Supplementary Information

For

**Chronic synaptic insulin resistance after traumatic brain injury abolishes insulin protection from amyloid beta and tau oligomer-induced synaptic dysfunction**

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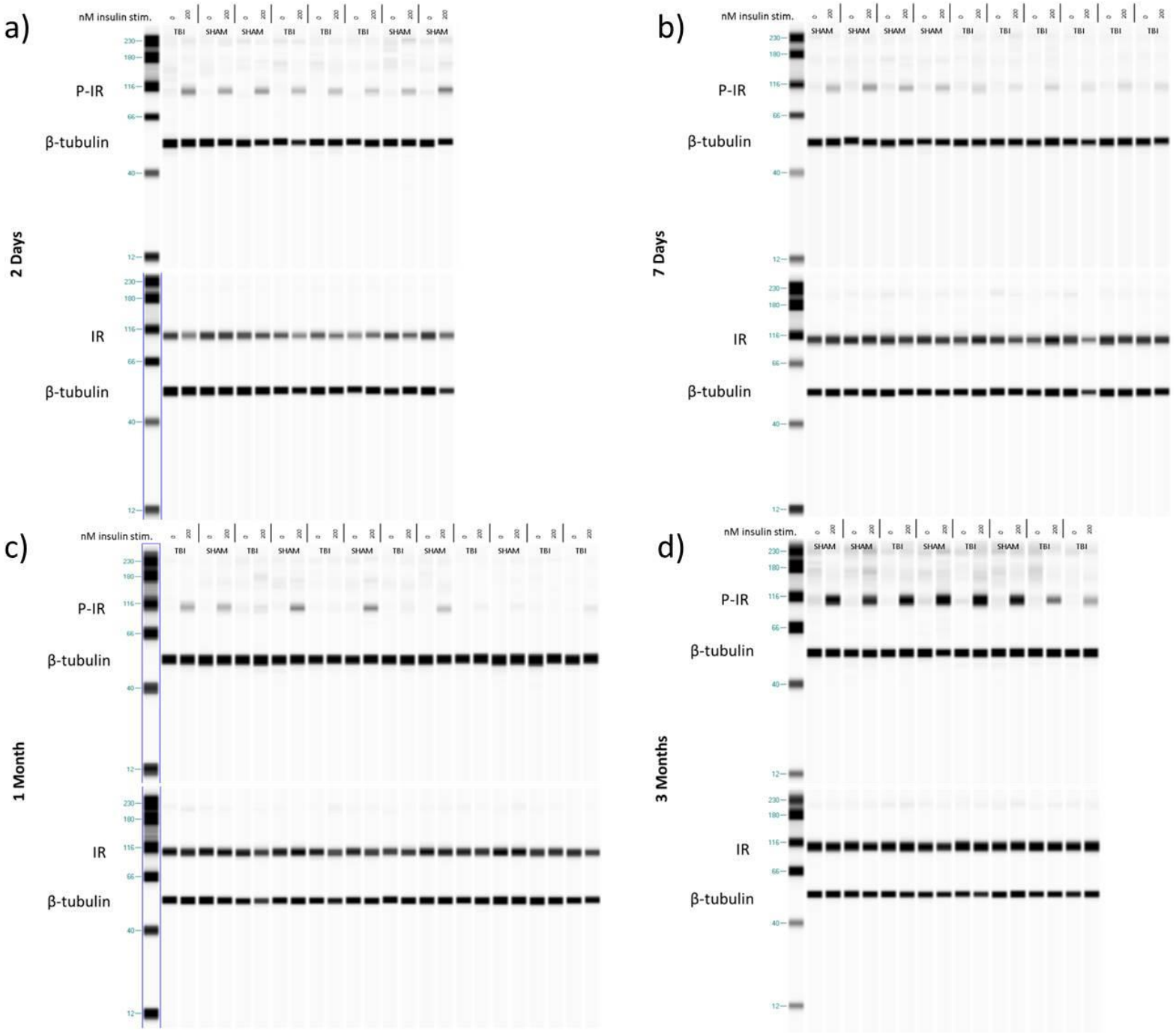
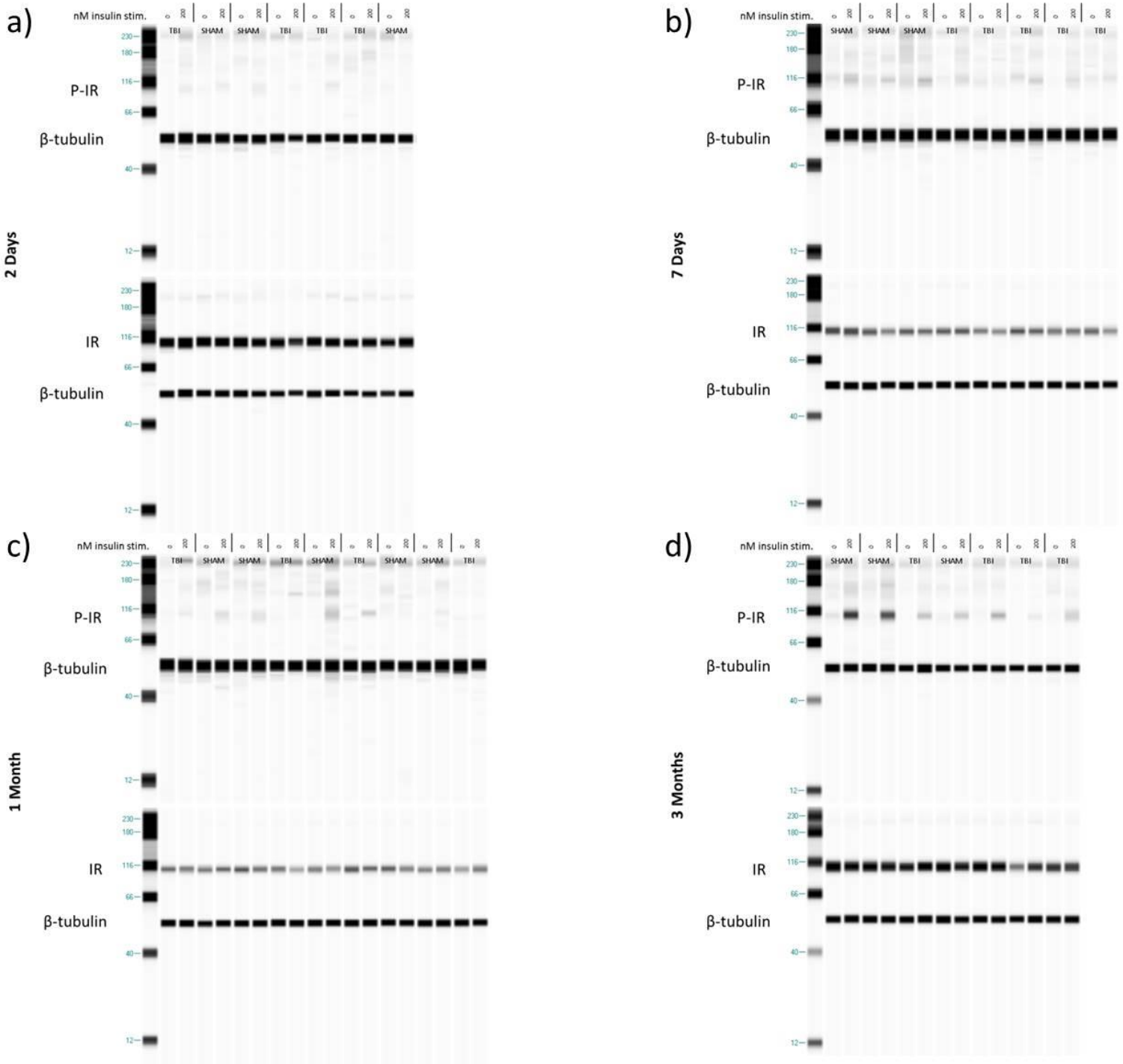
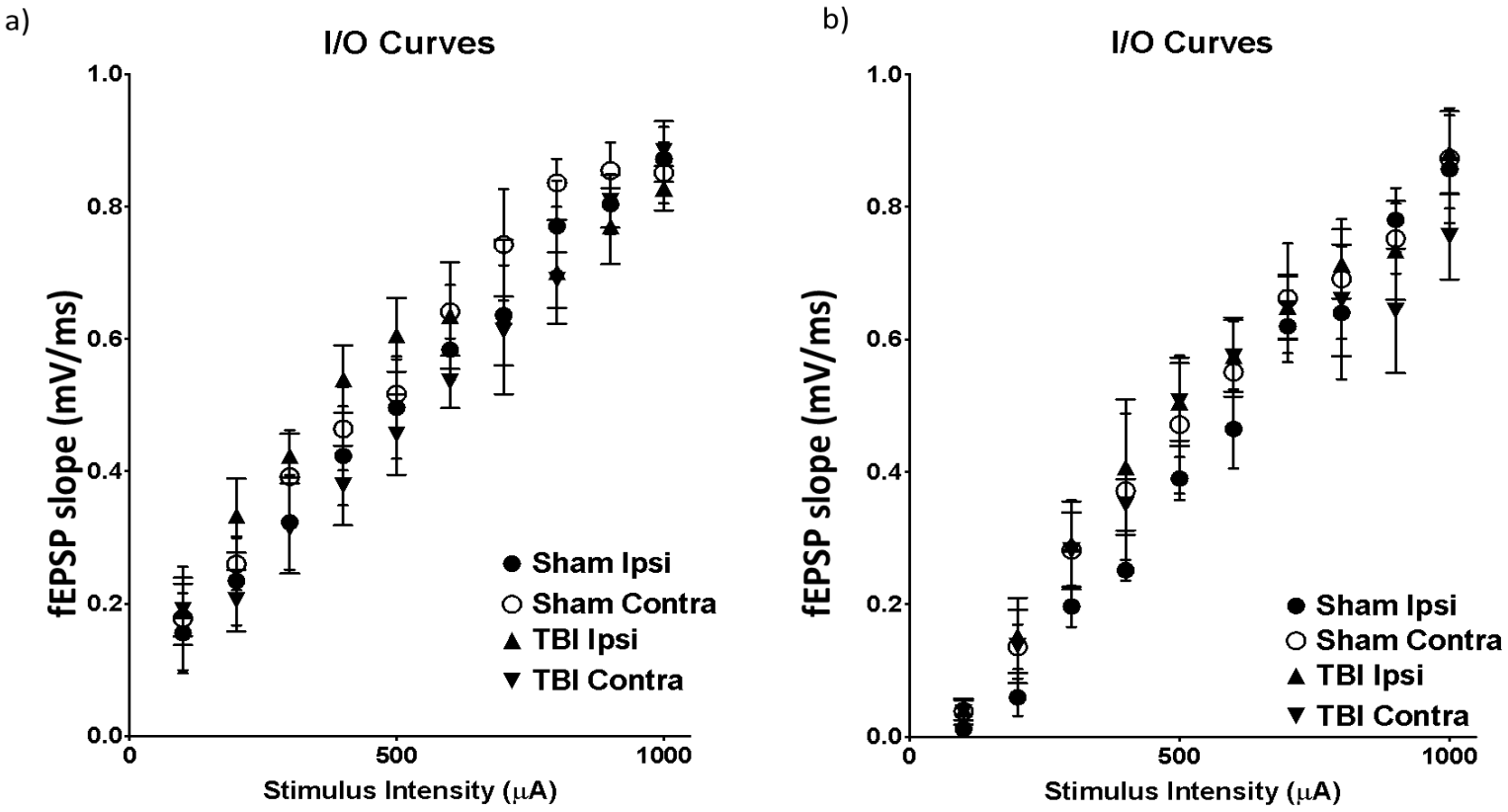



**Supplementary Figure S1: Uncropped WES analysis of Insulin Responsiveness in Ipsilateral Hippocampi (Figure 1a).** WES analysis of insulin-stimulated and unstimulated synaptosomes isolated from the ipsilateral hippocampus at **(a)** 2 DPI (n =4 for both sham and TBI), **(b)** 7 DPI (n= 4 sham, n=6 TBI), **(c)** 1 MPI (n= 5 sham, n=7 TBI), and **(d)** 3 MPI (n= 4 for both sham and TBI) animals. β-tubulin was used as a loading control for each WES run.




**Supplementary Figure S2: Uncropped WES analysis of Insulin Responsiveness in Contralateral Hippocampi (Figure 1e).** WES analysis of insulin-stimulated and unstimulated synaptosomes isolated from the ipsilateral hippocampus at **(a)** 2 DPI (n =3 sham, n=4 TBI), **(b)** 7 DPI (n= 3 sham, n=5 TBI), **(c)** 1 MPI (n= 5 sham, n=4 TBI), and **(d)** 3 MPI (n= 3 sham, n= 4 TBI) animals. β-tubulin was used as a loading control for each WES run.

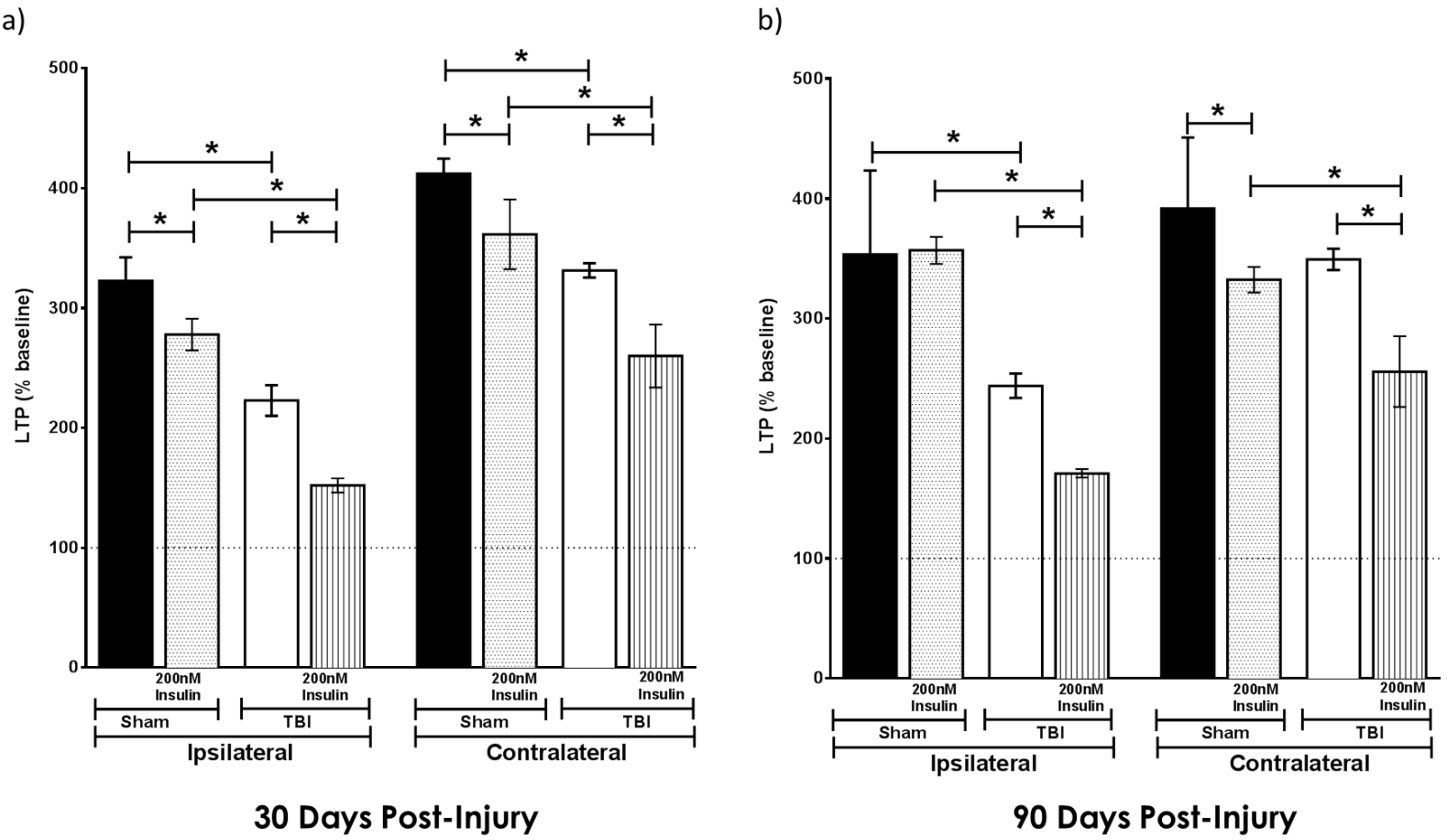



**Supplementary Figure S3: Input/output curves for ipsilateral and contralateral hippocampi for sham and TBI animal slices.** The fEPSP slope (mV/ms) obtained at increasing stimulus intensities (μA) at both **(a)** 1 month post-injury and **(b)** 3 months post-injury show no significant differences in the basal synaptic strength. 1 MPI n= 4 animals; 3 MPI n= 3-5 animals. Two-way ANOVA with Tukey's post hoc analysis was used to determine statistical significance. [For 1 MPI: $F_{3, 12}$=0.4943 P=0.6929] [For 3 MPI: $F_{3, 15}$=0.3794 P=0.7692]. Error bars represent standard error.

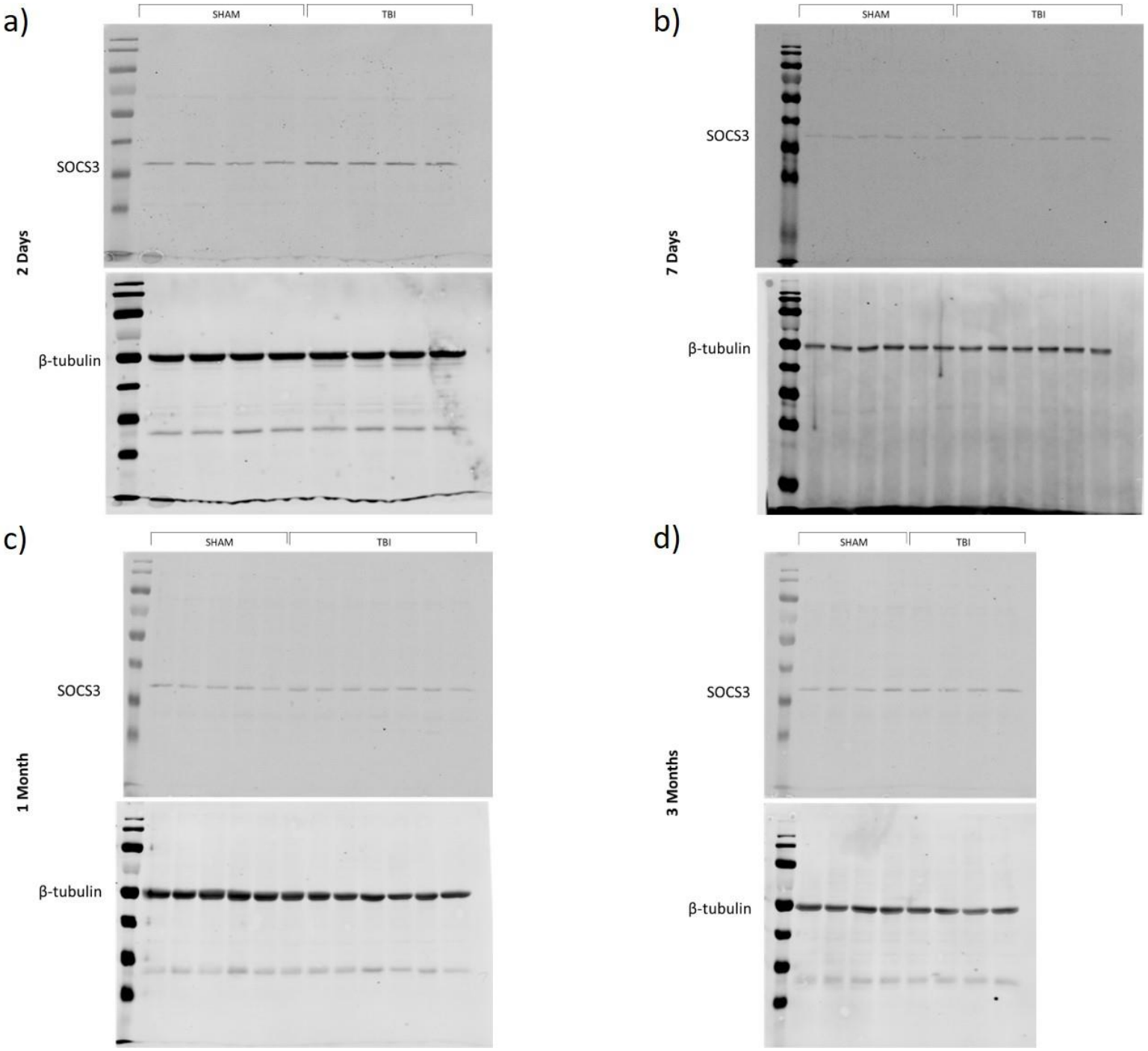
| | Stimulus Intensity (μA) | Sham Ipsi N=4 | | Sham Contra N=4 | | TBI Ipsi N=4 | | TBI Contra N=4 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SEM | Mean | SEM | Mean | SEM | Mean | SEM |
| 1 Month Post-Injury | 100 | 0.15538 | 0.06061 | 0.17774 | 0.07839 | 0.18857 | 0.05088 | 0.19052 | 0.03968 |
| | 200 | 0.23462 | 0.06699 | 0.25993 | 0.03961 | 0.33334 | 0.056 | 0.2046 | 0.04662 |
| | 300 | 0.32319 | 0.0717 | 0.39207 | 0.07035 | 0.424 | 0.03303 | 0.3137 | 0.06839 |
| | 400 | 0.4236 | 0.07473 | 0.4642 | 0.06285 | 0.53959 | 0.05103 | 0.3788 | 0.06026 |
| | 500 | 0.4963 | 0.0773 | 0.51687 | 0.05246 | 0.60612 | 0.05584 | 0.45581 | 0.06096 |
| | 600 | 0.58383 | 0.04578 | 0.64143 | 0.04051 | 0.63561 | 0.08049 | 0.53544 | 0.03988 |
| | 700 | 0.63621 | 0.0753 | 0.74263 | 0.08424 | 0.63347 | 0.11664 | 0.61223 | 0.05223 |
| | 800 | 0.77062 | 0.06893 | 0.83599 | 0.03643 | 0.70151 | 0.07803 | 0.6889 | 0.04207 |
| | 900 | 0.80377 | 0.0453 | 0.85449 | 0.0425 | 0.77073 | 0.05749 | 0.80816 | 0.04009 |
| | 1000 | 0.87211 | 0.04834 | 0.85124 | 0.04608 | 0.82797 | 0.03364 | 0.88349 | 0.04598 |

| | Stimulus Intensity (μA) | Sham Ipsi N=3 | | Sham Contra N=3 | | TBI Ipsi N=5 | | TBI Contra N=8 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SEM | Mean | SEM | Mean | SEM | Mean | SEM |
| 3 Months Post-Injury | 100 | 0.01205 | 0.00576 | 0.03876 | 0.01862 | 0.04144 | 0.01613 | 0.03684 | 0.01841 |
| | 200 | 0.05983 | 0.02806 | 0.13585 | 0.03354 | 0.15318 | 0.05669 | 0.13649 | 0.05556 |
| | 300 | 0.19674 | 0.03101 | 0.28162 | 0.07565 | 0.29104 | 0.06446 | 0.28094 | 0.05795 |
| | 400 | 0.25149 | 0.01553 | 0.37158 | 0.11674 | 0.40737 | 0.10237 | 0.35058 | 0.03902 |
| | 500 | 0.38991 | 0.03247 | 0.47136 | 0.10418 | 0.50553 | 0.05869 | 0.50577 | 0.06681 |
| | 600 | 0.46487 | 0.05972 | 0.55063 | 0.07699 | 0.57517 | 0.05408 | 0.57327 | 0.05971 |
| | 700 | 0.62002 | 0.05415 | 0.66217 | 0.08278 | 0.6497 | 0.04848 | 0.64719 | 0.04798 |
| | 800 | 0.64021 | 0.10051 | 0.69131 | 0.09032 | 0.71411 | 0.05218 | 0.65916 | 0.08442 |
| | 900 | 0.78051 | 0.04833 | 0.75233 | 0.053 | 0.73439 | 0.0745 | 0.64343 | 0.09388 |
| | 1000 | 0.85716 | 0.08151 | 0.8735 | 0.07562 | 0.88217 | 0.06257 | 0.75534 | 0.06505 |

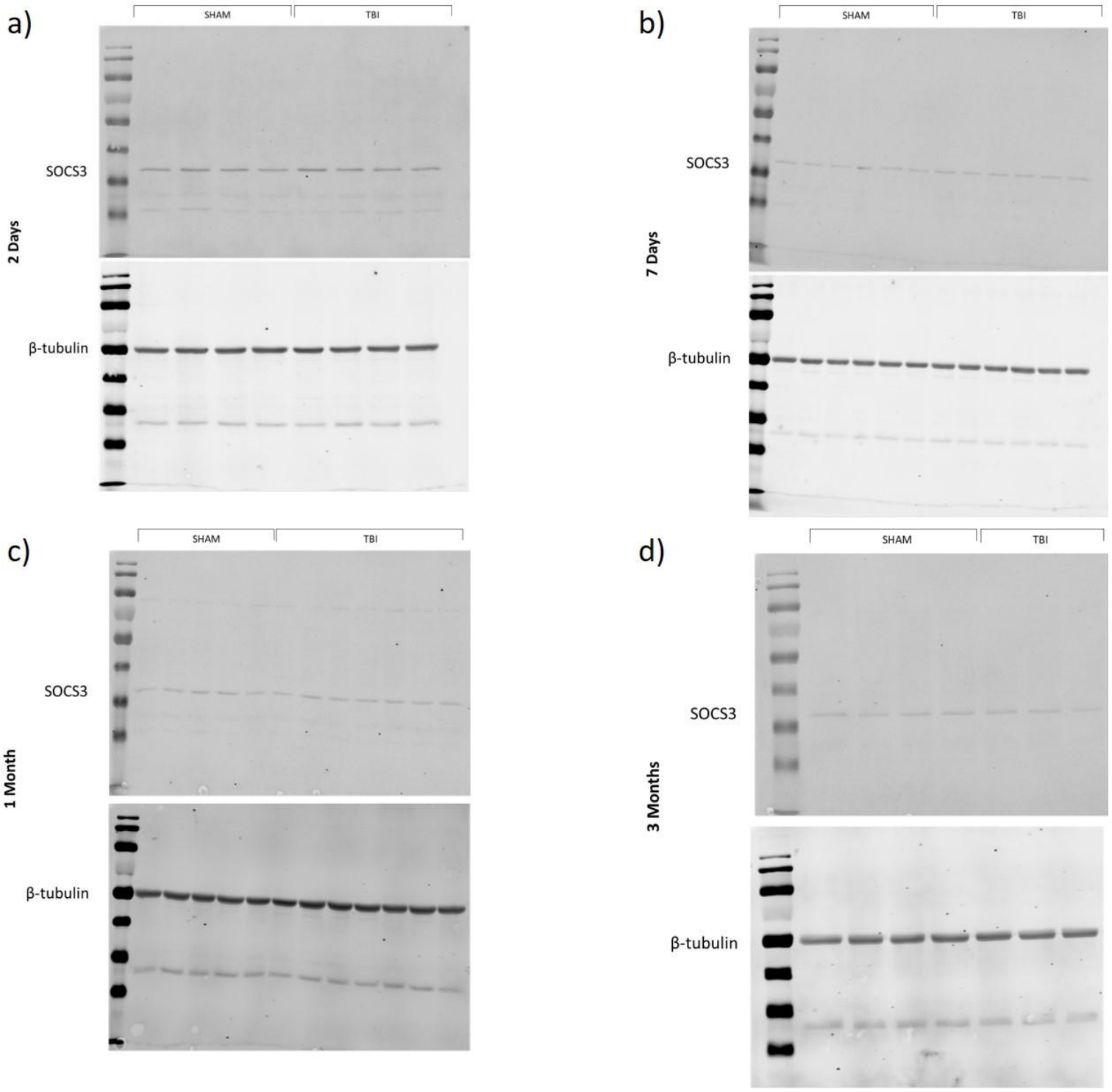
**Supplementary Table S1: Input-Output Averages for ipsilateral and contralateral hippocampi for sham and TBI animal slices.** The averages of the slopes (mV/ms) measured after increasing stimulus intensities. There was no change in the slopes. N= number of slices per condition. Two-way ANOVA with Tukey's post hoc analysis was used to determine statistical significance. [For 1 MPI: $F_{3, 12}$=0.4943 P=0.6929] [For 3 MPI: $F_{3, 15}$=0.3794 P=0.7692].




**Supplementary Figure S4: Long-term potentiation (LTP) in hippocampal slices either untreated or exposed to an acute insulin treatment.** Schaffer collateral field recordings were performed to measure LTP in slices from sham and TBI animals. Graphs showing the average of the fEPSP slope for the final 10 minutes (time points 60-70 minutes post high frequency stimulation) as an indication of LTP for each condition at **(a)** 1-month post-injury and **(b)** 3 months post-injury. 1 MPI n= 4 animals and 3-6 slices per condition; 3 MPI n= 3-5 animals and 3-7 slices per condition. One-way ANOVA with Bonferroni's post hoc analysis was used to determine statistical significance. Error bars represent standard error. *$p < 0.05$.




**Supplementary Figure S5: Uncropped Western Blot Analysis of Synaptosomes From Ipsilateral Hippocampi (Figure 8a).** Western blots probed with SOCS3 antibody and reprobed using β-tubulin antibody as a total loading control for each sample from the ipsilateral hippocampus at **(a)** 2 DPI (n =4 for both sham and TBI), **(b)** 7 DPI (n =6 for both sham and TBI), **(c)** 1 MPI (n= 5 sham, n=7 TBI), and **(d)** 3 MPI (n= 4 for both sham and TBI) animals.




**Supplementary Figure S6: Uncropped Western Blot Analysis of Synaptosomes From Contralateral Hippocampi (Figure 8c).** Western blots probed with SOCS3 antibody and reprobed using β-tubulin antibody as a total loading control for each sample from the contralateral hippocampus at **(a)** 2 DPI (n =4 for both sham and TBI), **(b)** 7 DPI (n =6 for both sham and TBI), **(c)** 1 MPI (n= 5 sham, n=7 TBI), and **(d)** 3 MPI (n= 4 sham, n=3 TBI) animals.