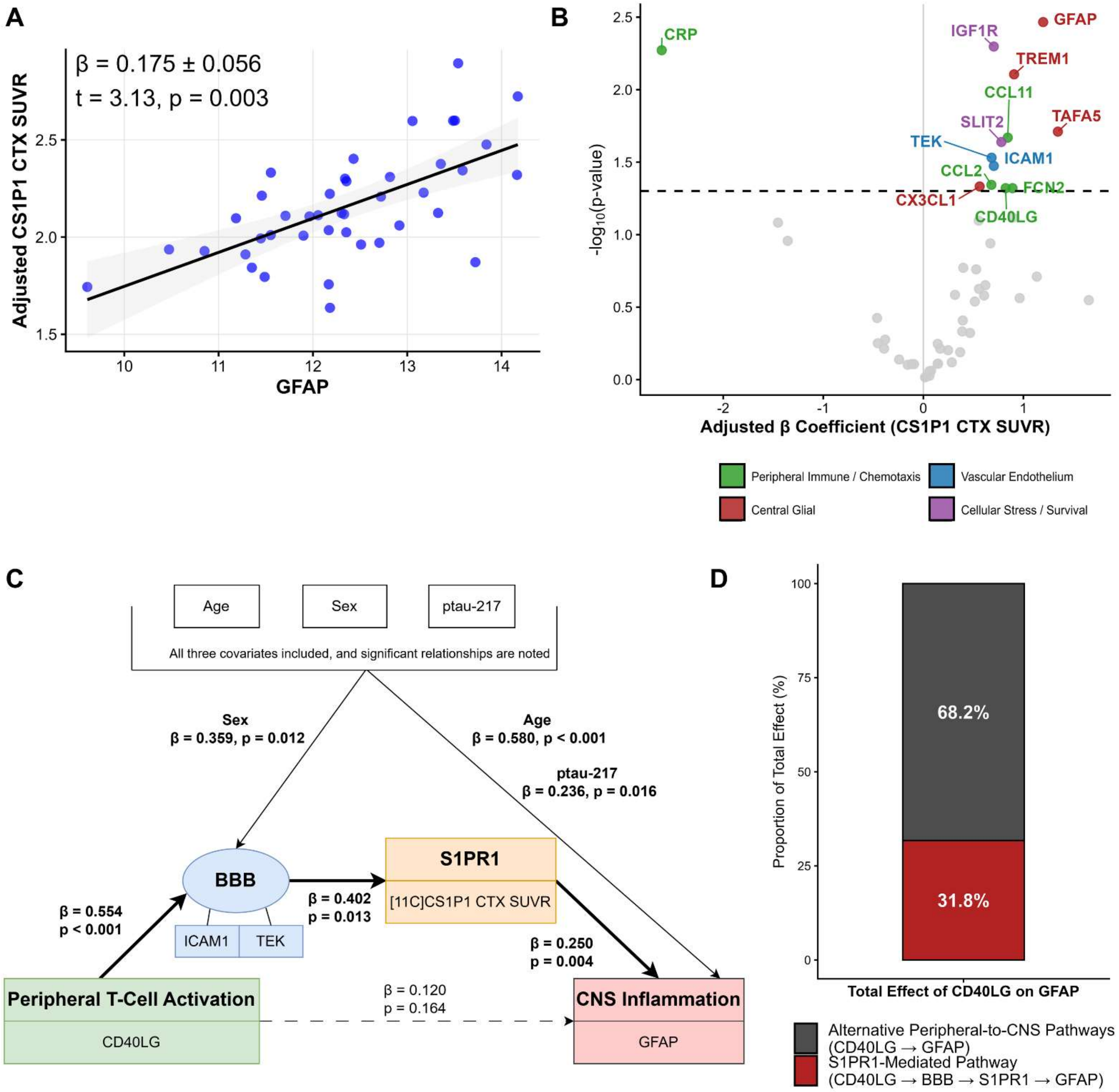
Supplementary Figure 1. Although the cortical CS1P1 SUVRs using the cerebellum-cortex have high test-retest reliability, there is poor discriminability between subjects, with all SUVRs hovering around 1. Many SUVRs are less than one, indicating the cerebellum-cortex has more uptake than the cortex and is not a preferred reference region for this tracer.



Supplementary Figure 2. Pathway-specific correlations and causal mediation of the S1PR1 neuroimmune cascade. (A) Pairwise scatter plots illustrating the age, sex, and Aβ42/40 adjusted relationships between sequential nodes of the modeled SEM cascade (Peripheral CD40LG → BBB Integrity → CS1P1 SUVR → GFAP). (B) Stacked bar chart quantifying the formal causal mediation analysis. The specific S1PR1-mediated endothelial cascade accounts for 25.5% of the total inflammatory drive from peripheral CD40LG to central GFAP. (C) Hierarchically clustered Spearman correlation heatmap of the upregulated inflammatory proteins and [11C]-CS1P1 SUVR. Color intensity reflects the strength and direction of significant correlations ($p < 0.05$); non-significant correlations are left blank.



Supplementary Figure 3: Re-evaluation of the S1PR1 neuroimmune cascade excluding plasma Aβ42/40 as a covariate. (A) Linear regression demonstrating a significant positive association between adjusted cortical [^{11}C]CS1P1 SUVR and plasma GFAP (β = 0.157 ± 0.052, p = 0.005), controlling only for age and sex. (B) Volcano plot of the differential abundance analysis evaluating inflammatory plasma proteins against cortical [11C]CS1P1 SUVR. Removing Aβ42/40 as a covariate introduces additional significant peripheral and central markers (e.g., TAFA5, CX3CL1, CCL2) into the uncorrected significance threshold. (C) Structural Equation Modeling (SEM) path diagram isolating the astrocytic signaling cascade without adjusting for baseline amyloid pathology. Failure to account for the inflammatory variance driven by Aβ42/40 suppresses the S1PR1 signal, rendering the specific pathway from blood-brain barrier (BBB) disruption to central S1PR1 upregulation statistically insignificant ($\beta = 0.287$, $p = 0.072$). This indicates that adjusting for baseline AD pathology is required to isolate the independent peripheral-to-central neurovascular pathway.



Supplementary Figure 4: Sensitivity analysis of the S1PR1 neuroimmune cascade utilizing plasma ptau-217 as a covariate. To ensure the structural model was not dependent on the specific Alzheimer's pathology biomarker utilized, analyses were re-evaluated using NULISAseq plasma brain derived ptau-217 in place of the Aβ42/40 ratio. (A) Linear regression demonstrates the positive association between adjusted cortical [^{11}C]CS1P1 SUVR and plasma GFAP remains significant (β = 0.175 ± 0.056, p = 0.003). (B) Volcano plot of the differential abundance analysis confirming that the peripheral immune, endothelial, and central glial markers remain significantly associated with [^{11}C]CS1P1 SUVR. (C) Structural Equation Modeling (SEM) path diagram. The primary sequential cascade remains significant. Notably, while ptau-217 significantly independently predicts reactive astrogliosis (GFAP; $\beta = 0.236$, $p = 0.016$), it does not predict S1PR1. (D) Mediation analysis estimates the S1PR1 pathway accounts for 31.8% of the total inflammatory drive from peripheral CD40LG to central GFAP under these covariate parameters.

Supplementary Table 1: Intraclass Correlation Coefficients (ICC) by Reference Region

Reference Region	Cortical SUVR ICC	95% CI	p-value
Cerebellum-Cortex	**0.802**	**[0.010, 0.990]**	**0.038**
Corpus Callosum	**0.735**	**[-0.640, 0.980]**	**0.101**
Brainstem	**0.669**	**[-0.240, 0.970]**	**0.094**
Whole Cerebellum	**0.535**	**[-0.290, 0.960]**	**0.138**
Cerebellum White Matter	**0.239**	**[-0.480, 0.910]**	**0.319**

Supplementary Table 2: Full Parameter Estimates for the S1PR1 Mediation Model

Structural Path / Parameter	Unstandardized Estimate	Standard Error	Z-Value	P-Value	Standardized β
BBB → ICAM1 (Factor Loading)	0.365	0.060	6.119	**< 0.001**	0.915
BBB → TEK (Factor Loading)	0.304	0.052	5.888	**< 0.001**	0.827
CD40LG → BBB	1.186	0.328	3.610	**< 0.001**	0.563
BBB → CS1P1 CTX SUVR	0.076	0.028	2.699	**0.007**	0.406
CS1P1 CTX SUVR → GFAP	0.815	0.406	2.006	**0.045**	0.196
CD40LG → GFAP	0.213	0.147	1.451	0.147	0.131
Age → BBB	0.007	0.011	0.673	0.501	0.105
Sex → BBB	1.175	0.507	2.316	**0.021**	0.341
Aβ42/40 → BBB	1.414	4.947	0.286	0.775	0.045
Age → CS1P1 CTX SUVR	-0.001	0.002	-0.484	0.629	-0.074
Sex → CS1P1 CTX SUVR	-0.158	0.090	-1.755	0.079	-0.246
Aβ42/40 → CS1P1 CTX SUVR	-2.467	0.896	-2.753	**0.006**	-0.426
Age → GFAP	0.033	0.005	6.163	**< 0.001**	0.626
Sex → GFAP	-0.263	0.243	-1.084	0.278	-0.099
Aβ42/40 → GFAP	-3.766	2.668	-1.412	0.158	-0.157
Indirect (Defined Effect)	0.073	0.048	1.528	0.127	0.045
Total (Defined Effect)	0.286	0.146	1.964	0.050	0.176
Proportion mediated (Defined Effect)	0.255	0.197	1.296	0.195	0.255

Supplementary Table 3: Structural Equation Model Configurations and Fit Comparisons

Model	χ^2	df	Model p-value	CFI	RMSEA	AIC	BIC
Ideal Fit Thresholds	**-**	**-**	**> 0.05**	**≥ 0.95**	**< 0.08**	**Lower is better***	**Lower is better***
1A. Primary Sequence: CD40LG → BBB → S1PR1 → GFAP	3.127	7	0.873	1.000	0.000	158.40	191.41
1B. Alt Sequence: CD40LG → BBB → GFAP → S1PR1	5.129	7	0.644	1.000	0.000	160.40	193.41
1C. Alt Sequence (Reverse): GFAP → S1PR1 → BBB → CD40LG	4.062	7	0.773	1.000	0.000	158.27	191.29
1D. Alt Sequence: CD40LG → S1PR1 → BBB → GFAP	15.201	7	0.034	**0.917**	**0.167**	170.47	203.49
2A. Microglial Outcome: GFAP swapped for TREM1	17.735	7	0.013	**0.879**	**0.191**	140.45	173.46
2B. Dual Outcome: Separate (GFAP + TREM1)	18.143	9	0.034	**0.930**	**0.156**	224.41	269.59
2C. Dual Outcome: Latent CNS (GFAP + TREM1)	23.332	13	0.038	**0.920**	**0.138**	221.60	259.83

*Note: AIC and BIC are relative parsimony indices. They can be directly compared within Group 1 (1A, 1B, 1C, 1D) because the models evaluate identical variables. Models evaluating alternative causal directions (1D) or microglial activation (2A, 2B, 2C) universally fail absolute fit criteria (CFI < 0.95, RMSEA > 0.08, red), confirming both the specific directionality and astrocytic specificity of the cascade.