

SUPPLEMENTAL DATA for “Brain region and epilepsy-associated differences in inflammatory mediator levels in medically refractory epilepsy”

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SUPPLEMENTAL DATA

Individual case details can be found in the supplemental data file **Patient_Data_Repository.xlsx**, available online.

S1. Custom VPLEX Assays

Table S1A. Assay Analytes and Tissue Dilutions

S2. Mediator Case Data and Distributions (Figures 2A – 2AA): Human hippocampus, entorhinal and temporal cortex inflammation-related mediators

S3. Mediator Levels Variability

Table S3B. Brain Inflammation-related Mediator Relative Tissue Concentrations

Table S3C. Mediator Levels Overall Coefficients of Variation

Table S3D. Mediator Coefficients of Variation by Tissues

Table S3E. Mediator Coefficients of Variation by Epilepsy Status

Table S3F. Mediator Coefficients of Variation by Tissues and Epilepsy Status

Table S3G. GM-CSF Measurements Homogeneity Analyses

Table S3H. IFN- γ Measurements Homogeneity Analyses

S4. Miscellaneous Supplemental Material

Table S4I. Phase-2 and Brain Inflammation-related Mediator Associations

Table S4J-K. Inflammation-related Mediator Brain & Consensus Blood Levels
Comparisons of median brain and estimated blood levels of inflammation-related mediators (table of citations referenced in **Table S4K**)

Figure 4A. Age-Related Correlations: VCAM-1 and IL-8

Figure 4B. Epilepsy Risk Factor Associations

Figure 4C. Relational Correlations of Mediators and Between Tissues

Highly correlated inflammation-related mediator levels in human hippocampus, entorhinal and temporal cortices

1. Custom VPLEX Assays

Table S1A. Assay Analytes and Tissue Dilutions

<p>Human Chemokine Panel 1 1:10 dilution</p> <p>Human Eotaxin Human IP-10 Human MCP-1 Human MCP-4 Human MIP-1α Human MIP-1β Human TARC</p>	<p>Human Proinflammatory Panel 1 1:3 dilution</p> <p>Human IFN-γ Human IL-10 Human IL-12p70 Human IL-1β Human IL-2 Human IL-4 Human IL-6 Human IL-8 Human TNF-α</p>
<p>Human Cytokine Panel 1 1:6 dilution</p> <p>Human GM-CSF Human IL-12/23 p40 Human IL-17A Human IL-1α Human TNF-β Human VEGF</p>	<p>Human Vascular Injury 1:4 dilution</p> <p>Human CRP Human ICAM-1 Human VCAM-1</p>

Each multiplex assay plate was prepared as recommended by the manufacturer (MSD). Brain soluble protein extracts were diluted (see above), enough for the four VPLEX plates in duplicate, in Buffer H containing Cøplete protease inhibitors and 0.2% fraction V bovine serum albumin, and added to the appropriate wells. Assays were carried out according to manufacturer's instructions and results read on the Sector 6000 electroluminescence plate reader (MSD).

2. Mediator Case Data and Distributions: Human hippocampus, entorhinal and temporal cortex inflammatory-related mediators (Figures 2A – 2AA)

Left top: Summary statistics on analyte assay data (pg / g tissue). All case values included.

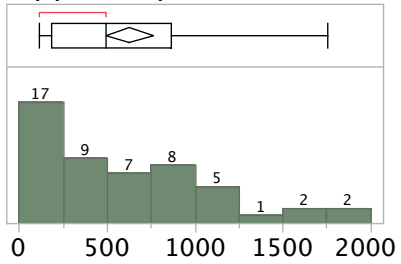
Right top: Nonepileptic (blue) and epileptic (red) specimen data (pg / g tissue). All values shown, except where a single outlier is more than 5-fold greater than the overall mean. Outlier(s) were removed based upon multivariate analysis Jackknife distance ($\alpha = 0.005$). Differences between the number of observations in the text and supplemental data indicate outlier removal.

Left Bottom: Region-specific data (pg / g tissue) showing group mean at the diamonds' center line, upper and lower triangles indicate 95% confidence interval. The grand mean for all data (excluding outliers) is indicated by a horizontal line on each graph.

Right Bottom: Case data by region, showing tissue levels (pg / g tissue) for each case, are presented to show possible trends across brain regions. A single case, 32 (nonepileptic), exhibited unusually high values in multiple mediators and all three brain regions. Many of the values for this case had already been removed during the outlier analysis phase of data processing.

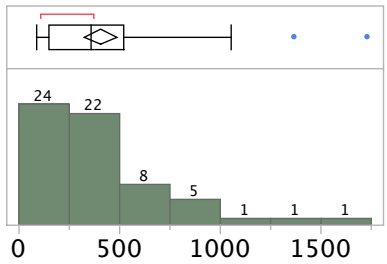
A. Eotaxin

Hippocampus



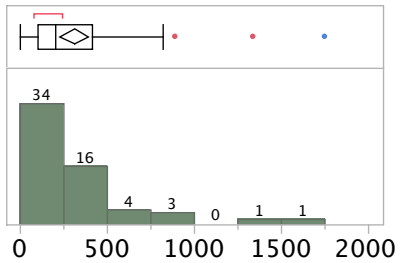
Summary Statistics	
Mean	627.39695
Std Dev	479.60428
Std Err Mean	67.158032
Upper 99.5% Mean	824.63768
Lower 99.5% Mean	430.15623
N	51
Median	495.28437

Entorhinal Cortex

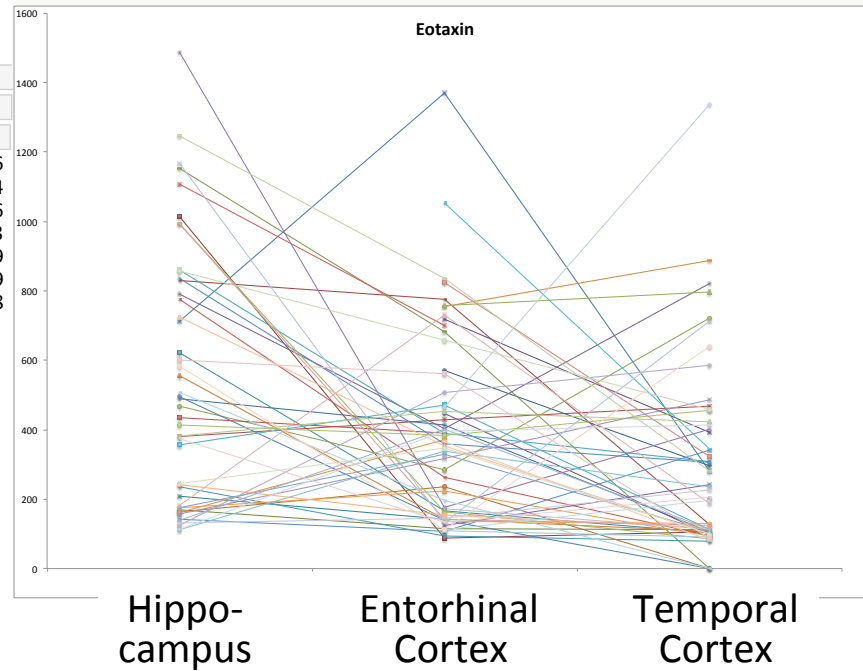
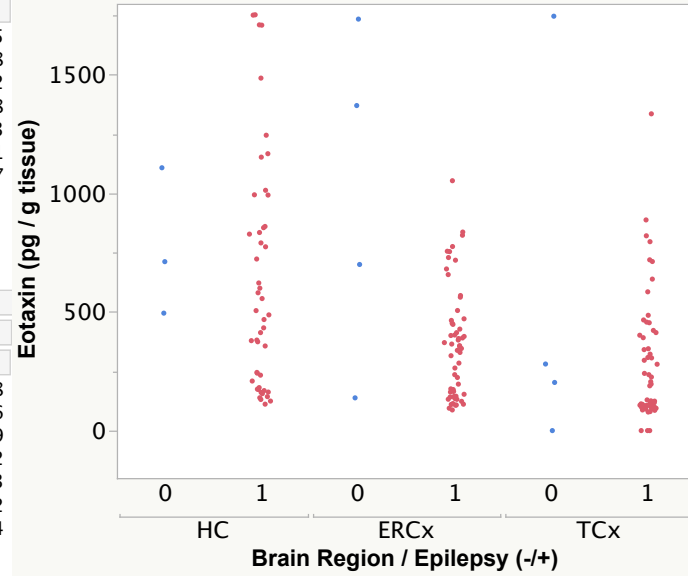


Summary Statistics	
Mean	404.03588
Std Dev	316.47896
Std Err Mean	40.192869
Upper 99.5% Mean	521.10682
Lower 99.5% Mean	286.96493
N	62
Median	356.17724

Temporal Cortex

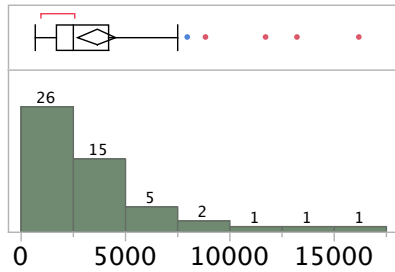


Summary Statistics	
Mean	306.71176
Std Dev	322.81264
Std Err Mean	42.026626
Upper 99.5% Mean	429.36203
Lower 99.5% Mean	184.06149
N	59
Median	203.0078



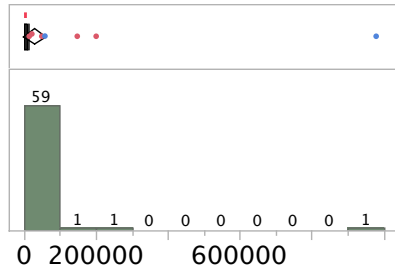
B. IP-10

Hippocampus



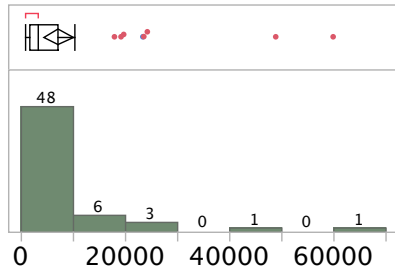
Summary Statistics	
Mean	3597.3037
Std Dev	3233.4141
Std Err Mean	452.76854
Upper 99.5% Mean	4927.0686
Lower 99.5% Mean	2267.5388
N	51
Median	2453.7824

Entorhinal Cortex

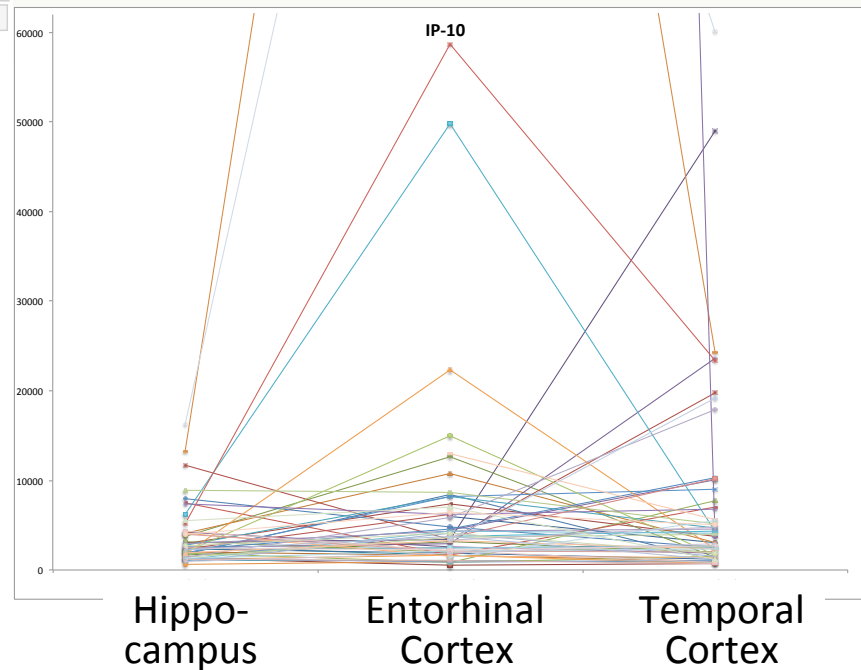
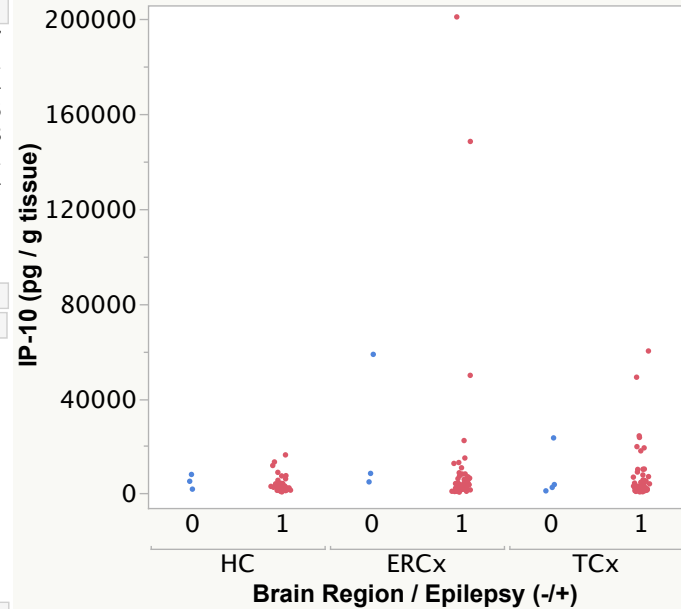


Summary Statistics	
Mean	27346.426
Std Dev	126966.83
Std Err Mean	16124.803
Upper 99.5% Mean	74313.613
Lower 99.5% Mean	-19620.76
N	62
Median	3661.8556

Temporal Cortex

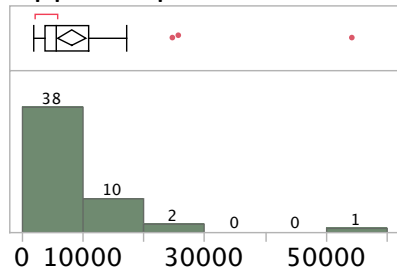


Summary Statistics	
Mean	7004.3431
Std Dev	10854.599
Std Err Mean	1413.1484
Upper 99.5% Mean	11128.468
Lower 99.5% Mean	2880.2186
N	59
Median	3029.3689



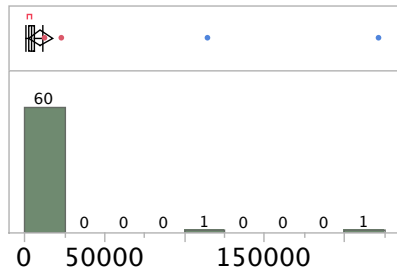
C. MCP-1

Hippocampus



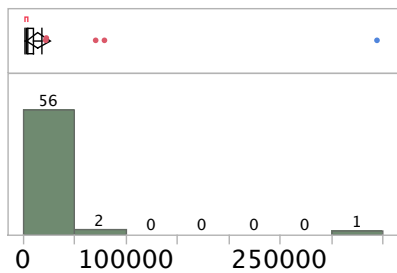
Summary Statistics	
Mean	8051.2261
Std Dev	8565.9279
Std Err Mean	1199.4698
Upper 99.5% Mean	11574.026
Lower 99.5% Mean	4528.4263
N	51
Median	5371.3781

Entorhinal Cortex

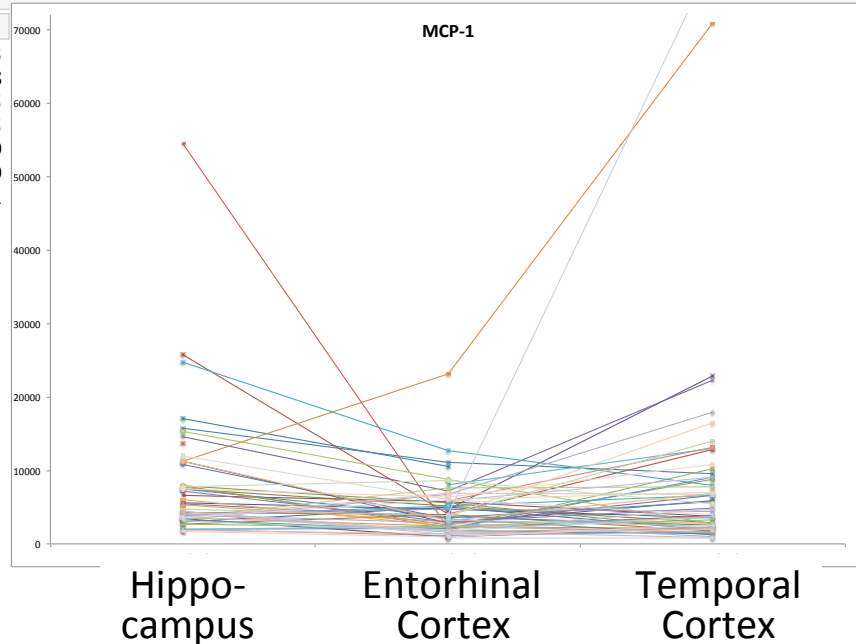
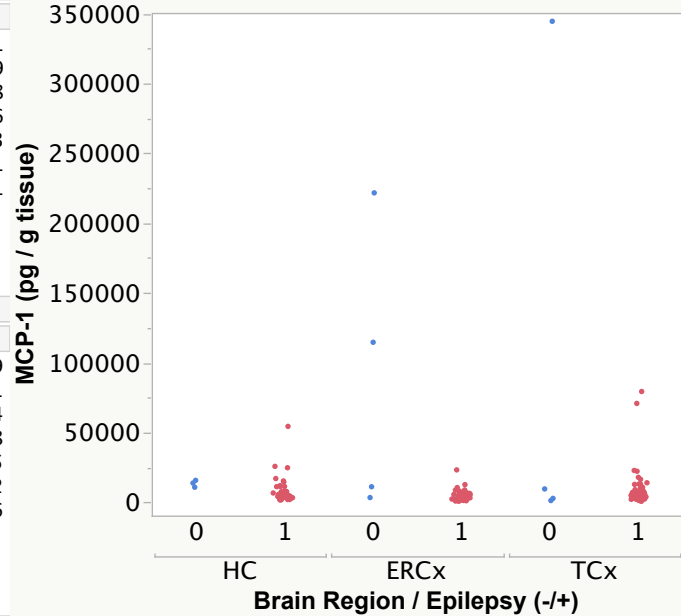


Summary Statistics	
Mean	9828.9269
Std Dev	30919.751
Std Err Mean	3926.8124
Upper 99.5% Mean	21266.668
Lower 99.5% Mean	-1608.815
N	62
Median	3840.2336

Temporal Cortex



Summary Statistics	
Mean	14138.823
Std Dev	45838.378
Std Err Mean	5967.6485
Upper 99.5% Mean	31554.775
Lower 99.5% Mean	-3277.129
N	59
Median	4424.941

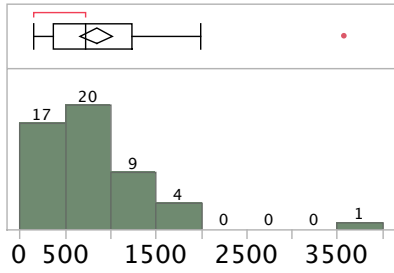


Individual cases where ERCx is lowest

ERCx < HC	ERCx < TCx	Total
37	21	
73%	36%	53%

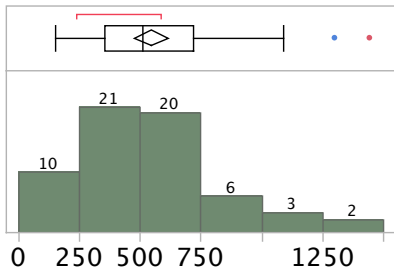
D. MCP-4

Hippocampus



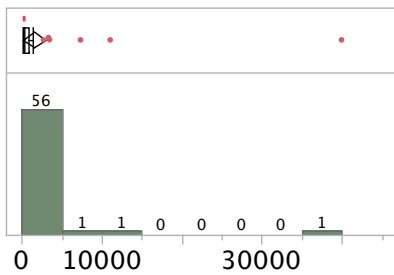
Summary Statistics	
Mean	839.44975
Std Dev	637.46631
Std Err Mean	89.263138
Upper 99.5% Mean	1101.6124
Lower 99.5% Mean	577.28712
N	51
Median	713.79987

Entorhinal Cortex

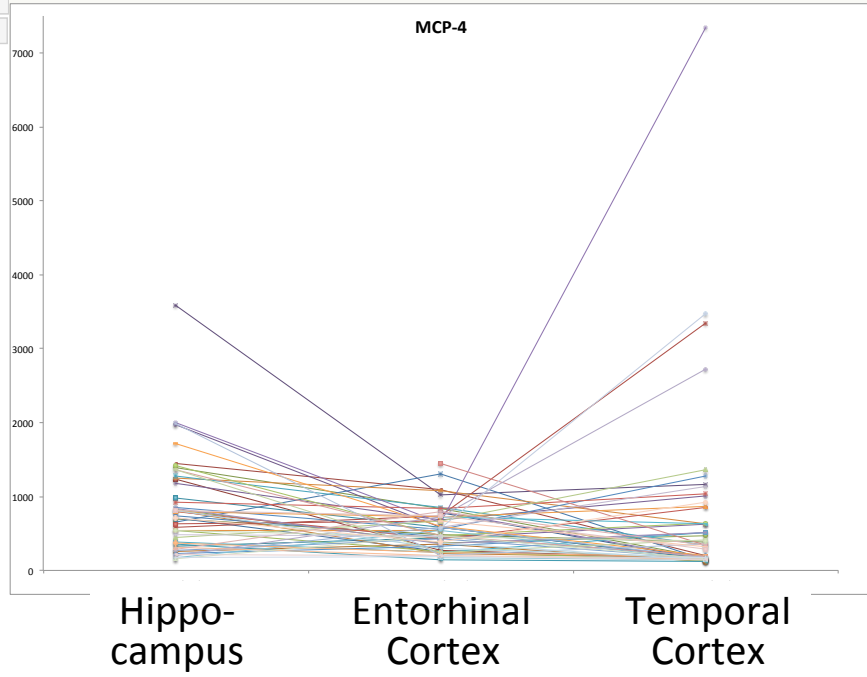
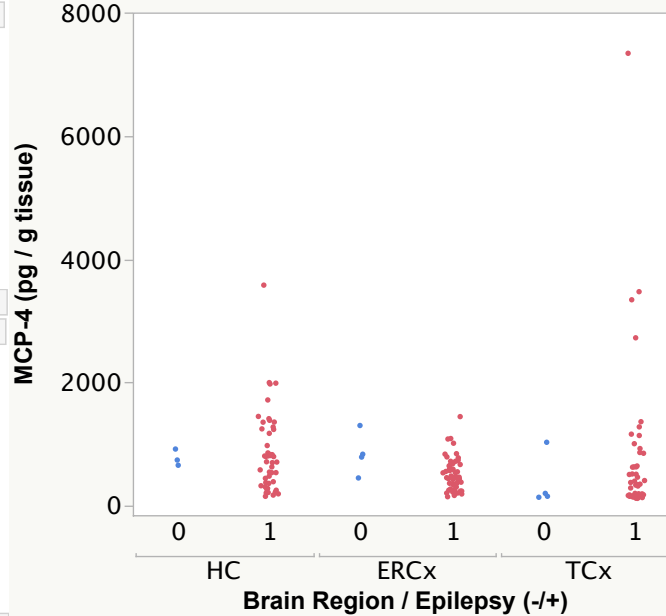


Summary Statistics	
Mean	544.63204
Std Dev	275.70603
Std Err Mean	35.0147
Upper 99.5% Mean	646.62038
Lower 99.5% Mean	442.64369
N	62
Median	508.82556

Temporal Cortex



Summary Statistics	
Mean	1518.4119
Std Dev	5388.1495
Std Err Mean	701.47732
Upper 99.5% Mean	3565.5994
Lower 99.5% Mean	-528.7757
N	59
Median	335.92794

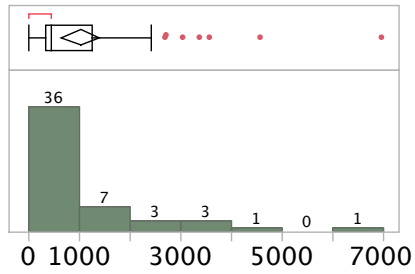


Individual cases where ERCx is lowest

ERCx < HC	ERCx < TCx	Total
39	34	67%
76%	59%	67%

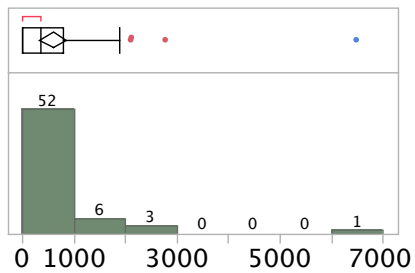
E. MIP-1 α

Hippocampus



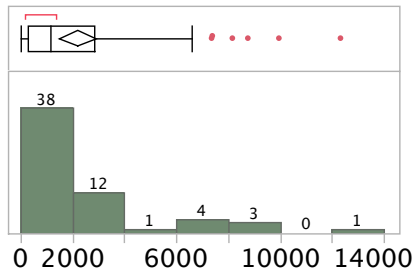
Summary Statistics	
Mean	1007.8384
Std Dev	1348.5148
Std Err Mean	188.82984
Upper 99.5% Mean	1562.4249
Lower 99.5% Mean	453.25194
N	51
Median	436.096

Entorhinal Cortex

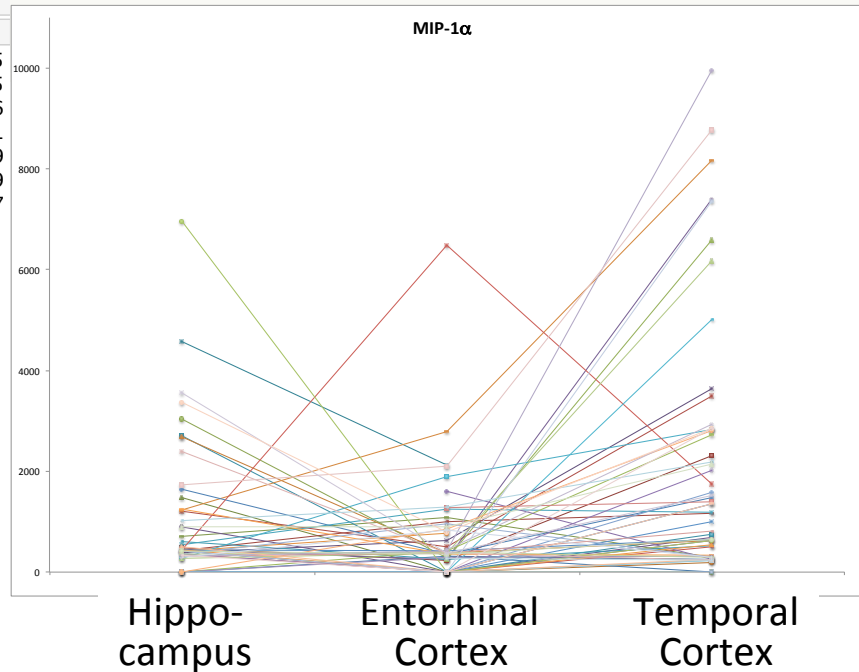
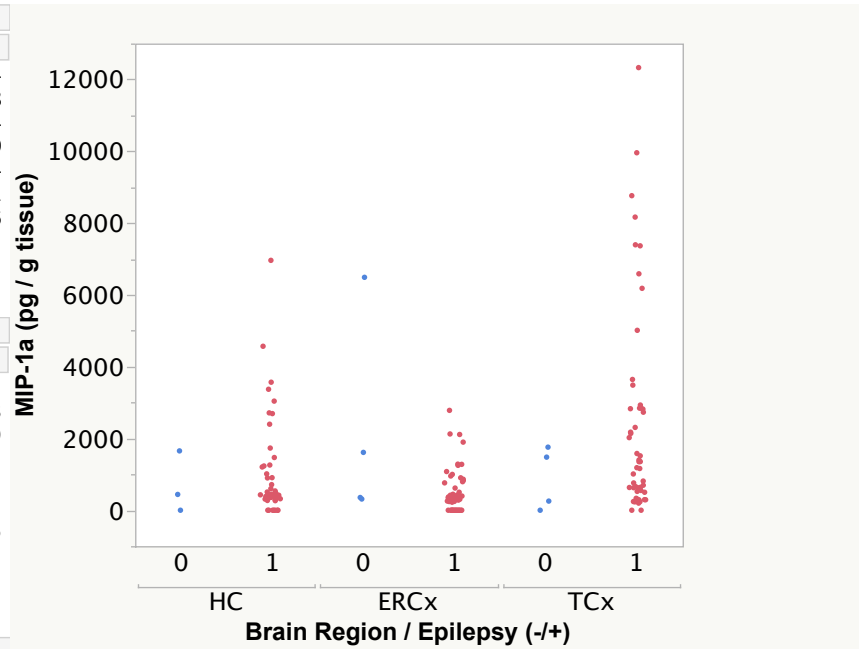


Summary Statistics	
Mean	589.93033
Std Dev	975.30528
Std Err Mean	123.86389
Upper 99.5% Mean	950.71233
Lower 99.5% Mean	229.14833
N	62
Median	347.99526

Temporal Cortex

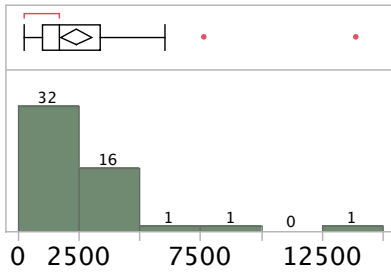


Summary Statistics	
Mean	2186.9905
Std Dev	2770.6965
Std Err Mean	360.71396
Upper 99.5% Mean	3239.6961
Lower 99.5% Mean	1134.2849
N	59
Median	1162.137



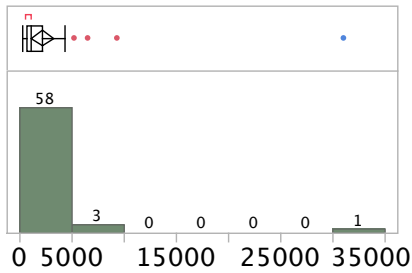
F. MIP-1 β

Hippocampus



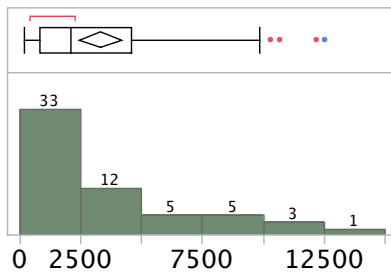
Summary Statistics	
Mean	2361.731
Std Dev	2217.6256
Std Err Mean	310.5297
Upper 99.5% Mean	3273.7455
Lower 99.5% Mean	1449.7164
N	51
Median	1671.8643

Entorhinal Cortex

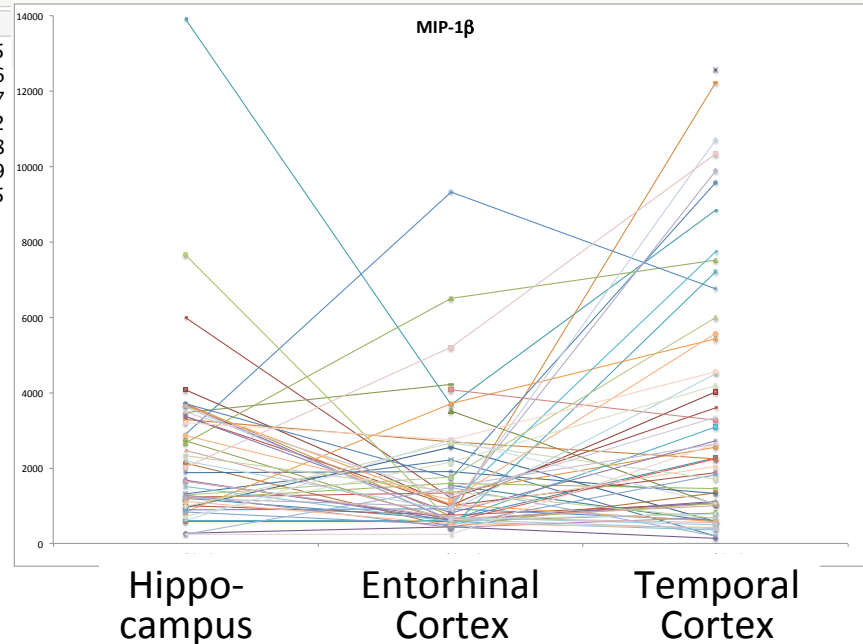
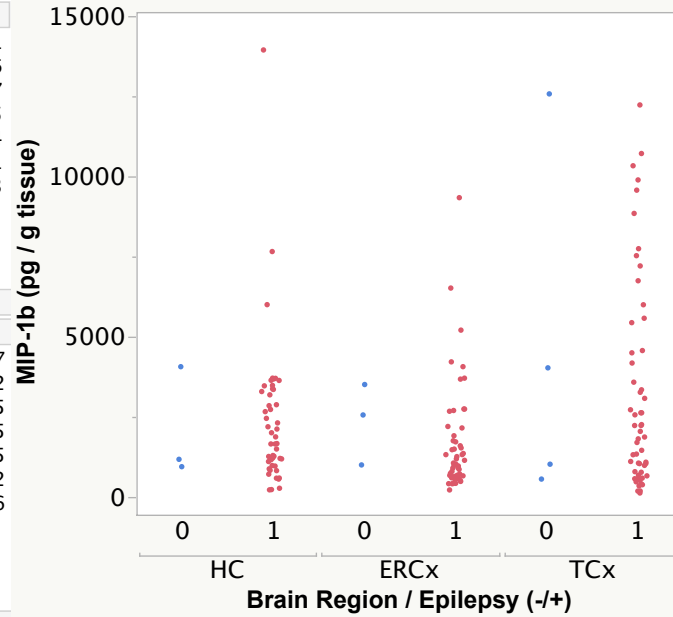


Summary Statistics	
Mean	2111.3537
Std Dev	4077.0412
Std Err Mean	517.78475
Upper 99.5% Mean	3619.5205
Lower 99.5% Mean	603.18685
N	62
Median	1018.9196

Temporal Cortex

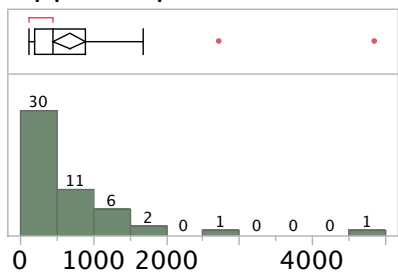


Summary Statistics	
Mean	3306.2185
Std Dev	3359.3066
Std Err Mean	437.34447
Upper 99.5% Mean	4582.5622
Lower 99.5% Mean	2029.8748
N	59
Median	2052.3525



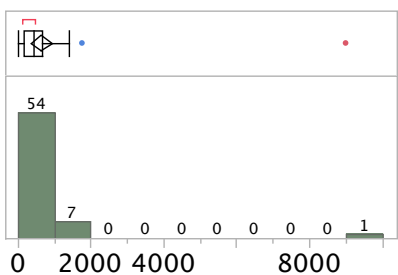
G. TARC

Hippocampus



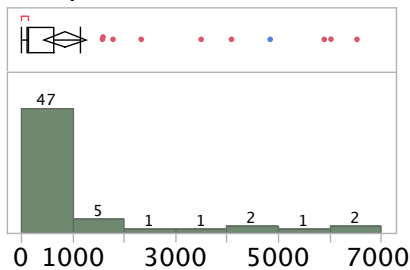
Summary Statistics	
Mean	665.85435
Std Dev	795.59463
Std Err Mean	111.40553
Upper 99.5% Mean	993.0484
Lower 99.5% Mean	338.66031
N	51
Median	426.77107

Entorhinal Cortex

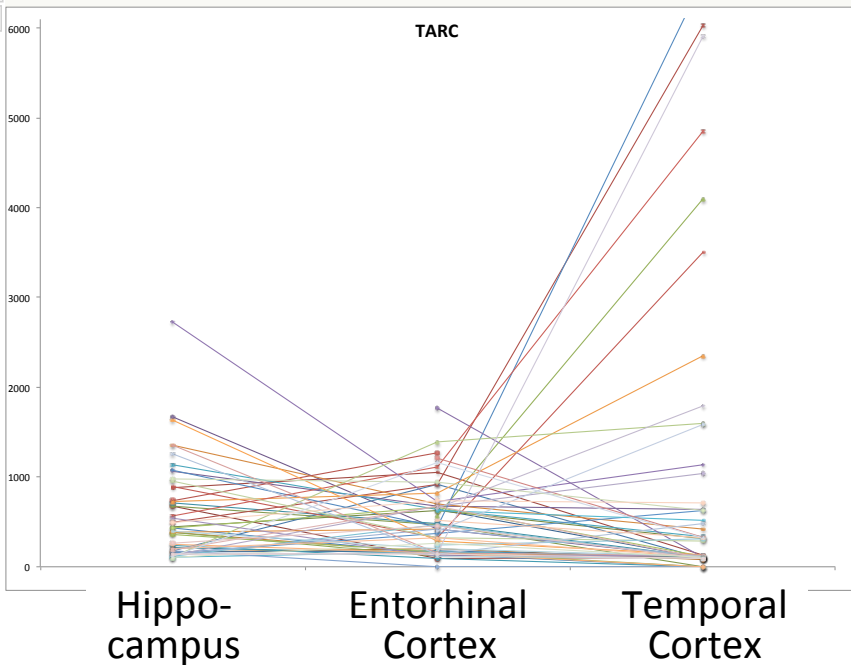
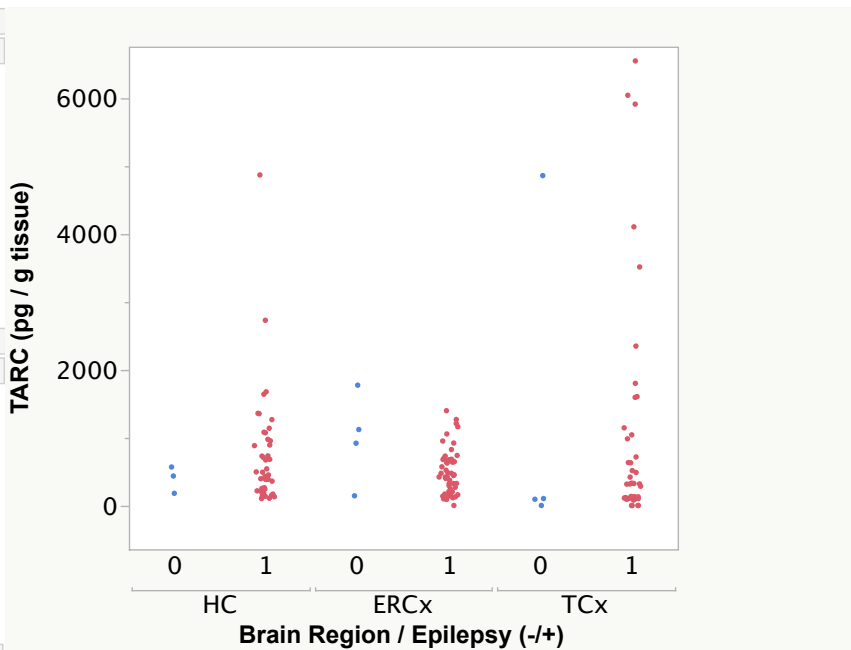


Summary Statistics	
Mean	637.9818
Std Dev	1143.4874
Std Err Mean	145.22305
Upper 99.5% Mean	1060.9772
Lower 99.5% Mean	214.98637
N	62
Median	430.47761

Temporal Cortex

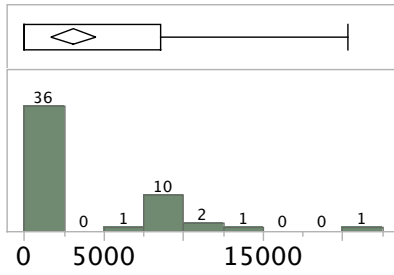


Summary Statistics	
Mean	854.89899
Std Dev	1576.1304
Std Err Mean	205.1947
Upper 99.5% Mean	1453.7381
Lower 99.5% Mean	256.05992
N	59
Median	128.32976



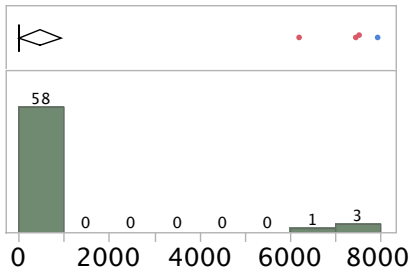
H. GM-CSF

Hippocampus



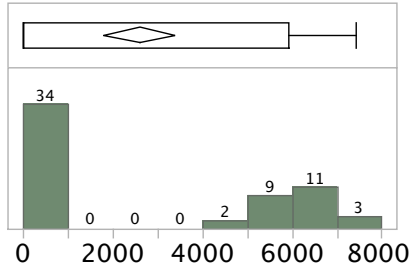
Summary Statistics	
Mean	3062.07
Std Dev	5068.9838
Std Err Mean	709.79971
Upper 99.5% Mean	5146.7262
Lower 99.5% Mean	977.41372
N	51
Median	0

Entorhinal Cortex

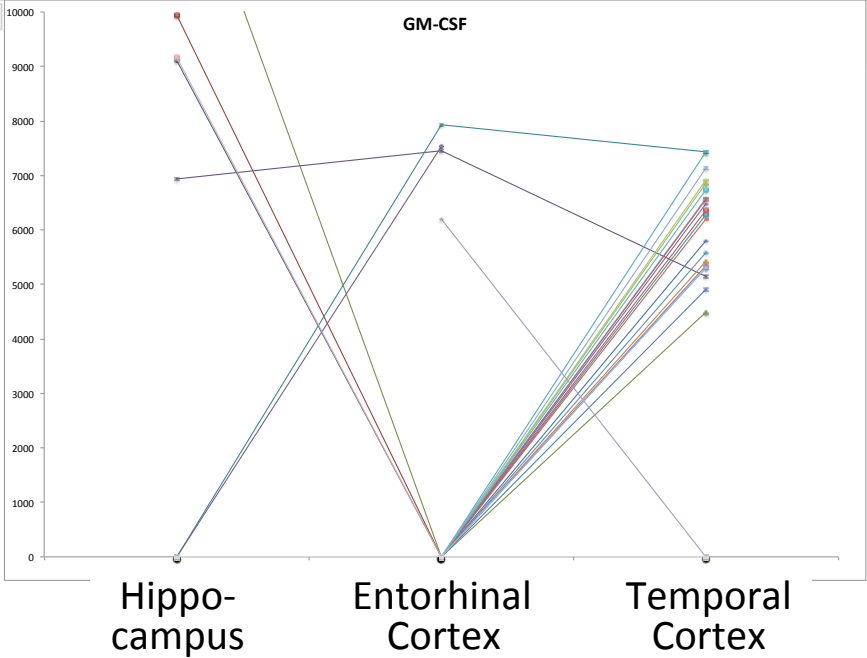
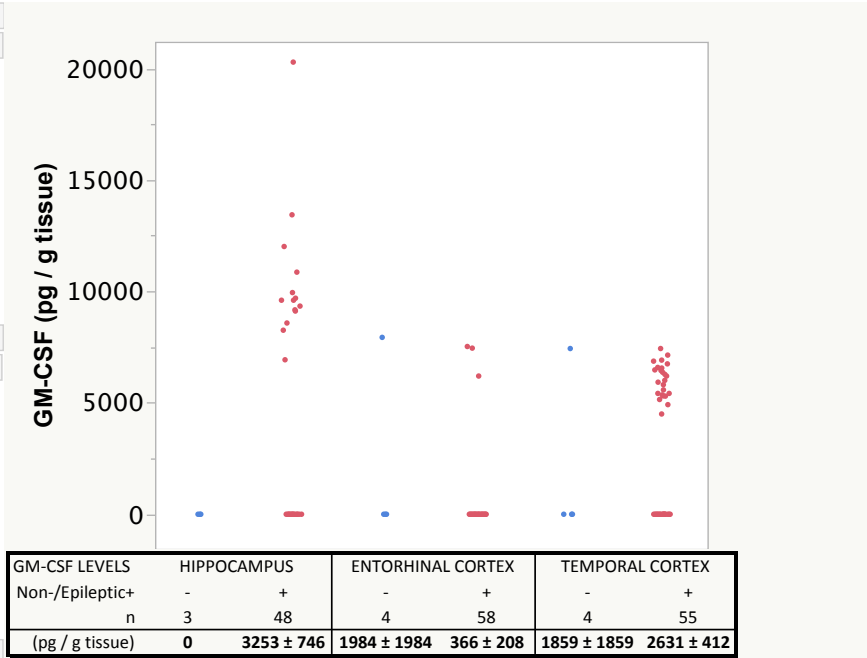


Summary Statistics	
Mean	469.58711
Std Dev	1810.3773
Std Err Mean	229.91815
Upper 99.5% Mean	1139.2764
Lower 99.5% Mean	-200.1022
N	62
Median	0

Temporal Cortex

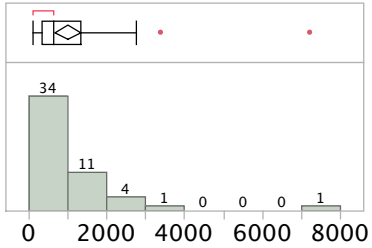


Summary Statistics	
Mean	2578.7104
Std Dev	3075.8234
Std Err Mean	400.4381
Upper 99.5% Mean	3747.3467
Lower 99.5% Mean	1410.074
N	59
Median	0



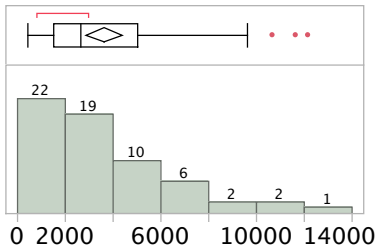
I. IL-1 α

Hippocampus



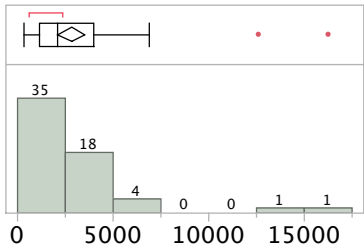
Summary Statistics	
Mean	991.79428
Std Dev	1157.6925
Std Err Mean	162.10937
Upper 99.5% Mean	1467.9037
Lower 99.5% Mean	515.68487
N	51
Median	607.24832

Entorhinal Cortex

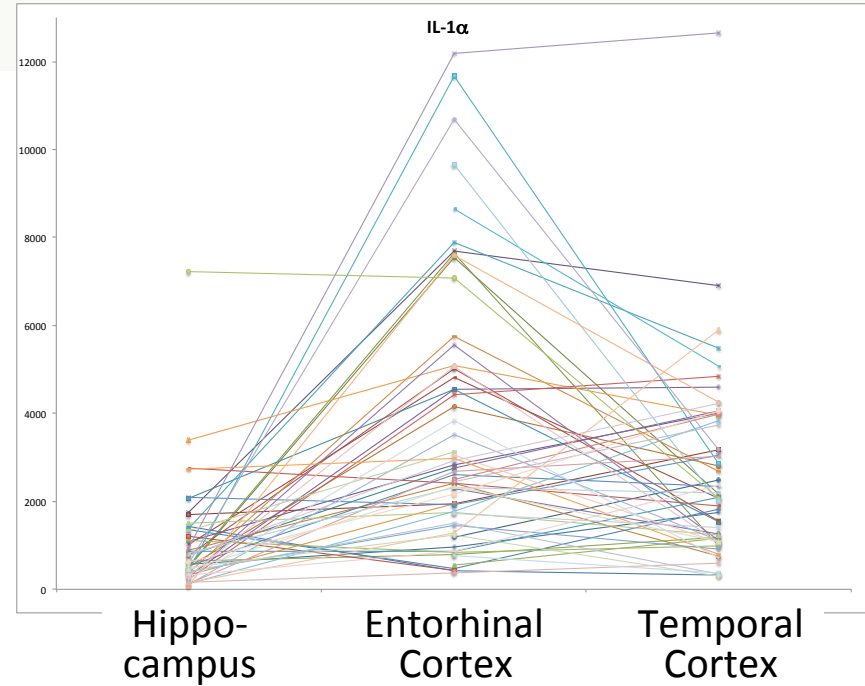
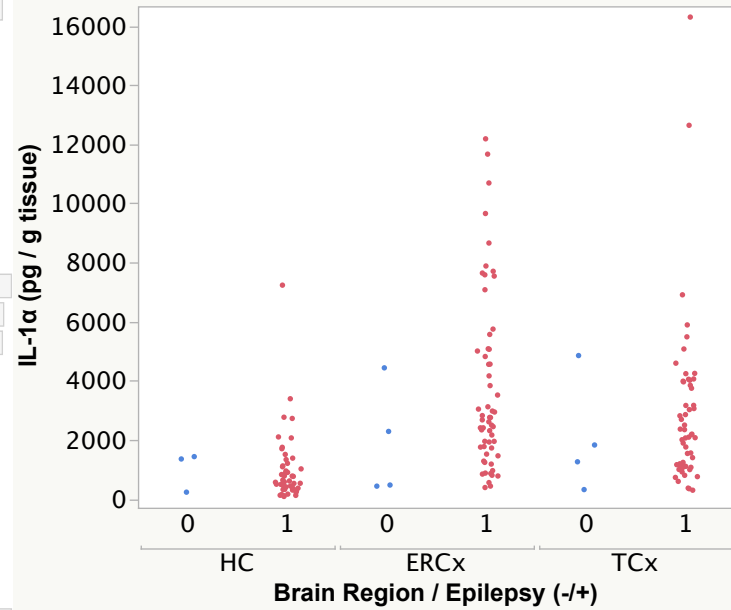


Summary Statistics	
Mean	3616.1414
Std Dev	2926.1712
Std Err Mean	371.62412
Upper 99.5% Mean	4698.5819
Lower 99.5% Mean	2533.701
N	62
Median	2639.8208

Temporal Cortex

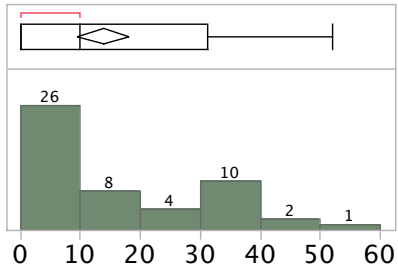


Summary Statistics	
Mean	2808.4881
Std Dev	2714.781
Std Err Mean	353.43439
Upper 99.5% Mean	3839.9491
Lower 99.5% Mean	1777.0271
N	59
Median	2089.163



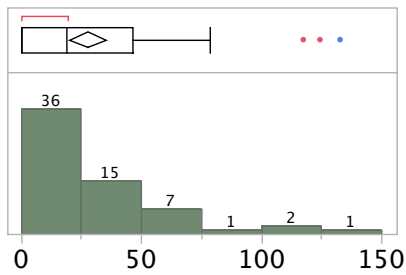
J. IL-1 β

Hippocampus



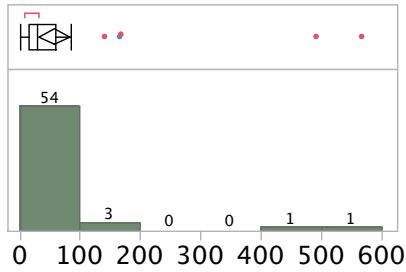
Summary Statistics	
Mean	13.832381
Std Dev	15.433618
Std Err Mean	2.1611388
Upper 99.5% Mean	20.179568
Lower 99.5% Mean	7.485194
N	51
Median	9.8099062

Entorhinal Cortex

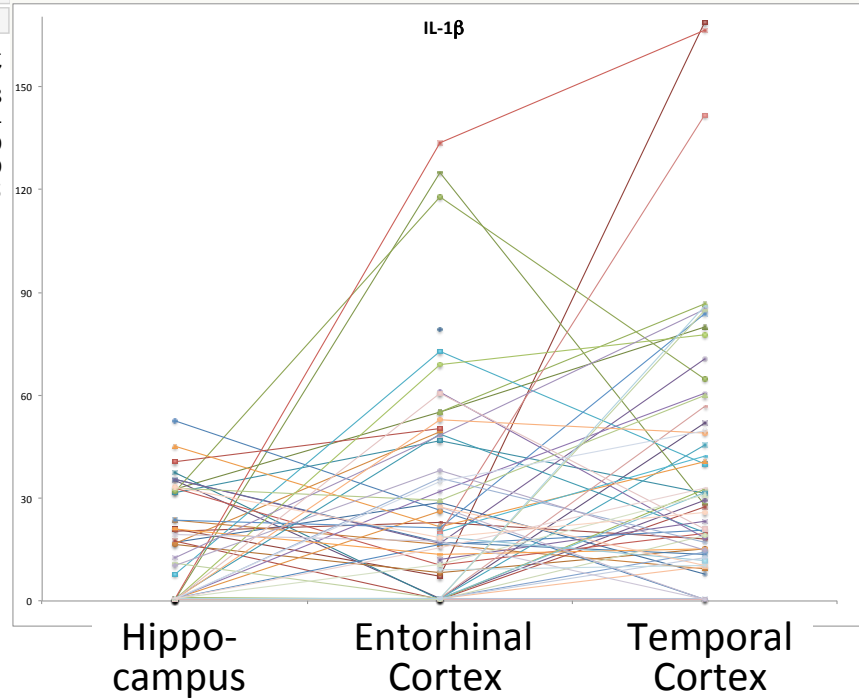
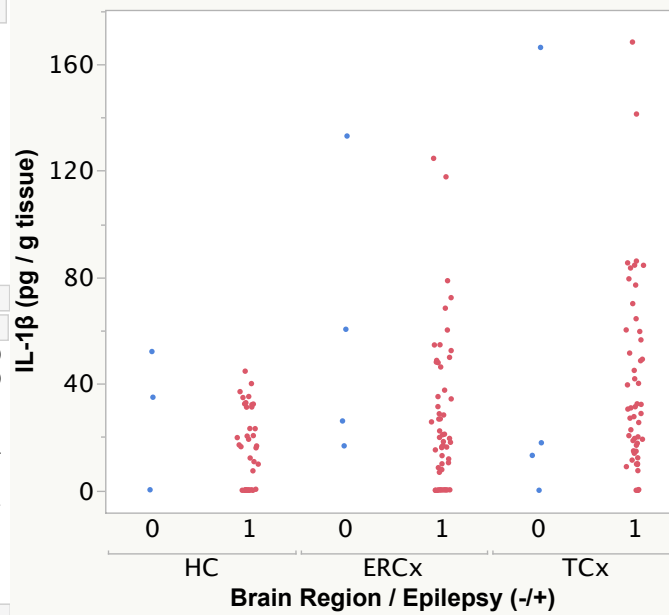


Summary Statistics	
Mean	27.81259
Std Dev	30.56279
Std Err Mean	3.8814782
Upper 99.5% Mean	39.118285
Lower 99.5% Mean	16.506894
N	62
Median	18.858961

Temporal Cortex

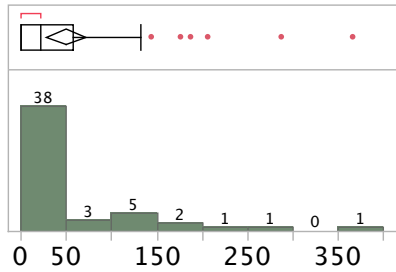


Summary Statistics	
Mean	56.275181
Std Dev	97.146367
Std Err Mean	12.64738
Upper 99.5% Mean	93.185224
Lower 99.5% Mean	19.365139
N	59
Median	28.803695



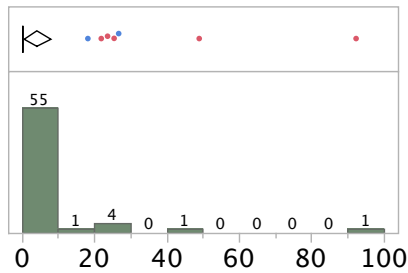
K. IL-2

Hippocampus



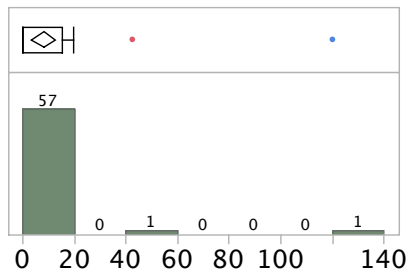
Summary Statistics	
Mean	49.624907
Std Dev	78.613536
Std Err Mean	11.008097
Upper 99.5% Mean	81.955293
Lower 99.5% Mean	17.294522
N	51
Median	22.276405

Entorhinal Cortex

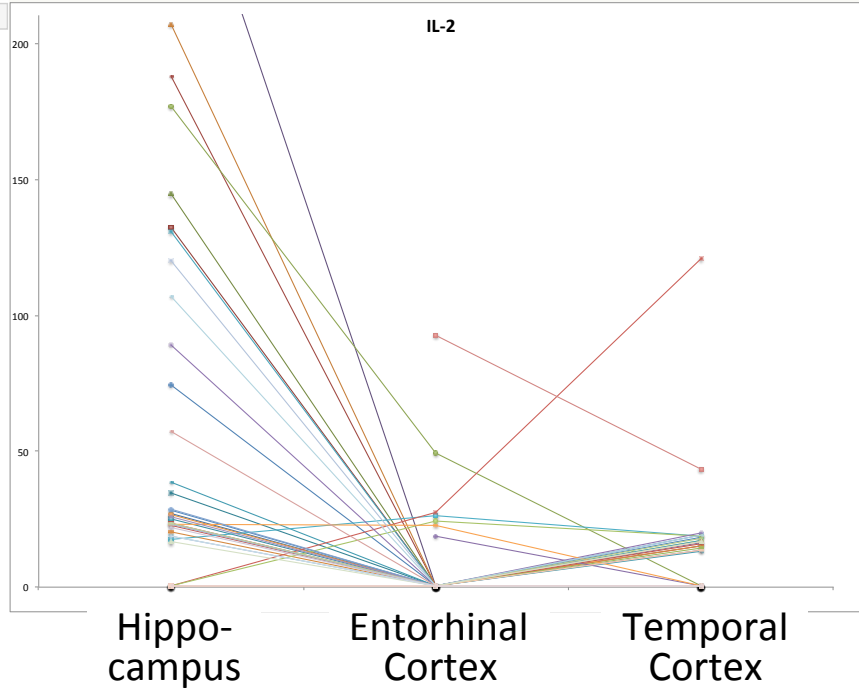
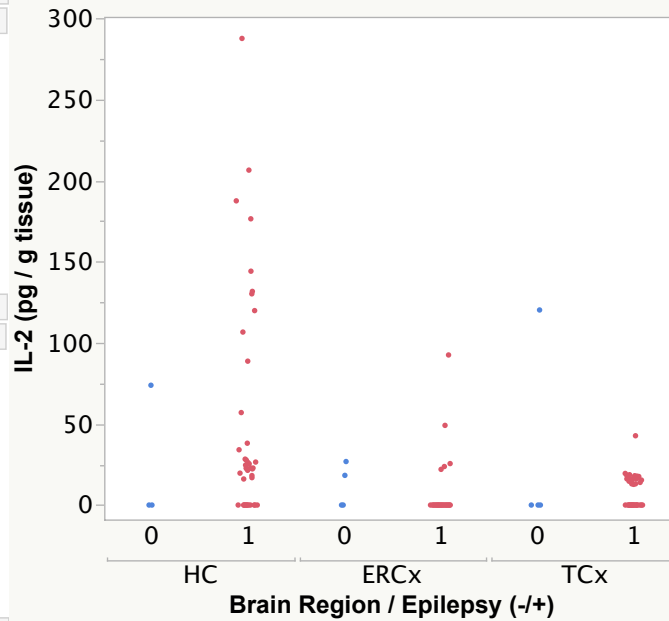


Summary Statistics	
Mean	4.1611047
Std Dev	14.39908
Std Err Mean	1.828685
Upper 99.5% Mean	9.487569
Lower 99.5% Mean	-1.16536
N	62
Median	0

Temporal Cortex

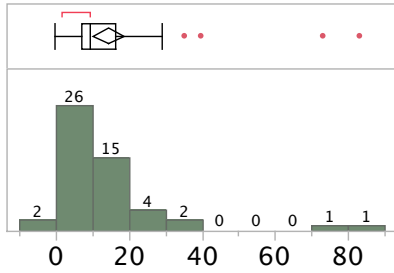


Summary Statistics	
Mean	7.9718566
Std Dev	17.409582
Std Err Mean	2.2665345
Upper 99.5% Mean	14.586498
Lower 99.5% Mean	1.3572149
N	59
Median	0



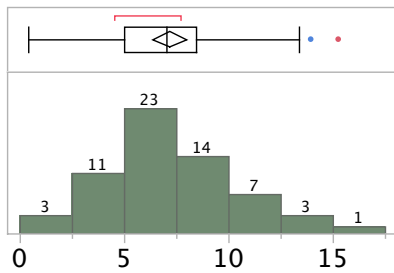
L. IL-4

Hippocampus



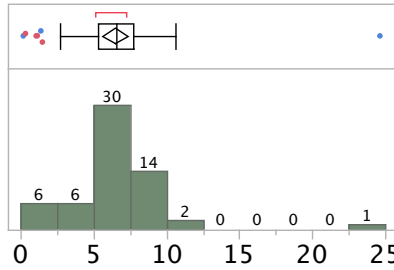
Summary Statistics	
Mean	14.261259
Std Dev	15.47387
Std Err Mean	2.1667751
Upper 99.5% Mean	20.625
Lower 99.5% Mean	7.897518
N	51
Median	8.9967163

Entorhinal Cortex

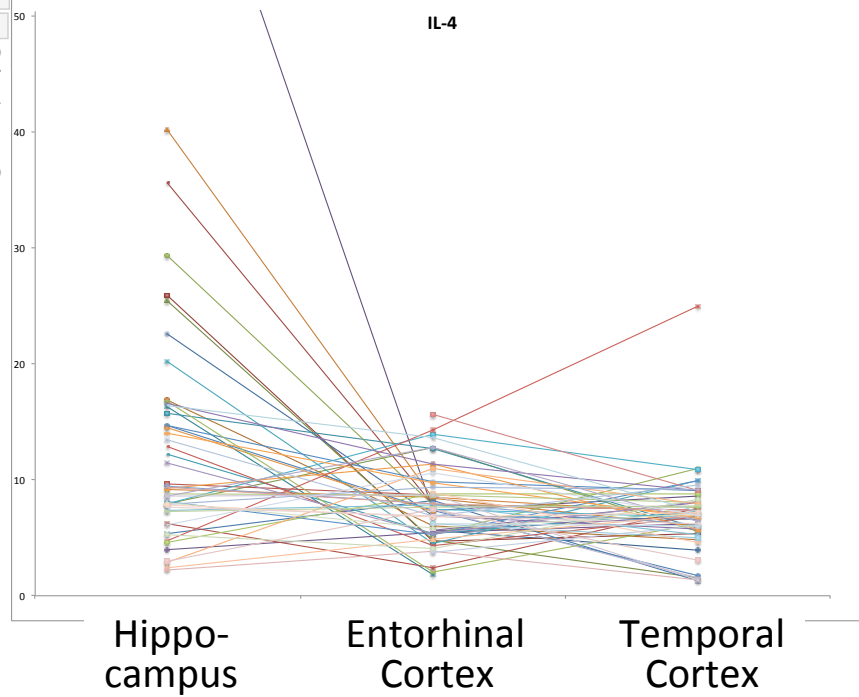
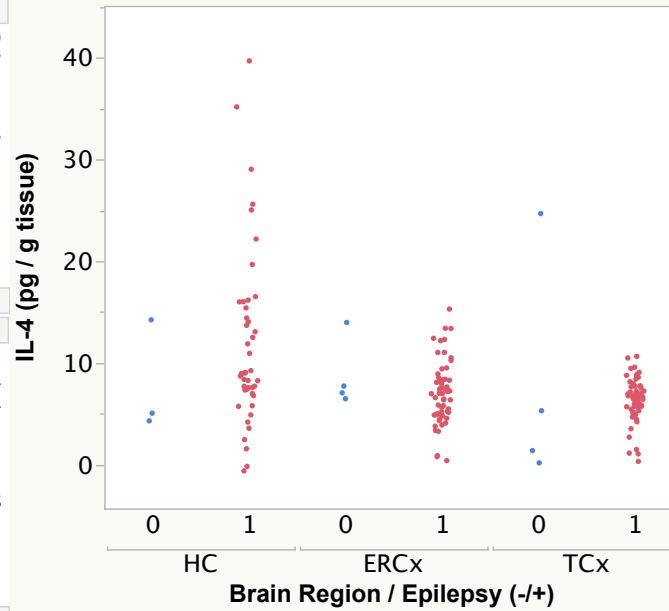


Summary Statistics	
Mean	7.1697472
Std Dev	3.1402124
Std Err Mean	0.3988074
Upper 99.5% Mean	8.3313652
Lower 99.5% Mean	6.0081293
N	62
Median	7.0182008

Temporal Cortex

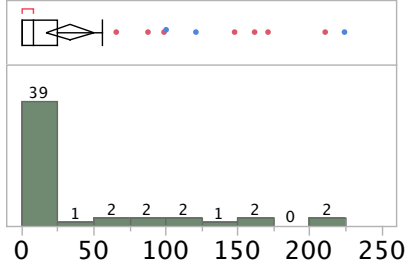


Summary Statistics	
Mean	6.4481769
Std Dev	3.3879187
Std Err Mean	0.4410694
Upper 99.5% Mean	7.7353915
Lower 99.5% Mean	5.1609622
N	59
Median	6.5068842



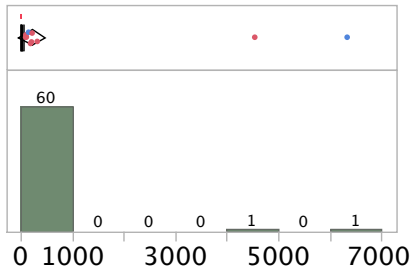
M. IL-6

Hippocampus



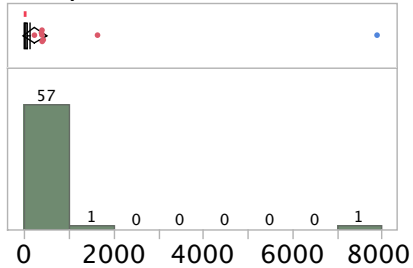
Summary Statistics	
Mean	33.358479
Std Dev	58.234582
Std Err Mean	8.1544726
Upper 99.5% Mean	57.307872
Lower 99.5% Mean	9.4090857
N	51
Median	8.4504144

Entorhinal Cortex

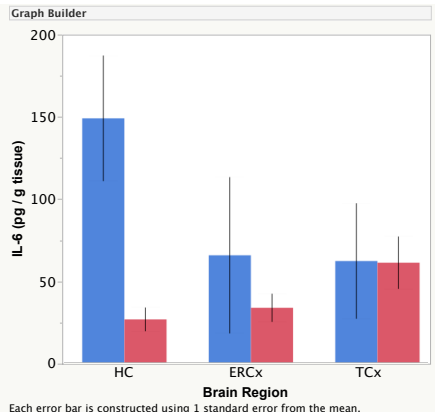
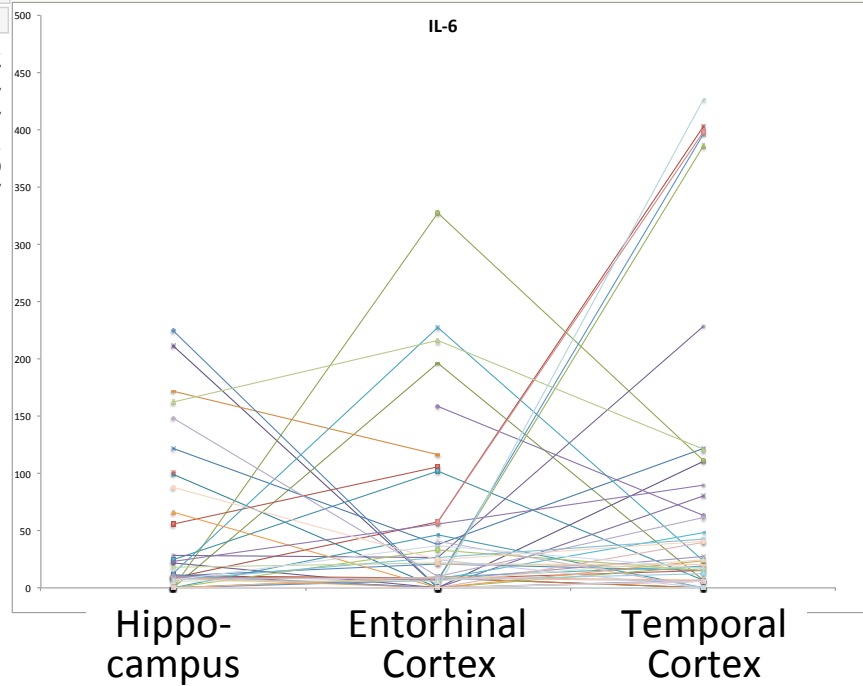
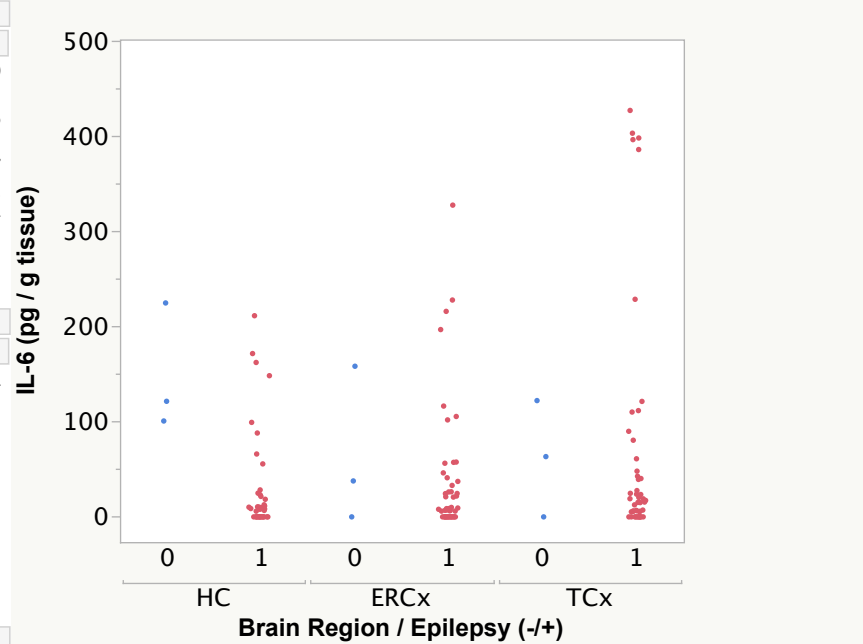


Summary Statistics	
Mean	209.28161
Std Dev	979.0813
Std Err Mean	124.34345
Upper 99.5% Mean	571.46043
Lower 99.5% Mean	-152.8972
N	62
Median	8.3029382

Temporal Cortex

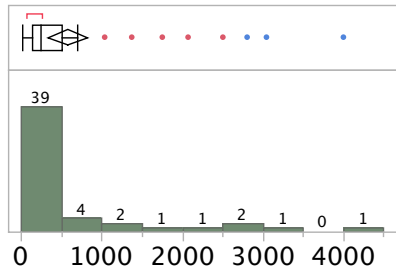


Summary Statistics	
Mean	220.35951
Std Dev	1043.3167
Std Err Mean	135.82827
Upper 99.5% Mean	616.75997
Lower 99.5% Mean	-176.041
N	59
Median	15.527197



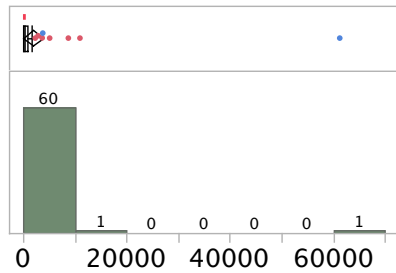
N. IL-8

Hippocampus



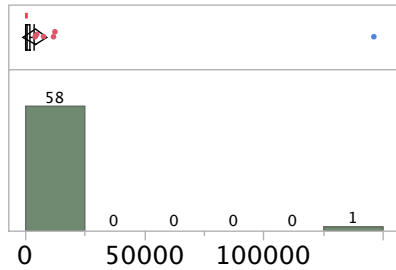
Summary Statistics	
Mean	569.66385
Std Dev	860.36765
Std Err Mean	120.47557
Upper 99.5% Mean	923.49627
Lower 99.5% Mean	215.83143
N	51
Median	242.83711

Entorhinal Cortex

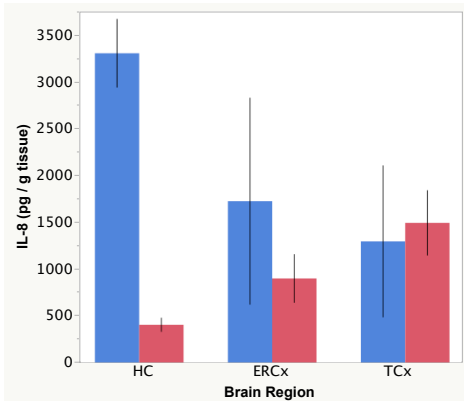
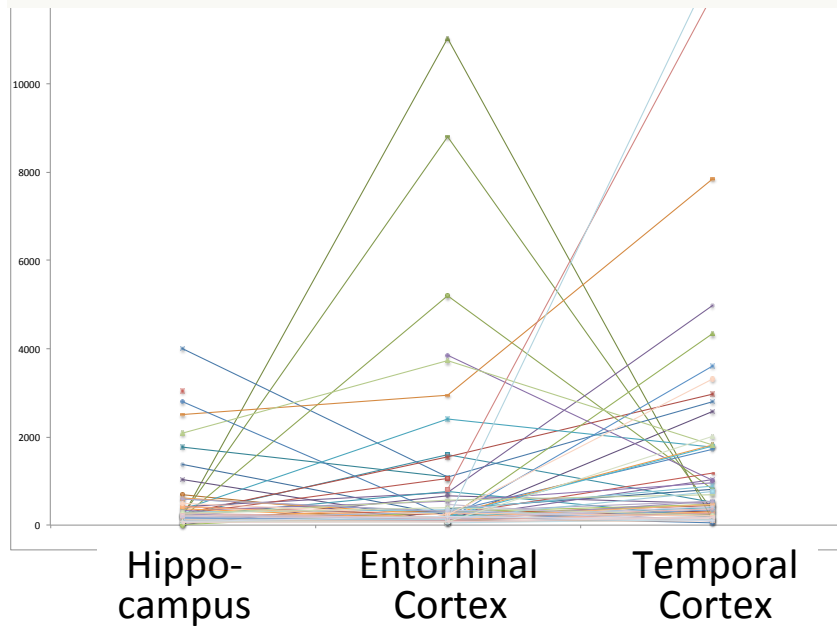
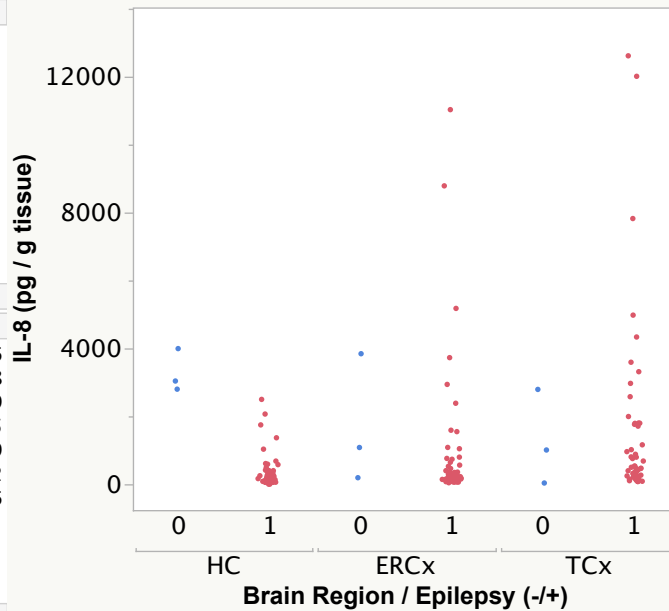


Summary Statistics	
Mean	1905.9706
Std Dev	7907.0708
Std Err Mean	1004.199
Upper 99.5% Mean	4830.9305
Lower 99.5% Mean	-1018.989
N	62
Median	241.63866

Temporal Cortex



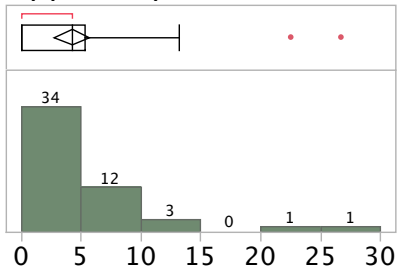
Summary Statistics	
Mean	3928.4278
Std Dev	19024.88
Std Err Mean	2476.8283
Upper 99.5% Mean	11156.79
Lower 99.5% Mean	-3299.934
N	59
Median	484.88101



Each error bar is constructed using 1 standard error from the mean.

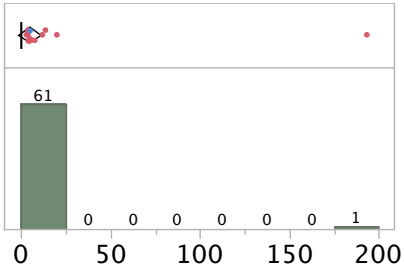
O. IL-10

Hippocampus



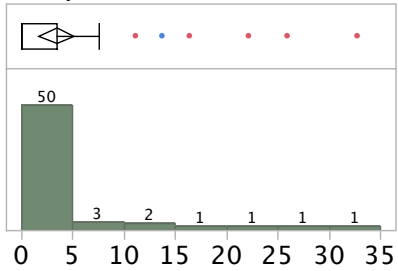
Summary Statistics	
Mean	4.211043
Std Dev	5.3194884
Std Err Mean	0.7448774
Upper 99.5% Mean	6.3987211
Lower 99.5% Mean	2.0233649
N	51
Median	4.2476791

Entorhinal Cortex

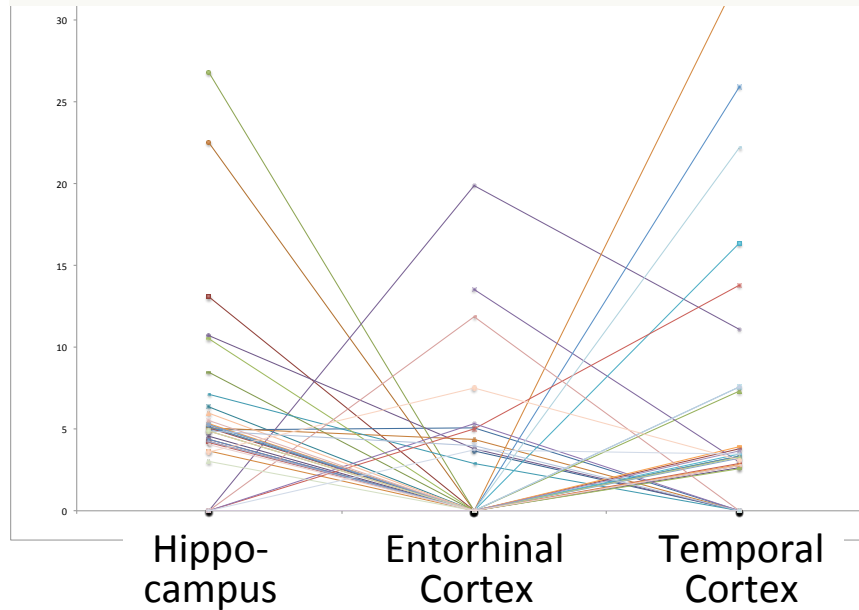
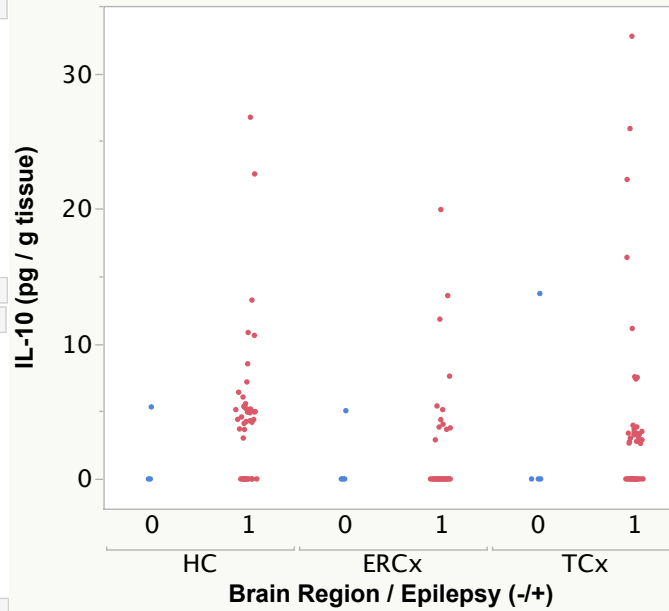


Summary Statistics	
Mean	4.5855709
Std Dev	24.620203
Std Err Mean	3.1267689
Upper 99.5% Mean	13.693002
Lower 99.5% Mean	-4.521861
N	62
Median	0

Temporal Cortex

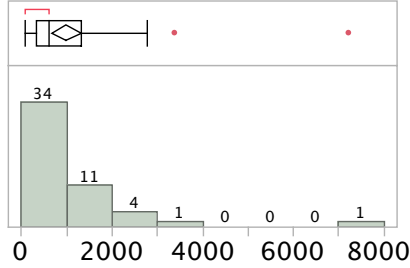


Summary Statistics	
Mean	3.3735657
Std Dev	6.5513844
Std Err Mean	0.8529176
Upper 99.5% Mean	5.8627157
Lower 99.5% Mean	0.8844157
N	59
Median	0



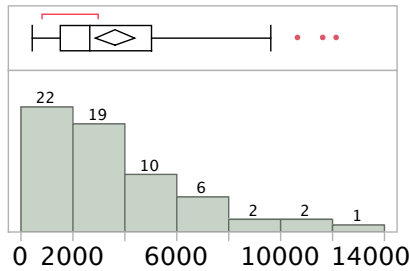
P. IL-12/23 p40 [see supplemental data 2AA for IL-12/23p40:IL-12p70 ratio]

Hippocampus



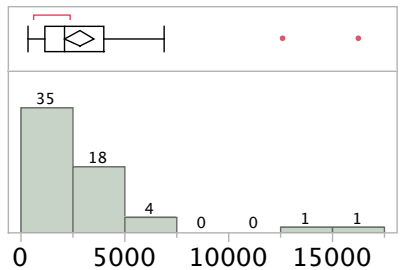
Summary Statistics	
Mean	991.60372
Std Dev	1157.6942
Std Err Mean	162.10961
Upper 99.5% Mean	1467.7138
Lower 99.5% Mean	515.49362
N	51
Median	607.24832

Entorhinal Cortex

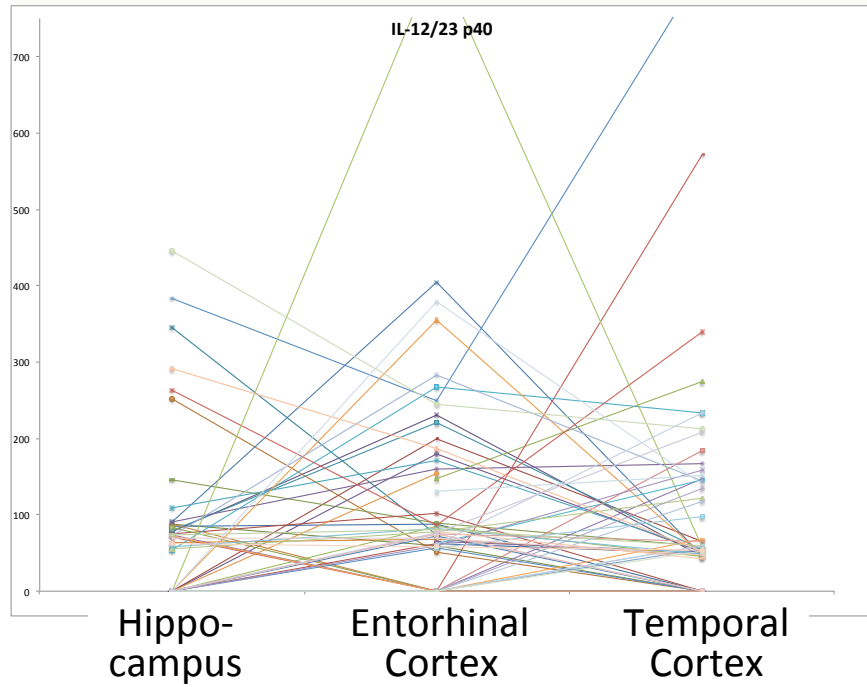
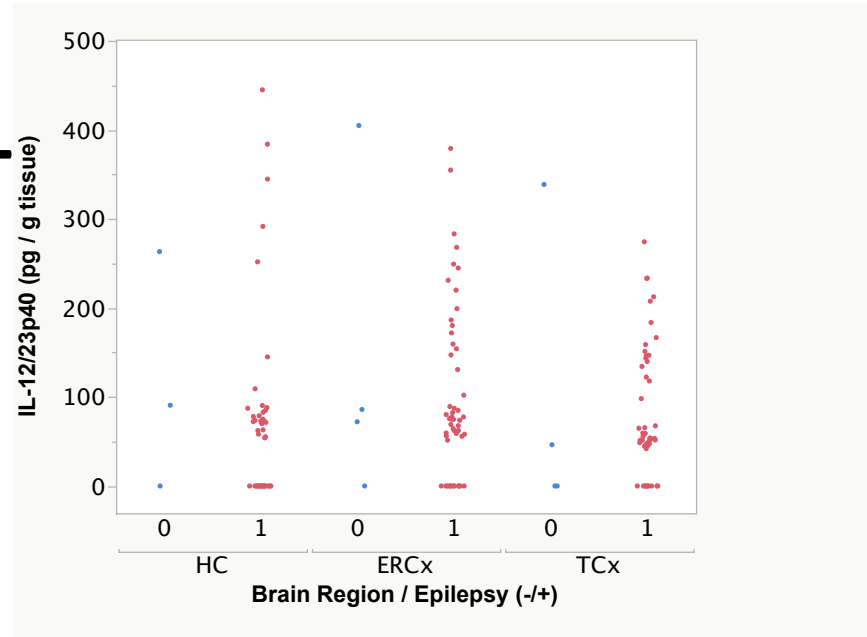


Summary Statistics	
Mean	3616.1477
Std Dev	2926.1655
Std Err Mean	371.62339
Upper 99.5% Mean	4698.5861
Lower 99.5% Mean	2533.7094
N	62
Median	2639.96

Temporal Cortex



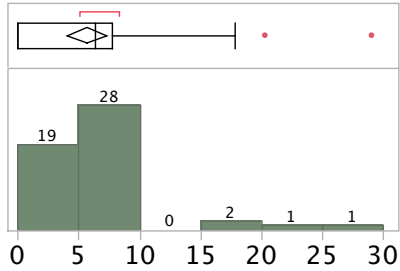
Summary Statistics	
Mean	2808.4707
Std Dev	2714.7821
Std Err Mean	353.43453
Upper 99.5% Mean	3839.932
Lower 99.5% Mean	1777.0093
N	59
Median	2089.0416



Q. IL-12 p70

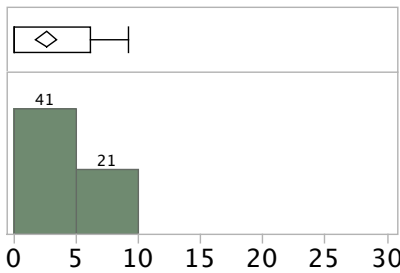
[see supplemental data 2Z for IL-12p70:IL-12/23p40 ratio]

Hippocampus



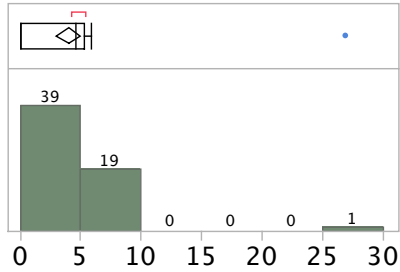
Summary Statistics	
Mean	5.6366689
Std Dev	5.8279984
Std Err Mean	0.816083
Upper 99.5% Mean	8.0334753
Lower 99.5% Mean	3.2398624
N	51
Median	6.3309553

Entorhinal Cortex

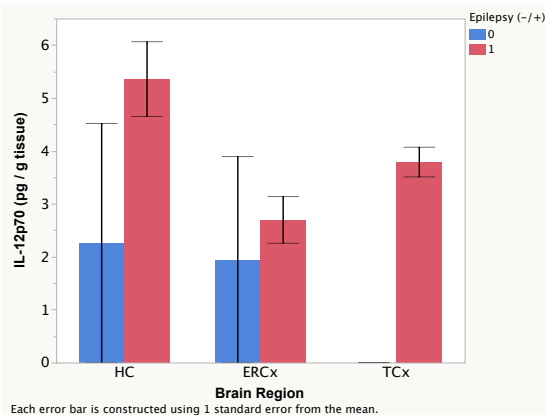
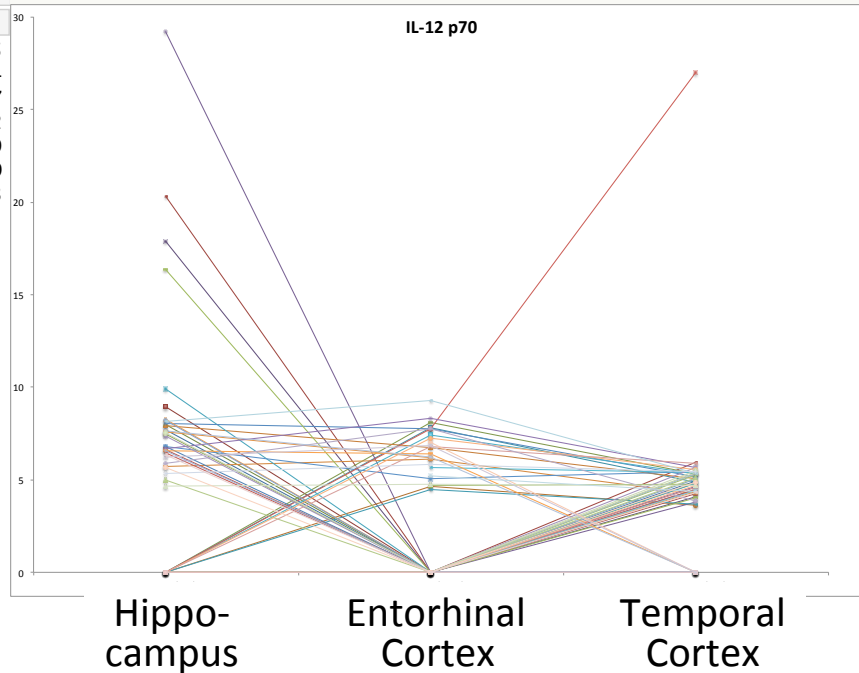
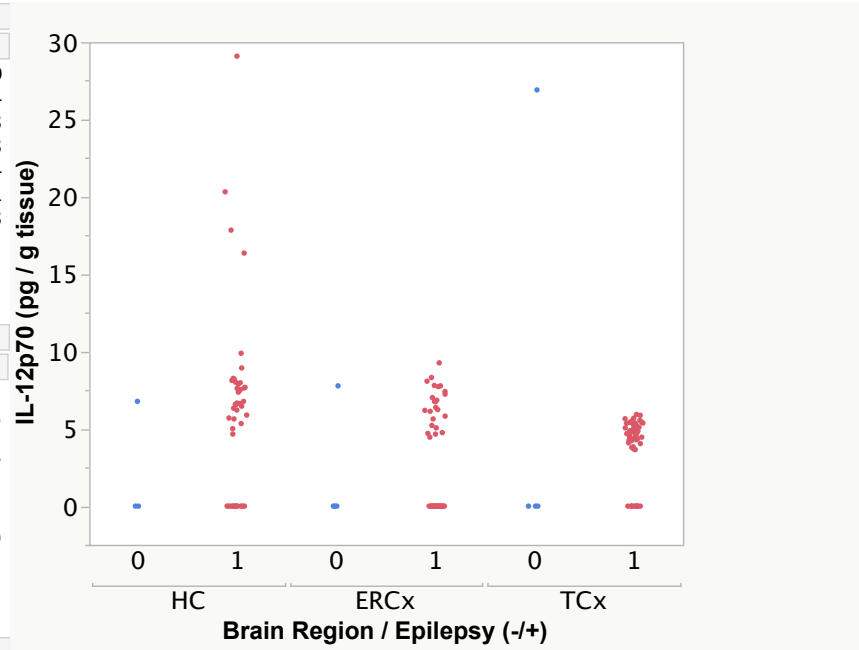


Summary Statistics	
Mean	2.6456181
Std Dev	3.3462496
Std Err Mean	0.4249741
Upper 99.5% Mean	3.8834527
Lower 99.5% Mean	1.4077835
N	62
Median	0

Temporal Cortex



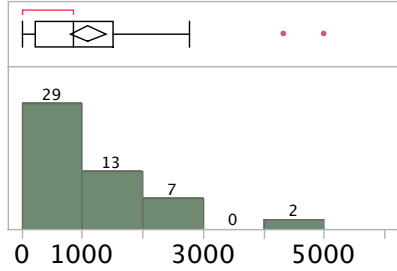
Summary Statistics	
Mean	3.9873365
Std Dev	3.739264
Std Err Mean	0.4868107
Upper 99.5% Mean	5.4080422
Lower 99.5% Mean	2.5666309
N	59
Median	4.5896543



Each error bar is constructed using 1 standard error from the mean.

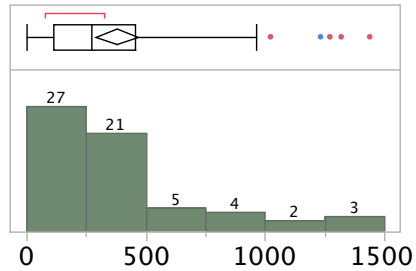
R. IL-17A

Hippocampus



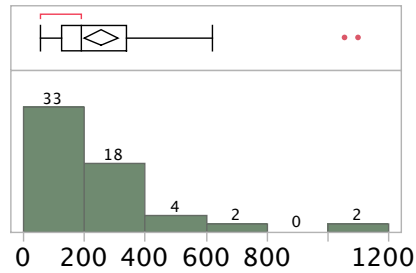
Summary Statistics	
Mean	1094.9051
Std Dev	1059.5481
Std Err Mean	148.36641
Upper 99.5% Mean	1530.6519
Lower 99.5% Mean	659.15826
N	51
Median	855.98746

Entorhinal Cortex

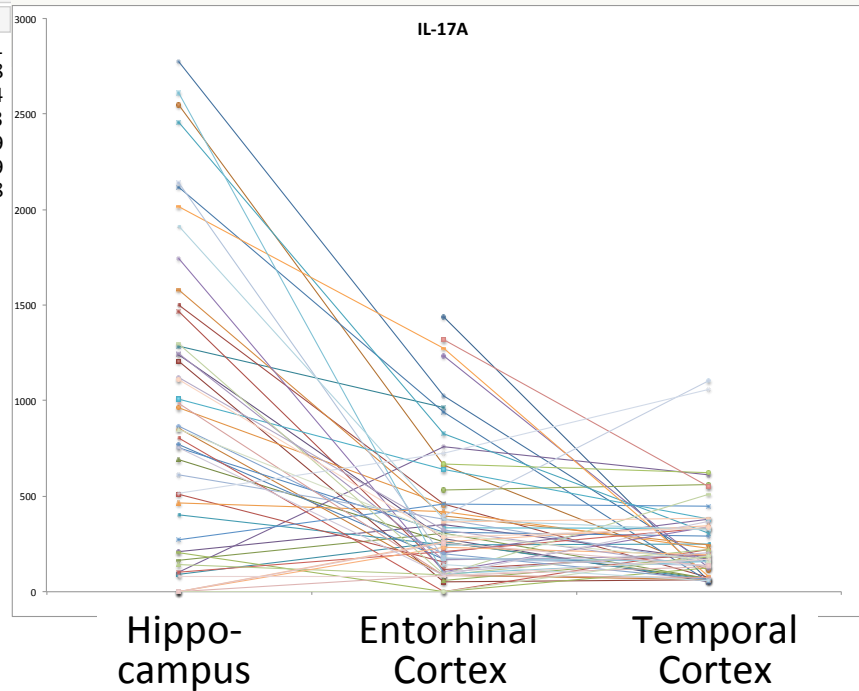
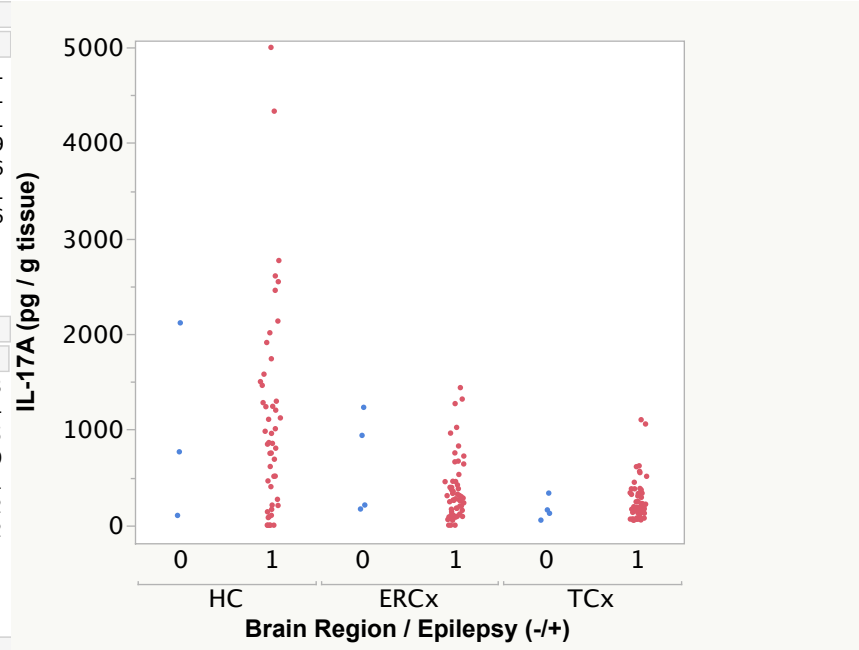


Summary Statistics	
Mean	378.2263
Std Dev	348.22324
Std Err Mean	44.224395
Upper 99.5% Mean	507.03999
Lower 99.5% Mean	249.41261
N	62
Median	269.85302

Temporal Cortex

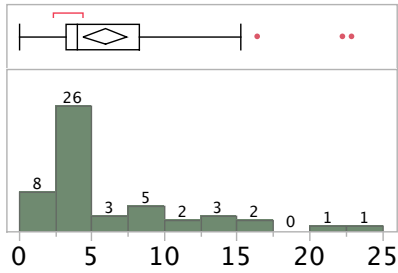


Summary Statistics	
Mean	252.44311
Std Dev	216.17428
Std Err Mean	28.143494
Upper 99.5% Mean	334.57693
Lower 99.5% Mean	170.30929
N	59
Median	187.04788



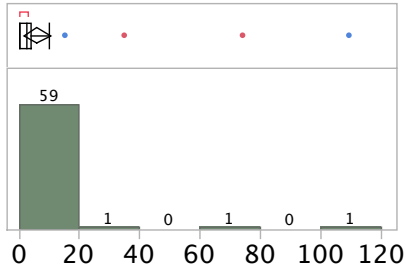
S. TNF- α

Hippocampus



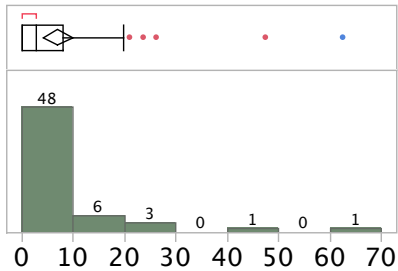
Summary Statistics	
Mean	5.8935805
Std Dev	5.3182121
Std Err Mean	0.7446986
Upper 99.5% Mean	8.0807337
Lower 99.5% Mean	3.7064274
N	51
Median	4.0127758

Entorhinal Cortex

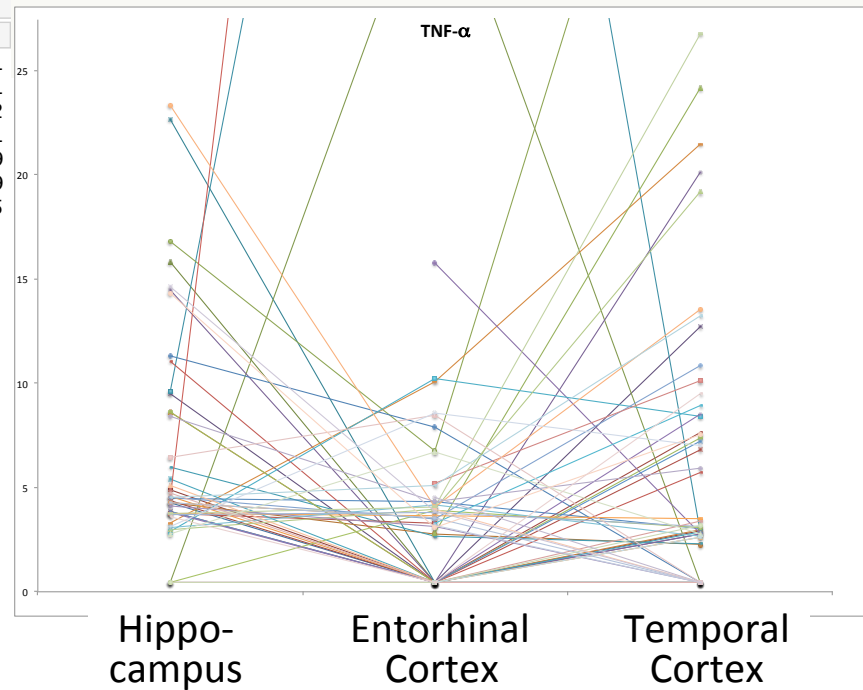
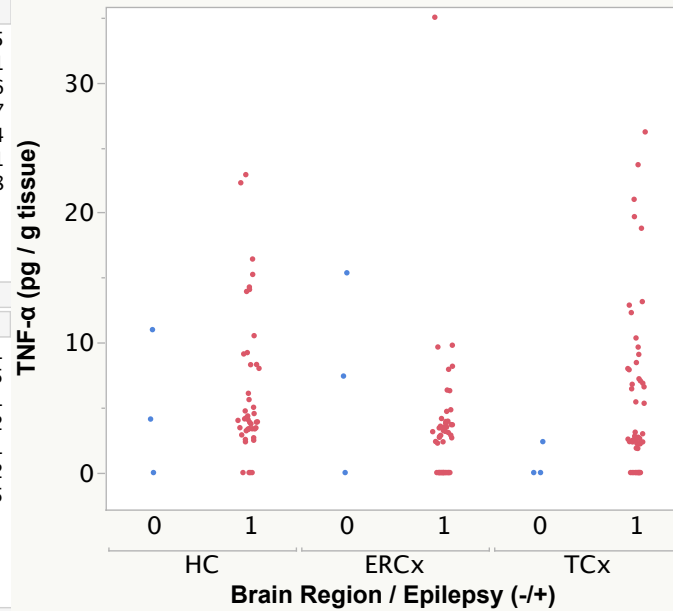


Summary Statistics	
Mean	6.0244851
Std Dev	16.912055
Std Err Mean	2.1478331
Upper 99.5% Mean	12.280542
Lower 99.5% Mean	-0.231571
N	62
Median	2.7473985

Temporal Cortex



Summary Statistics	
Mean	6.9439251
Std Dev	11.121801
Std Err Mean	1.4479352
Upper 99.5% Mean	11.169571
Lower 99.5% Mean	2.718279
N	59
Median	2.6231055

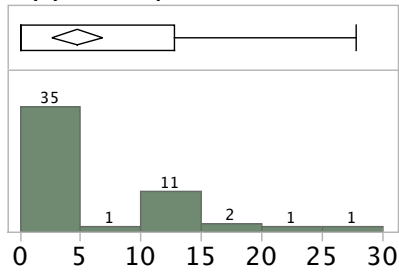


Individual cases where ERCx is lowest

ERCx < HC	ERCx < TCx	Total
35	30	
69%	52%	60%

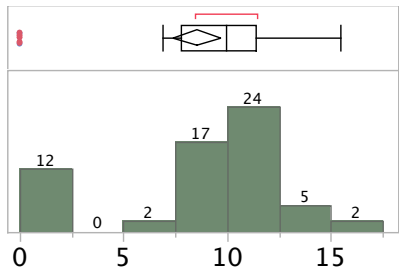
T. TNF-β

Hippocampus



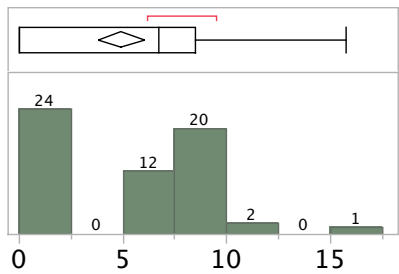
Summary Statistics	
Mean	4.6765331
Std Dev	7.4026206
Std Err Mean	1.0365742
Upper 99.5% Mean	7.7209143
Lower 99.5% Mean	1.6321518
N	51
Median	0

Entorhinal Cortex

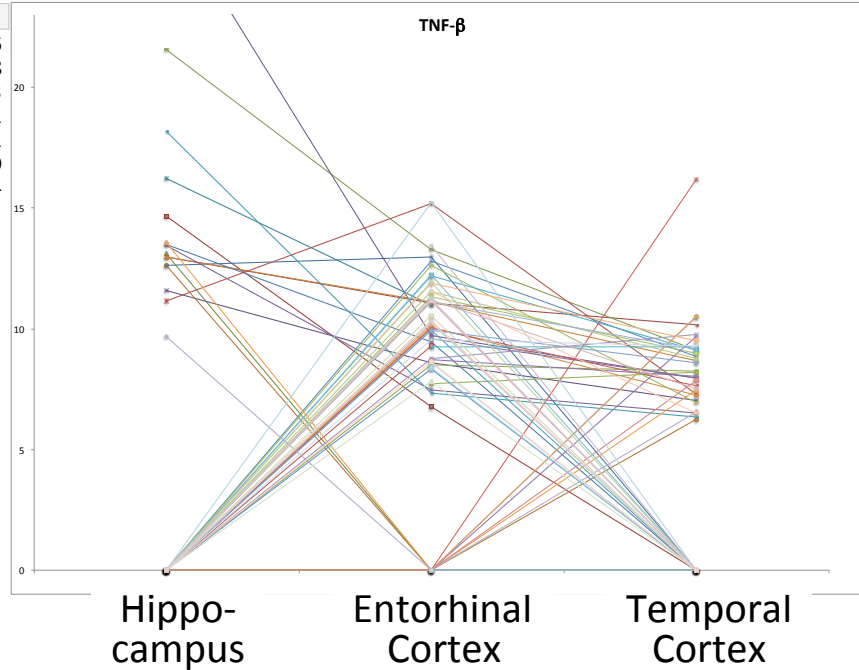
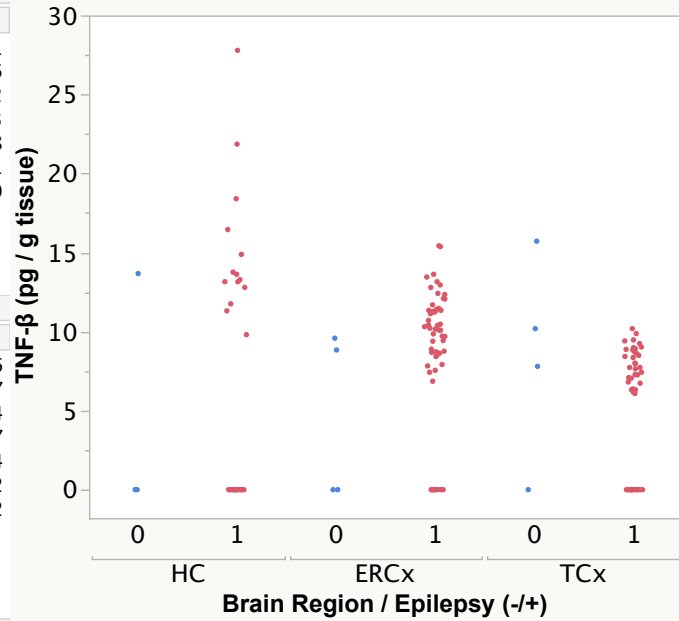


Summary Statistics	
Mean	8.5208356
Std Dev	4.5503767
Std Err Mean	0.5778984
Upper 99.5% Mean	10.204097
Lower 99.5% Mean	6.837574
N	62
Median	9.9696702

Temporal Cortex



Summary Statistics	
Mean	4.9002616
Std Dev	4.3051228
Std Err Mean	0.5604793
Upper 99.5% Mean	6.5359611
Lower 99.5% Mean	3.2645621
N	59
Median	6.7361784

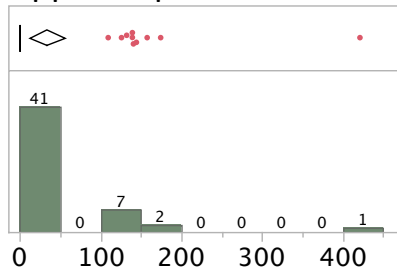


Individual cases where ERCx is highest

ERCx > HC	ERCx > TCx	Total
37	49	
76%	83%	80%

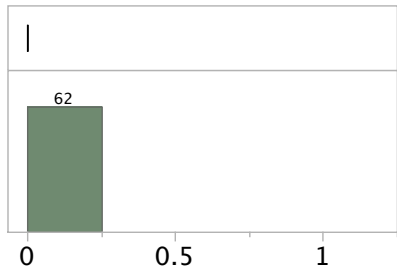
U. IFN- γ

Hippocampus



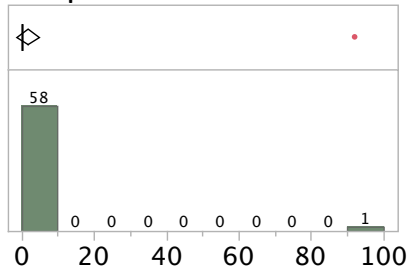
Summary Statistics	
Mean	33.071243
Std Dev	77.752997
Std Err Mean	10.887597
Upper 99.5% Mean	65.047726
Lower 99.5% Mean	1.0947612
N	51
Median	0

Entorhinal Cortex

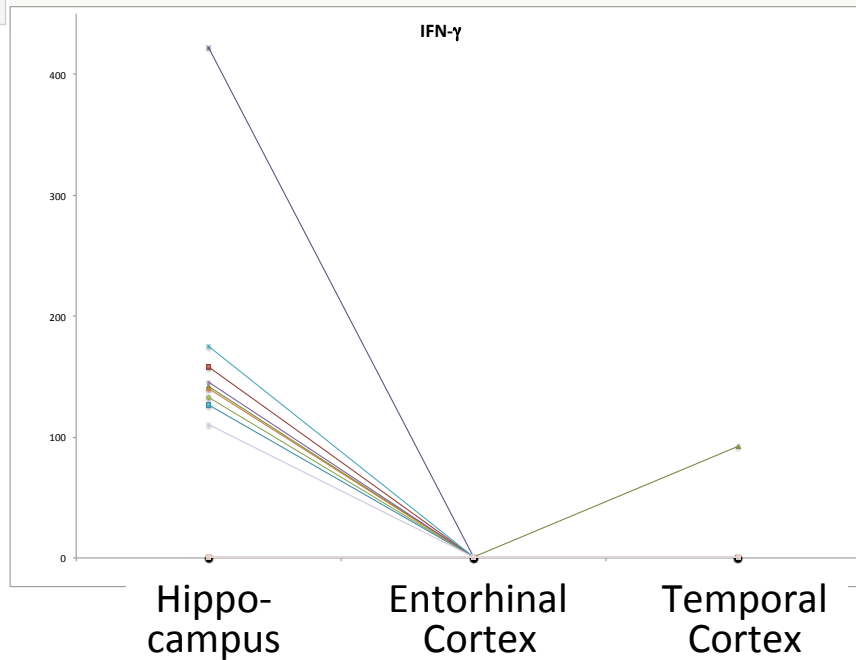
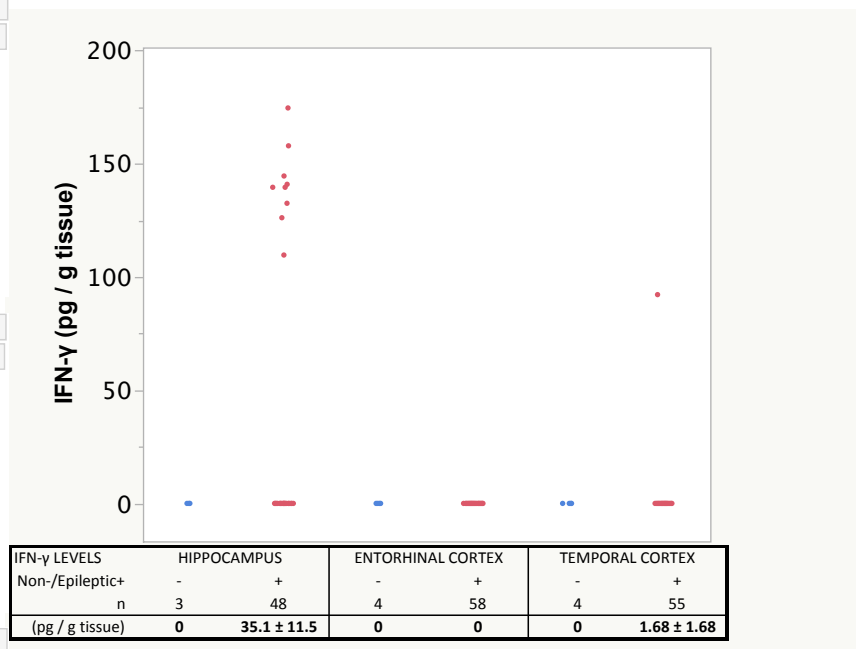


Summary Statistics	
Mean	0
Std Dev	0
Std Err Mean	0
Upper 99.5% Mean	0
Lower 99.5% Mean	0
N	62
Median	0

Temporal Cortex

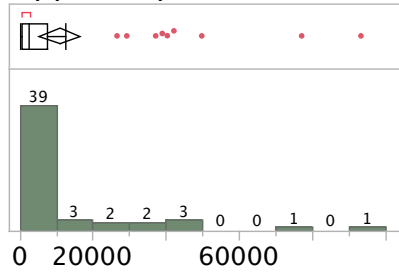


Summary Statistics	
Mean	1.5624119
Std Dev	12.001114
Std Err Mean	1.5624119
Upper 99.5% Mean	6.1221461
Lower 99.5% Mean	-2.997322
N	59
Median	0



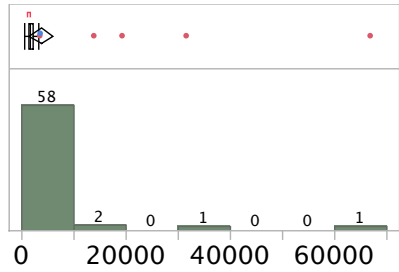
V. VEGF

Hippocampus



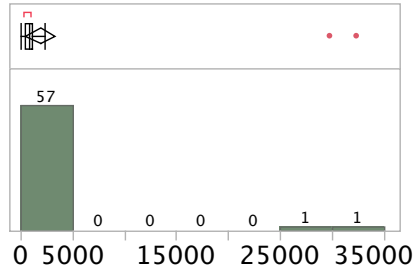
Summary Statistics	
Mean	10760.95
Std Dev	19951.405
Std Err Mean	2793.7555
Upper 99.5% Mean	18966.109
Lower 99.5% Mean	2555.7902
N	51
Median	2514.8936

Entorhinal Cortex

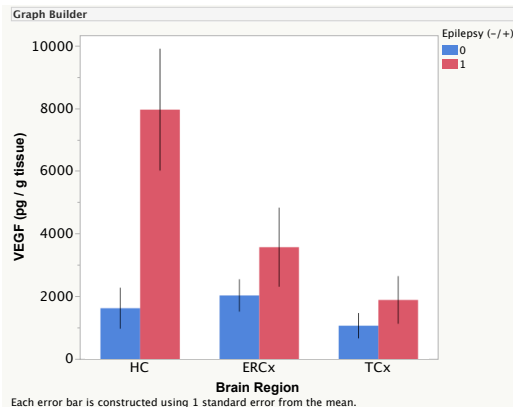
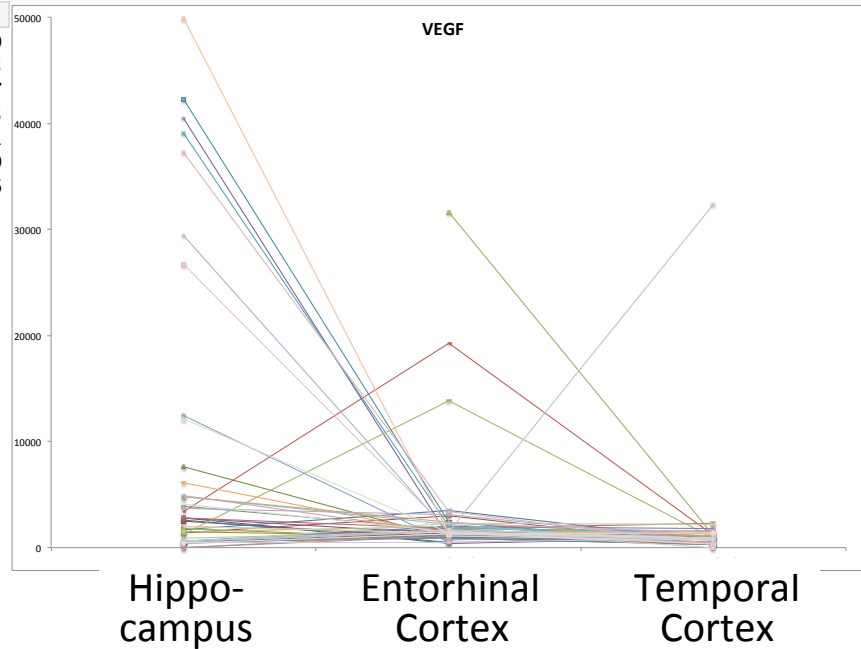
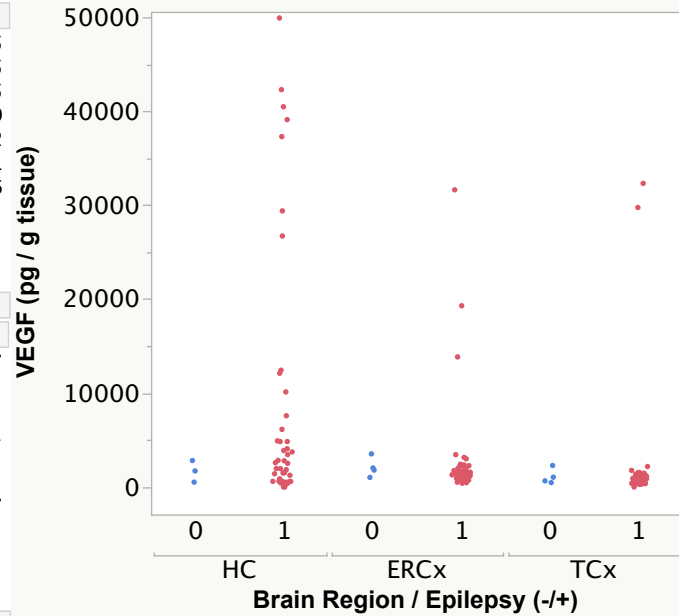


Summary Statistics	
Mean	3553.3387
Std Dev	9441.1732
Std Err Mean	1199.0302
Upper 99.5% Mean	7045.7891
Lower 99.5% Mean	60.888255
N	62
Median	1417.007

Temporal Cortex



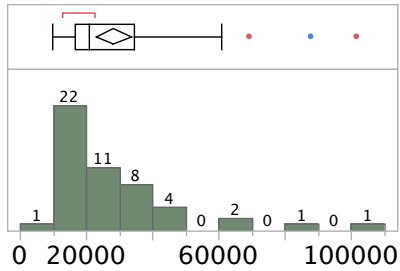
Summary Statistics	
Mean	1888.8149
Std Dev	5530.0145
Std Err Mean	719.94657
Upper 99.5% Mean	3989.903
Lower 99.5% Mean	-212.2731
N	59
Median	871.0026



Each error bar is constructed using 1 standard error from the mean.

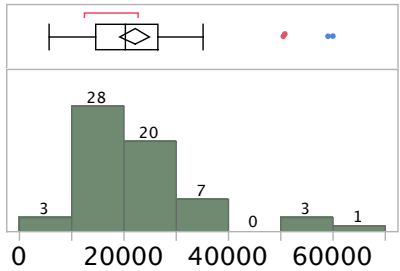
W. CRP

Hippocampus



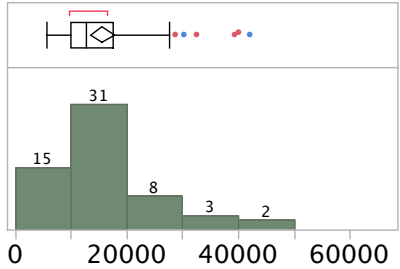
Summary Statistics	
Mean	28043.072
Std Dev	18705.723
Std Err Mean	2645.3888
Upper 99.5% Mean	35819.8
Lower 99.5% Mean	20266.344
N	50
Median	20676.619

Entorhinal Cortex

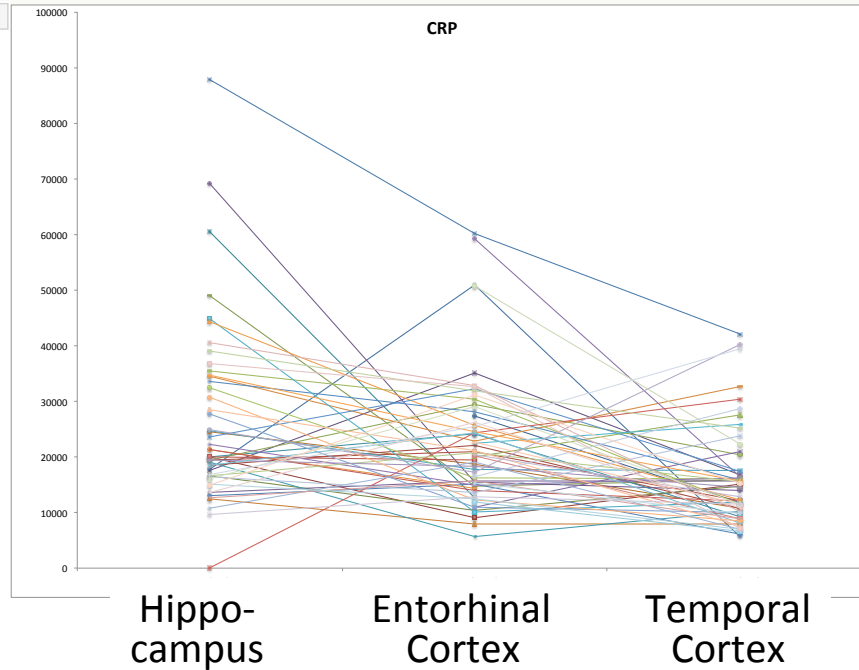
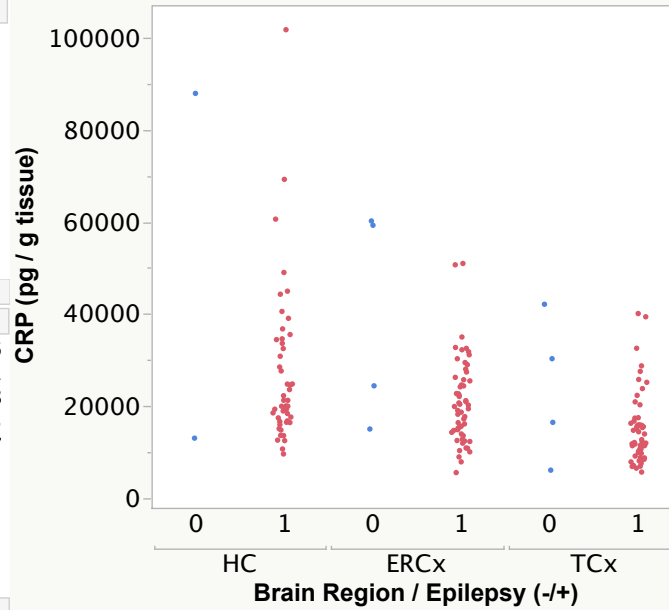


Summary Statistics	
Mean	22069.276
Std Dev	11300.121
Std Err Mean	1435.1168
Upper 99.5% Mean	26249.383
Lower 99.5% Mean	17889.17
N	62
Median	20093.62

Temporal Cortex

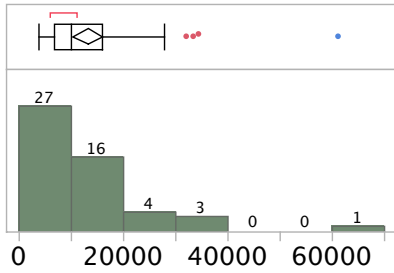


Summary Statistics	
Mean	15624.415
Std Dev	8562.1777
Std Err Mean	1114.7006
Upper 99.5% Mean	18877.551
Lower 99.5% Mean	12371.279
N	59
Median	12750.651



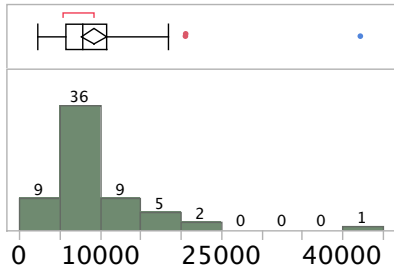
X. ICAM-1

Hippocampus



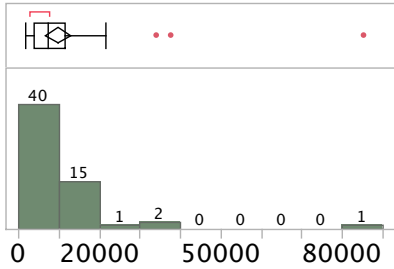
Summary Statistics	
Mean	13053.495
Std Dev	10388.719
Std Err Mean	1454.7117
Upper 99.5% Mean	17325.931
Lower 99.5% Mean	8781.0586
N	51
Median	9842.5197

Entorhinal Cortex

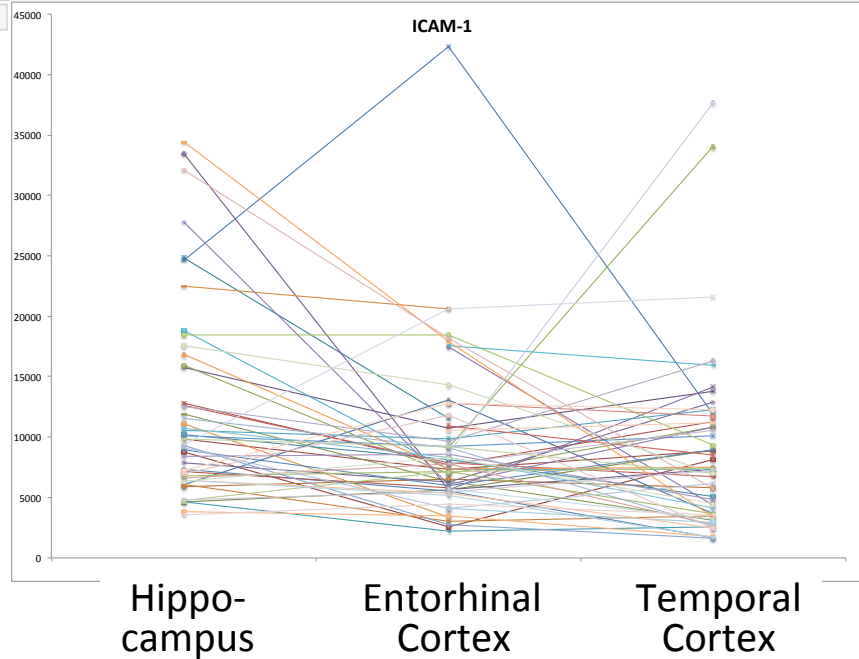
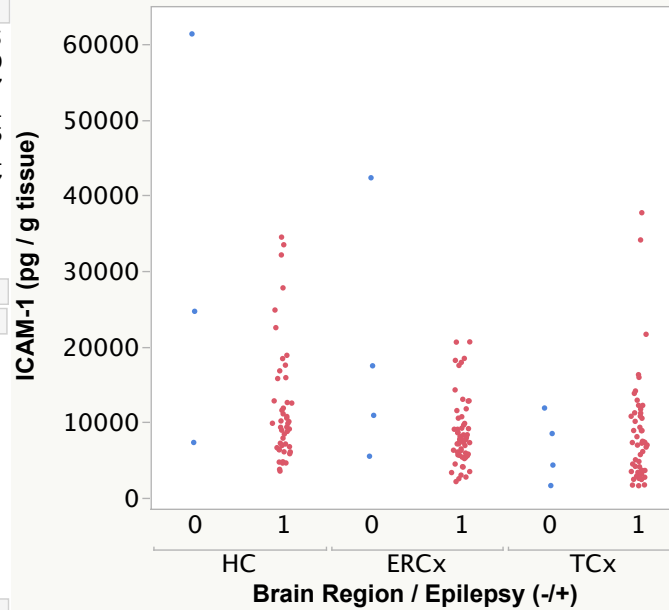


Summary Statistics	
Mean	9242.5856
Std Dev	6191.7494
Std Err Mean	786.35297
Upper 99.5% Mean	11533.019
Lower 99.5% Mean	6952.1522
N	62
Median	7735.5743

Temporal Cortex

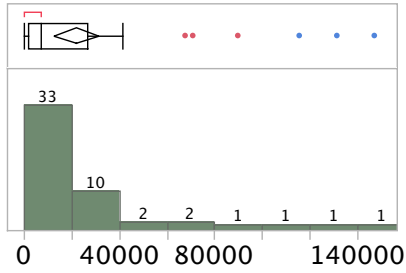


Summary Statistics	
Mean	9599.2779
Std Dev	12119.166
Std Err Mean	1577.781
Upper 99.5% Mean	14203.865
Lower 99.5% Mean	4994.6905
N	59
Median	7243.9565



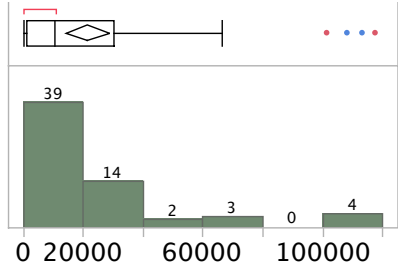
Y. VCAM-1

Hippocampus



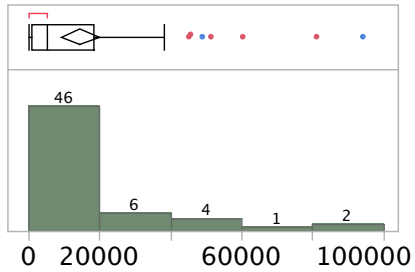
Summary Statistics	
Mean	21887.106
Std Dev	33950.217
Std Err Mean	4753.9813
Upper 99.5% Mean	35849.378
Lower 99.5% Mean	7924.8332
N	51
Median	7342.8571

Entorhinal Cortex

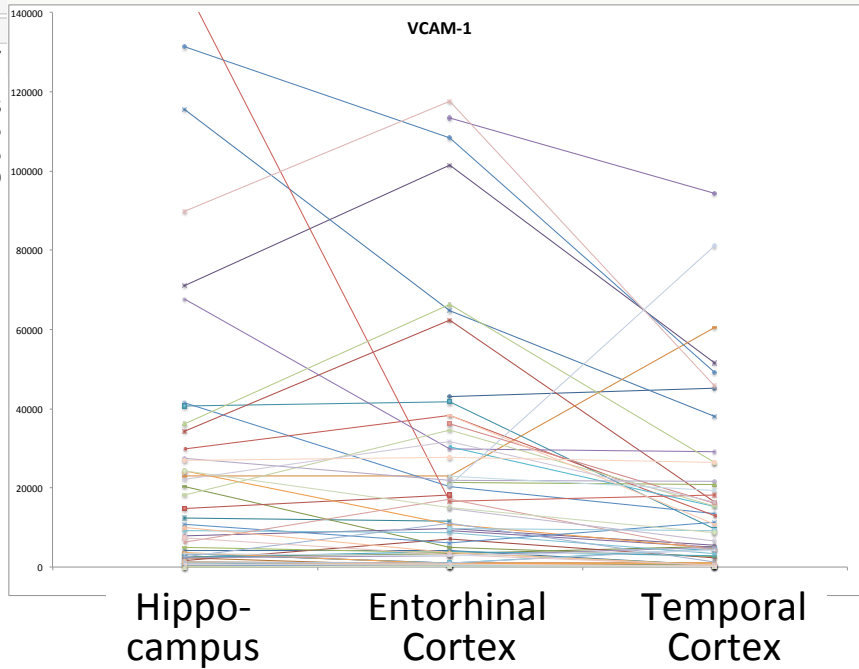
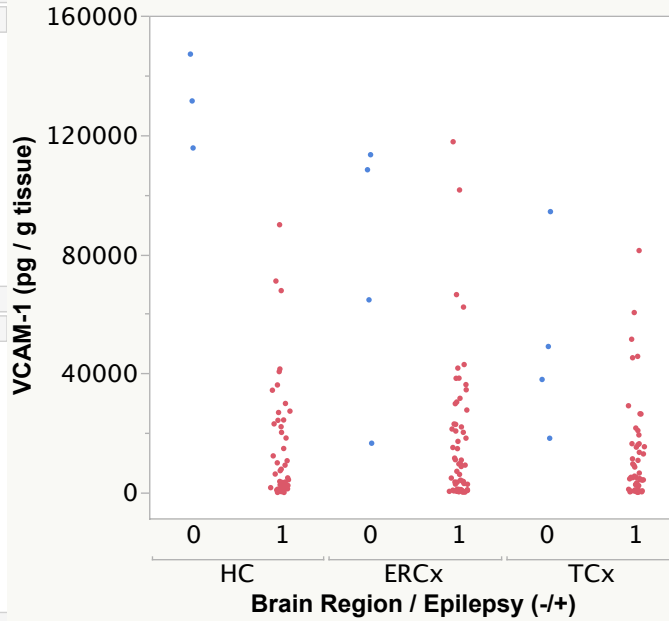


Summary Statistics	
Mean	21350.517
Std Dev	28814.645
Std Err Mean	3659.4636
Upper 99.5% Mean	32009.544
Lower 99.5% Mean	10691.489
N	62
Median	10324.652

Temporal Cortex

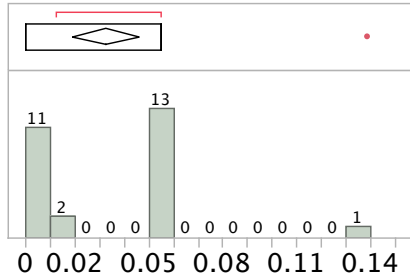


Summary Statistics	
Mean	14427.377
Std Dev	20213.632
Std Err Mean	2631.5908
Upper 99.5% Mean	22107.396
Lower 99.5% Mean	6747.3566
N	59
Median	5119.3743



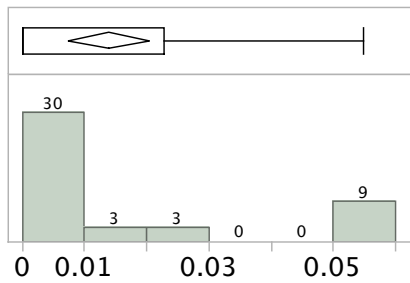
Z. IL-12 p70:p40 Molar Ratio [See note on ratio calculations, Supp Data 3AA]

Hippocampus



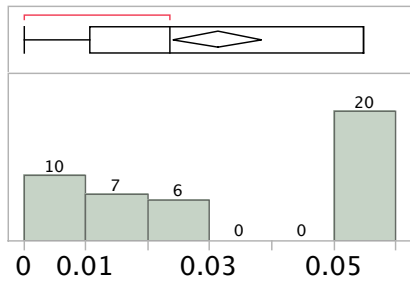
Summary Statistics	
Mean	0.0323905
Std Dev	0.0341189
Std Err Mean	0.0065662
Upper 99.5% Mean	0.0525284
Lower 99.5% Mean	0.0122526
N	27
Median	0.0548411

Entorhinal Cortex

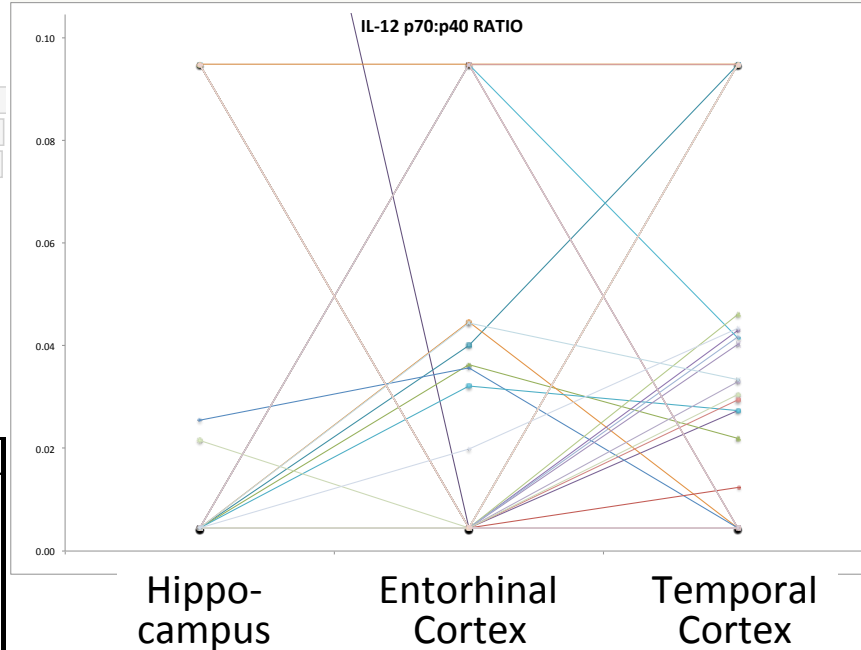
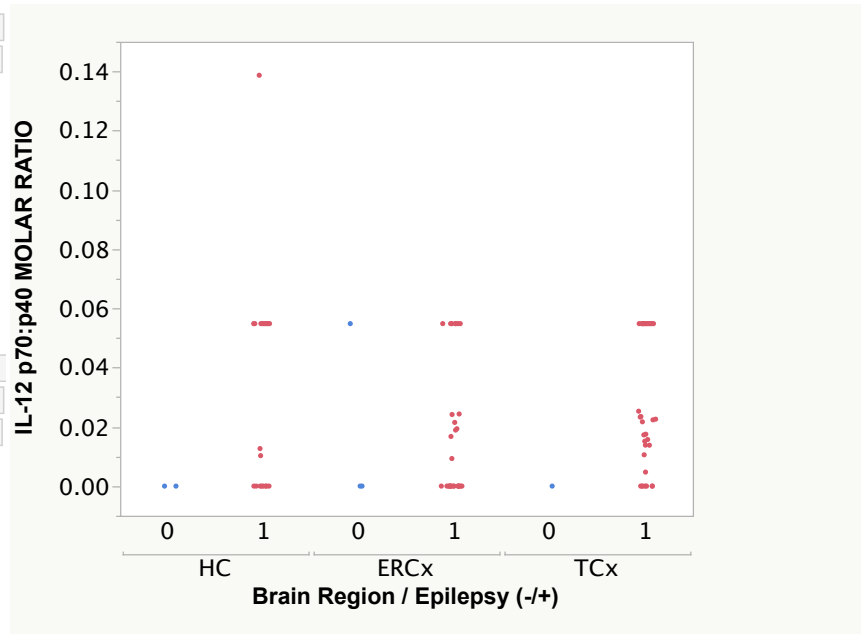


Summary Statistics	
Mean	0.0139531
Std Dev	0.0218698
Std Err Mean	0.0032602
Upper 99.5% Mean	0.0235886
Lower 99.5% Mean	0.0043176
N	45
Median	0

Temporal Cortex



Summary Statistics	
Mean	0.0312585
Std Dev	0.0233748
Std Err Mean	0.0035646
Upper 99.5% Mean	0.0418204
Lower 99.5% Mean	0.0206967
N	43
Median	0.0234773



MOLAR RATIO		Hippocampus	Entorhinal Cx	Temporal Cx
IL-12 p70:p40	Mean	0.032	0.014	0.031
	Std Err	0.007	0.003	0.004
	N	27	45	43
IL-12 p40:p70	Mean	13.2	22.6	31.5
	Std Err	3.8	5.2	5.7
	N	32	25	42

3. Mediator Variability Measures

Table S3B. Brain Inflammatory-related Mediator Relative Tissue Concentrations

		(pg / g tissue)		
	MEDIATOR	MEDIAN	MEAN	C.V. (%)
> 5 ng / g tissue	CRP	17490	21121	60
	VCAM-1	8203	19135	146
	ICAM-1	7885	9755	72
1 – 5 ng / g tissue	MCP-1	4170	6942	139
	IP-10	2987	5700	157
	IL-1 α	1752	2481	99
	MIP-1 β	1364	2429	107
	VEGF	1268	4175	236
0.1 – 1 ng / g tissue	MCP-4	495	677	114
	MIP-1 α	442	1262	158
	TARC	358	672	157
	Eotaxin	340	437	90
	IL-8	299	1008	195
	IL-17A	280	499	113
5 – 100 pg/ g tissue	IL-12/23p40	61.4	87.1	117
	IL-1 β	19.1	27.6	114
	IL-6	8.67	43.2	195
	TNF- β	7.49	5.92	91
	IL-4	7.11	8.22	69
0 – 10 pg / g tissue	IL-12p70	4.53	3.71	99
	TNF- α	3.19	4.70	122
	GM-CSF	0	1962	185
	IL-2	0	15.3	232
	IFN- γ	0	10.3	436
	IL-10	0	2.95	183

Table S3C – F. Mediator Levels by Coefficients of Variation (C.V.)

MEDIATOR	S3C. Overall C.V.	S3D. Variation by Tissue			S3E. Variation by Epilepsy Status		
	Mean C.V. (%)	HC	ERCx	TCx	MEDIATOR	Nonepileptic, 0	Epileptic, 1
VEGF	235.5	<u>169.2</u>	<u>265.7</u>	<u>292.8</u>	VEGF *	61.3	<u>233.1</u>
IL-2	231.5	143.9	<u>346.0</u>	<u>218.4</u>	IL-2	<u>182.6</u>	<u>237.0</u>
IL-6	195.2	<u>174.6</u>	<u>188.2</u>	<u>188.8</u>	IL-6 *	81.1	<u>208.3</u>
IL-8	194.7	<u>151.0</u>	<u>209.9</u>	<u>171.0</u>	IL-8 *	72.8	<u>208.0</u>
IL-10	182.5	126.3	<u>246.0</u>	<u>194.2</u>	IL-10	<u>198.6</u>	<u>181.7</u>
MIP-1α	157.6	133.8	<u>165.3</u>	126.7	MIP-1α	142.3	<u>159.1</u>
IP-10	156.8	89.9	<u>159.8</u>	<u>155.0</u>	IP-10	<u>150.5</u>	<u>151.1</u>
TARC	156.5	119.5	75.7	<u>184.4</u>	TARC	<u>152.7</u>	<u>156.7</u>
VCAM-1	146.3	<u>155.1</u>	135.0	140.1	VCAM-1	56.7	137.6
MCP-1	139.3	106.4	79.2	<u>162.7</u>	MCP-1	63.3	<u>143.4</u>
TNF-α	122.4	90.2	<u>165.0</u>	121.4	TNF-α	126.0	122.6
IL-12/23p40	117.1	144.7	102.0	114.8	IL-12/23p40	124.4	115.8
IL-1β	114.2	111.6	109.9	95.9	IL-1β	115.2	110.9
MCP-4	114.1	75.9	50.6	<u>169.4</u>	MCP-4	58.1	116.9
IL-17A	113.1	82.4	92.1	85.6	IL-17A	114.8	113.3
MIP-1β	106.8	93.9	99.4	101.6	MIP-1β	113.6	106.0
IL-1α	98.99	116.7	80.9	80.0	IL-1α	92.8	98.6
IL-12p70	98.86	93.2	126.5	61.3	IL-12p70	<u>211.4</u>	95.1
TNF-β	91.02	<u>162.3</u>	53.4	87.9	TNF-β	102.4	90.5
Eotaxin	90.23	76.4	78.3	105.2	Eotaxin	81.9	88.0
ICAM-1	72.41	65.0	67.0	82.4	ICAM-1	90.3	69.5
IL-4	69.27	71.8	43.8	52.5	IL-4	85.5	68.3
CRP	59.77	58.6	51.2	54.8	CRP	74.3	53.3
GM-CSF	-						
IFN-γ	-						
		<u>Means</u>			<u>Means</u>		
		113.6	130.0	132.5		111.0	133.3
Grand Mean	125%	(105, <u>146.2</u>) 99.5% C.I.					

C.V. = (sample standard deviation) / (sample mean) • 100%. Underlined C.V.'s indicate above the 99.5% confidence interval between all mediators. “-” indicates an incalculable C.V. due to insufficient measurable values among the tissue samples. *Coefficients of variation for these mediators in hippocampus (HC), entorhinal cortex (ERCx) and temporal cortex (TCx) were 1.5- to 7-fold greater among the epileptic cases compared to nonepileptic cases.

Table S3F. Mediator Coefficients of Variation by Tissue and Epilepsy Status

Mediator	HC, 0	HC, 1	ERCx, 0	ERCx, 1	TCx, 0	TCx, 1
VEGF	68.5	165.1	50.1	267.0	73.9	294.2
IL-2	173.2	143.1	119.5	393.4	200.0	145.7
IL-6	44.6	191.9	126.5	195.7	98.8	193.3
IL-8	19.2	130.0	111.1	220.5	108.7	173.5
IL-10	173.2	124.1	200.0	248.9	200.0	195.7
MIP-1 α	122.7	134.1	133.5	127.7	100.2	124.4
IP-10	62.6	92.6	125.4	138.2	137.3	157.7
TARC	50.0	119.6	67.9	71.7	189.8	185.2
VCAM-1	12.0	133.4	59.6	134.4	64.6	141.6
MCP-1	18.5	112.9	75.7	79.8	97.6	162.4
TNF- α	110.3	90.1	101.2	172.3	173.2	117.4
IL-12/23p40	113.4	149.3	128.0	98.9	169.4	111.4
IL-1 β	91.0	112.0	89.4	108.8	158.9	88.8
MCP-4	17.4	77.9	41.4	49.8	113.9	169.1
IL-17A	103.1	82.3	83.3	92.0	71.5	85.5
MIP-1 β	83.9	94.9	53.5	102.8	122.2	99.7
IL-1 α	67.1	119.7	99.5	79.2	95.2	79.6
IL-12p70	173.2	90.5	200.0	124.0		55.1
TNF- β	173.2	163.8	115.7	50.3	77.4	87.6
Eotaxin	40.3	79.1	71.9	64.6	143.8	92.5
ICAM-1	76.6	65.2	85.3	52.1	68.5	83.0
IL-4	70.5	71.5	39.6	44.2	145.2	34.9
CRP	104.8	50.4	58.9	44.1	66.3	51.4

(92, **131.8**) 99.5% C.I.

Of the 9 mediators that showed highest variability (Supplemental Data **3C**), only VEGF, IL-6, and VCAM-1 showed increased variation across all 3 brain regions only in epileptic cases. These deviations might be attributed to the larger number of observations in the epileptic cases, however, though the numbers of observations were comparable, for 10 of 23 measurable mediators, the C.V.'s across all tissues and epilepsy status were inside the 99.5% CI. Only these 3 mediators showed consistently higher coefficients of variation in all 3 brain regions of epileptic cases. No mediator(s) showed increased variability across all 3 brain regions of nonepileptic cases.

Table S3G. GM-CSF Homogeneity Analyses

Brain Region	Group	Outcomes n (%)	
A. Epilepsy Status			
		GM-CSF +	GM-CSF -
	Nonepileptic	4 (36%)	7 (64%)
	Epileptic	40 (25%)	121 (75%)
χ^2 (with Yate's correction)		0.2401 (df = 1, p = 0.380)	
B. Brain Region			
		GM-CSF +	GM-CSF -
Hippocampus		15 (29%)	36 (71%)
Entorhinal Cortex		4 (7%)	58 (93%)
Temporal Cortex		25 (42%)	34 (58%)
χ^2 (with Yate's correction)		19.03 (df = 2, p < 0.0001)	
C. Brain Region + Epilepsy			
		GM-CSF +	GM-CSF -
Hippocampus	Nonepileptic	0 (0)	3 (100%)
Hippocampus	Epileptic	15 (31%)	33 (69%)
Entorhinal Cortex	Nonepileptic	1 (25%)	3 (75%)
Entorhinal Cortex	Epileptic	3 (5%)	55 (95%)
Temporal Cortex	Nonepileptic	3 (75%)	1 (25%)
Temporal Cortex	Epileptic	22 (40%)	33 (60%)
χ^2 (with Yate's correction)		20.74 (df = 5, p = 0.0008)	

S3H. IFN- γ Homogeneity Analyses

Brain Region	Group	Outcomes n (%)	
A. Epilepsy Status			
		IFN-γ +	IFN-γ -
	Nonepileptic	0 (0)	11 (100%)
	Epileptic	10 (6%)	151 (94%)
χ^2 (with Yate's correction)		0.6765 (df = 1, p > 0.05)	
B. Brain Region			
		IFN-γ +	IFN-γ -
Hippocampus		9 (18%)	42 (82%)
Entorhinal Cortex		0 (0)	62 (100%)
Temporal Cortex		1 (2%)	58 (98%)
χ^2 (with Yate's correction)		14.96 (df = 2, p = 0.0006)	
C. Brain Region + Epilepsy			
		IFN-γ +	IFN-γ -
Hippocampus	Nonepileptic	0 (0)	3 (100%)
Hippocampus	Epileptic	9 (23%)	39 (77%)
Entorhinal Cortex	Nonepileptic	0 (0)	4 (100%)
Entorhinal Cortex	Epileptic	0 (0)	58 (100%)
Temporal Cortex	Nonepileptic	0 (0)	4 (100%)
Temporal Cortex	Epileptic	1 (2%)	53 (98%)
χ^2 (with Yate's correction)		17.07 (df = 5, p = 0.004)	

CONCLUSIONS

For GM-CSF:

A. there is homogeneity in GM-CSF levels between nonepileptic and epileptic brains;

B. there is NON-homogeneity in GM-CSF levels between the brain regions examined;

C. there is NON-homogeneity in GM-CSF levels between different brain regions AND epilepsy status.

For Interferon- γ :

A. there is homogeneity in IFN- γ levels between nonepileptic and epileptic brains;

B. there is NON-homogeneity in IFN- γ levels between the brain regions examined;

C. there is NON-homogeneity in IFN- γ levels between different brain regions AND epilepsy status.

4. Miscellaneous Supplemental Material

Table S4I. Phase-2 : Brain Inflammatory-related Mediator Associations

Eotaxin, IL-1 α , MCP-1, and MCP-4 showed overall greater levels in cases with prior electrode placement (n = 31), compared to cases with no prior neurosurgical intervention (n = 31). VEGF levels among the Phase-2 (-) group were greater in the hippocampus than in cortical regions.

Table S4J-K. Inflammatory-related Mediator Brain & Consensus Blood Levels

Comparisons of median brain and estimated blood levels of inflammatory-related mediators (table of citations referenced in **Table S4J**, below)

Supplemental Figure 4A. Age-Related Correlations

Upper Row: VCAM-1 levels in human brain; hippocampus correlated to age at surgery ($p < 0.02$). Lower Row: IL-8 levels in human brain; hippocampus correlated to age at surgery ($p < 0.05$). Due to age differences between epileptic and nonepileptic groups (**Table 1A**), and as a test of robustness, correlation analyses were repeated, excluding the older nonepileptics. No significant correlations were observed in this sub-analysis, thus, the older nonepileptic cases greatly influenced the correlation of hippocampal VCAM-1 and IL-8 with age.

Supplemental Figure 4B. Epilepsy Risk Factor Associations

VEGF: mCHI subgroup > All subgroups ($p = 0.0001$); hippocampus- hippocampus, mCHI > hippocampus, All subgroups ($p < 0.005$ for all except hypoxic/ischemic $p < 0.035$)

IL-12/23 p40: Infection > Febrile, CHI ($p = 0.035$); ENTORHINAL CORTEX- entorhinal cortex, Infection > entorhinal cortex [CHI, Devel, Cancer] ($p < 0.0004$ for all)

IP-10: Infection > All subgroups ($p = 0.0002$); entorhinal cortex, Infection > entorhinal cortex, All subgroups ($p < 0.035$ for all)

IL-1 α : Infection > CHI, Febrile ($p = 0.041$)

MIP-1 β : mCHI > Febrile, Devel, Infection, Cancer ($p < 0.002$, < 0.02 , < 0.02 , < 0.04 , respectively)

IL-6: CHI > Febrile ($p < 0.03$)

Supplemental Figure 4C. Relational Correlations of Inflammatory-related Mediators Between Tissues

Boxes and horizontal lines indicate cross-tissue correlations, *italics* show connections between relational groups.

Table S4I. Phase-2 and Brain Inflammation-related Mediator Associations

MEDIATOR	Over All Brain Regions ¹	By Brain Region ²		
		Hippo-campus	Entorhinal Cortex	Temporal Cortex
Eotaxin	(+) > (-)	-	(+) > (-) *	(+) > (-) *
MCP-1	(+) > (-)	-	(+) > (-) [§]	(+) > (-) [§]
MCP-4	(+) > (-)	-	(+) > (-) [§]	(+) > (-) [§]
IL-1α	(+) > (-)	-	(+) > (-) ^a	(+) > (-) ^a
CRP	(+) > (-)	-	-	(+) > (-) *
ICAM-1	(+) > (-)	-	-	(+) > (-) [§]

(+) indicates the group of epilepsy cases with electrode placement prior to resection, (-) indicates cases with no electrode placement. Results of Phase-2 \times Brain Region ANOVA: ¹Phase-2 effect $p < 0.05$ post hoc Tukey HSD; ²Phase-2 \times Brain Region interaction, * $p \leq 0.01$, [§] $p < 0.05$, ^a $p < 0.10$ post hoc Tukey HSD. HC = hippocampus, ERCx = entorhinal cortex, TCx = temporal cortex.

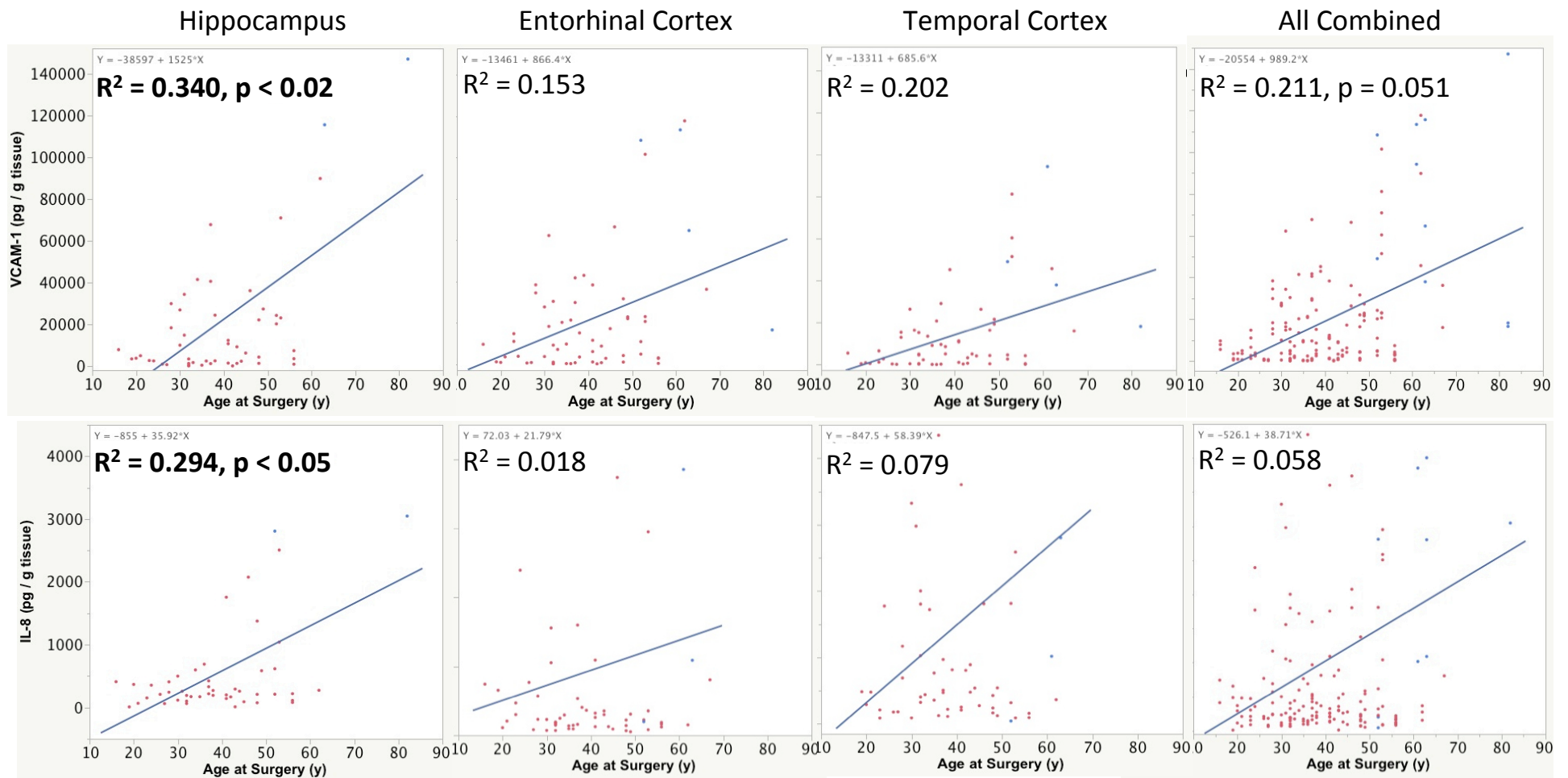
Table S4J. MEDIATOR LEVEL COMPARISONS

MEDIATOR	BRAIN (median) (pg / g tissue)	BLOOD (pg / mL)	CSF (pg / mL)	BLOOD & CSF REFERENCES estimated consensus levels (see Table S4J for citations)
Eotaxin	340	70 - 300	0 - 16	Heidigger 2015, Agarwal 2013, Hashimoto 2006, Rosa 2008, Hang 2014, Comar 2014, Kothur 2016, Yoshio 2016
IP-10	2987	50 - 1000	45 - 4000	Romagnani 2002, Simmons 2013, Xu 2005, Purohit 2015, Hang 2014, Comar 2014, Kothur 2016, Yoshio 2016
MCP-1	4170	165 - 1000	65 - 820	Garcia-Alonso 2009, Floris-Moore 2009, Purohit 2015, Pawlak 2006, Hang 2014, Dworacka 2014, Fontes2015, Schnabel 2008, Kothur 2016, Yoshio 2016
MCP-4	495	24 - 350		Breland 2010, Hashimoto 2006
MIP-1 α	442	3 - 600	0 - 16	Zinyama-Gutsire 2009, Terpos 2005, Pawlak 2006, Comar 2014, Quirico-Santos 2013, Kothur 2016, Yoshio 2016
MIP-1 β	1364	4 - 225	4 - 27	Flammand 2001, Pawlak 2006, Hang 2014, Kothur 2016, Yoshio 2016
TARC	358	10 - 720		Miyazaki 2007, Feng 2015
GM-CSF	0	0.5 - 75	180 - 444	Bilgici 2014, Surendar 2012, Navarro-Sobrinio 2009, Szaryska 2015, Kothur 2016
IFN- γ	0	0 - 230	0 - 40	Resende 2012, Nishida 2015, Uyanik 2015, Grant 2012, Comar 2014, Kothur 2016, Yoshio 2016
IL-1 α	1752	2 - 800		Rosa 2008, Jung 2010, Karamehic 2008, Chao 2008, Comar 2014,
IL-1 β	19	0.1 - 1150	0.03 - 13	Surendar 2012, Rosa 2008, Alapirtti 2009, Grant 2012, Uludag 2013, Bauer 2009, Quirico-Santos 2013, Nowak 2011, Kothur 2016, Yoshio 2016
IL-2	0	0 - 37	0 - 5.1	Petrikis 2015, Ichinose 2015, Grant 2012, Kothur 2016, Yoshio 2016
IL-4	7	1 - 400	0 - 3.7	Rosa 2008, Uyanik 2015, Zhang 2015, Nishida 2015, El-Kady 2005, Comar 2014, Kothur 2016, Yoshio 2016
IL-6	9	2 - 51	1.3 - 800	Xu 2005, Shiah 2005, Surendar 2012, Nishida 2015, Uyanik 2015, Rosa 2008, Chao 2008, Billiau 2007, Ichiyama 2008, Quirico-Santos 2013, Petrikis 2015, Sayed 2015, Grant 2012, Comar 2014, Fontes2015, Schnabel 2008, Uludag 2013, Bauer 2009, Nowak 2011, Kothur 2016, Yoshio 2016
IL-8	299	3 - 61	5 - 60	Sayed 2015, Nishida 2015, Billiau 2007, Hang 2014, Grant 2012, Tylman 2011, Comar 2014, Siregar 2015, Kothur 2016, Yoshio 2016
IL-10	0	3 - 60	0.1 - 4.4	Chao 2008, Billiau 2007, Rosa 2008, Uyanik 2015, Szaryska 2015, Grant 2012, Kothur 2016, Yoshio 2016
IL-12/23p40	61	1 - 230		Comar 2014
IL-12p70	5	1 - 14	0.05 - 16	Hang 2014, Rosa 2008, Billiau 2007, Kothur 2016
IL-17A	280	1.4 - 74	1 - 4	Rosa 2008, Grant 2012, Tylman 2011, Comar 2014, Kothur 2016, Yoshio 2016
TNF- α	3	4 - 15	0 - 16	Rosa 2008, Surendar 2012, Szary_ska 2015, Nishida 2015, Uyanik 2015, Chao 2008, Grant 2012, Hang 2014, Siregar 2015, Schnabel 2008, Quirico-Santos 2013, Nowak 2011, Kothur 2016, Yoshio 2016
TNF- β	7	0.6 - 5.1		Nishida 2015, Kim 2009, Comar 2014
VEGF	1268	22 - 450	1.5 - 64	Bilgici 2014, Hang 2014, Siregar 2015, Legros 2012, Wahl 2011, Legros 2014, Kothur 2016
CRP	17490	2.5k - 31k		Sayed 2015, Grant 2012, Ram 2013, Siemes 2006, Fontes 2015, Schnabel 2008
ICAM-1	7885	85k - 1.25M		Tylman 2011, Fontes 2015, Schnabel 2008, Aksoy 2015
VCAM-1	8203	0.4M - 11M		Dworacka 2014, Tylman 2011, Aksoy 2015

Table S4K. REFERENCES, BLOOD MEDIATOR LEVELS

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4A. Age-Related Correlations



4B. Epilepsy Risk Factor Associations

