| Gene/ Target | GenBank | Primer Sequence (5'-3') | Ref. |
|---|---|---|---|
| *Arc* | NM_018790.3 | Fwd: CAGATTGGTAAGTGCCGAGC<br>Rev:  GTGCAACCCTTTCAGCTCTC | |
| *Arg-1* | NM_007482.3 | Fwd: CGCCTTTCTCAAAAGGACAG<br>Rev: CCAGCTCTTCATTGGCTTTC | (Jang, Lee et al. 2013) |
| *Cd68* | NM_009853.1 | Fwd: CCACAGGCAGCACAGTGGACA<br>Rev: TCCACAGCAGAAGCTTTGGCCC | (Kobayashi, Imagama et al. 2013) |
| *Cd163* | NM_001170395.1 | Fwd: CCTCCTCATTGTCTTCCTCCTGTG<br>Rev: CATCCGCCTTTGAATCCATCTCTTG | (Ly, Baghat et al. 2010) |
| *Egr2* | NM_001373987.1 | Fwd: CGAGGGGACACACTGACTGTT<br>Rev:  CTGACTCTCTCCTGCCTGTGA | |
| *Fos* | NM_010234.3 | Fwd: GTTTCCGGCATCATCTAGGC<br>Rev:  GACGTGTAAGTAGTGCAGCC | |
| *Gapdh* | NM_008084.2 | Fwd: AGGTCGGTGTGAACGGATTTG<br>Rev: TGTAGACCATGTAGTTGAGGTCA | (Maung, Hoefer et al. 2014) |
| *Grm5* | NM_001081414.2 | Fwd: CTTGCCTGCTTCTCAGTTGTC<br>Rev: CTCAGGAAGCACCACTAGGAC | |
| *Homer1* | NM_147176.4 | Fwd: AGGGTTCTCAGCACCAATGG<br>Rev: AGCTGCCGGGAGGTGTAAG | |
| *iNOS* | NM_010927.3 | Fwd: TGACGCTCGGAACTGTAGCAC<br>Rev: TGATGGCCGACCTGATGTT | (Crain, Nikodemova et al. 2013) |
| *Lcn2* | NM_008491.1 | Fwd: CCAGTTCGCCATGGTATTTT<br>Rev:  GGTGGGGACAGAGAAGATGA | |
| *Mrc1* | NM_008625.2 | Fwd: TGGCTACCAGGAAGTCCATC<br>Rev: TGTAGCAGTGGCCTGCATAG | (Jang, Lee et al. 2013) |
| *Tnfα* | NM_013693.2 | Fwd: CATCTTCTCAAAATTCGAGTGACAA<br>Rev: ACTTGGGCAGATTGACCTCAG | (Jang, Lee et al. 2013) |

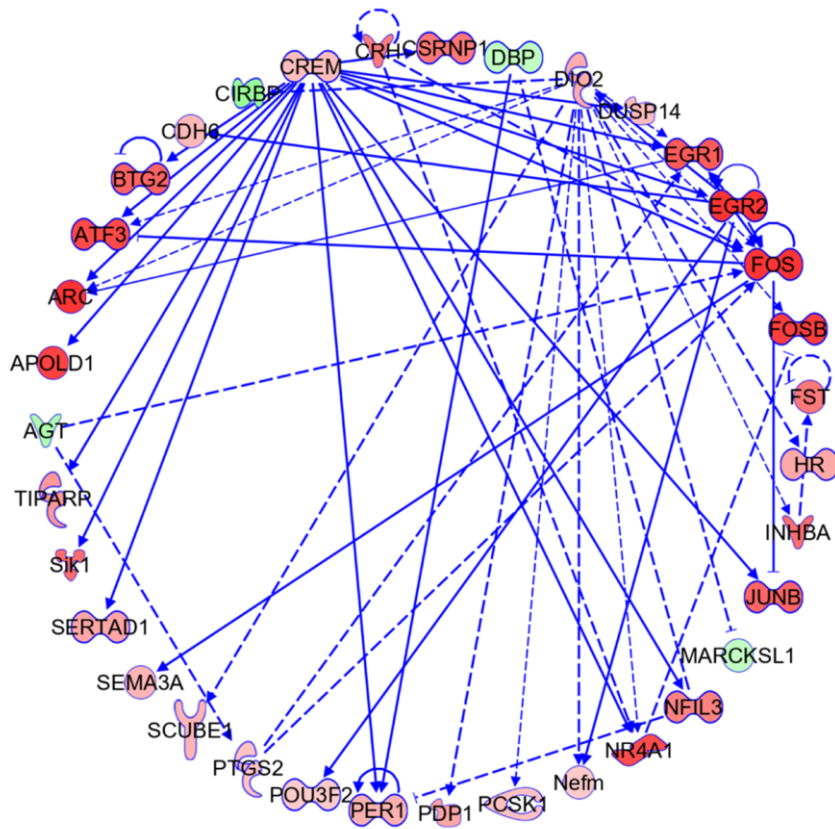**Supplementary Table 1. List of primers used for qRT-PCR.**

**Figure S1. Top upregulated networks predicted by IPA.** The top functions associated with the network of hDEGs in early prion disease were 'Neurological Disease' and 'Lipid Metabolism'. Color gradient is representative of fold change with highest up- or down-regulated genes having the darkest color. Red = genes significantly upregulated, and green = genes significantly downregulated.
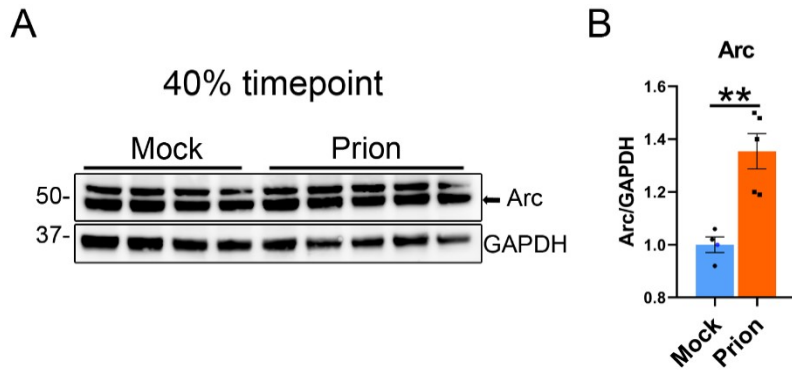
**Figure S2. Arc is significantly increased in the hippocampus of 22L-infected mice versus mock-inoculated mice at the 40% timepoint (third male cohort).** (A-B) Immunoblot of Arc at the 40% timepoint compared to age-matched, mock-inoculated controls. $n$ = 4 - 5 male mice per group. Welch's $t$-test, *$P$ ≤ 0.05; **$P$ ≤ 0.01.
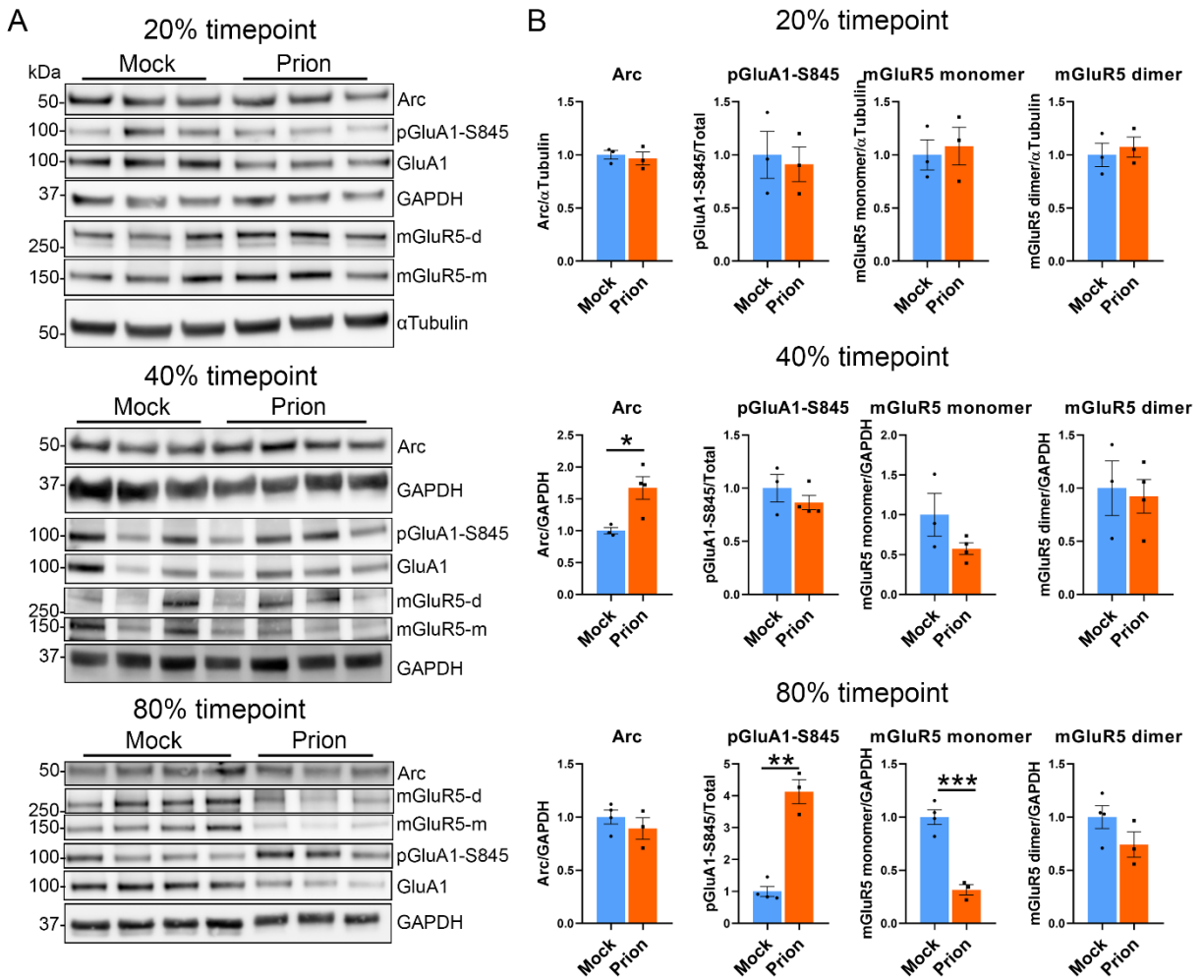
**Figure S3. Comparison of Arc, mGluR5, and pGluA1-S845 in the hippocampus of mock- and 22L-inoculated mice collected at the 20%, 40%, and 80% timepoints.** (A) Immunoblots of Arc, pGluA1-S845, and mGluR5 at the 20%, 40%, and 80% timepoints in prion-infected mice compared to age-matched, mock-inoculated controls. (B) Quantification. *n* = 3 - 4 male mice per group. Welch's *t*-test, *$P \leq 0.05$; **$P \leq 0.01$.
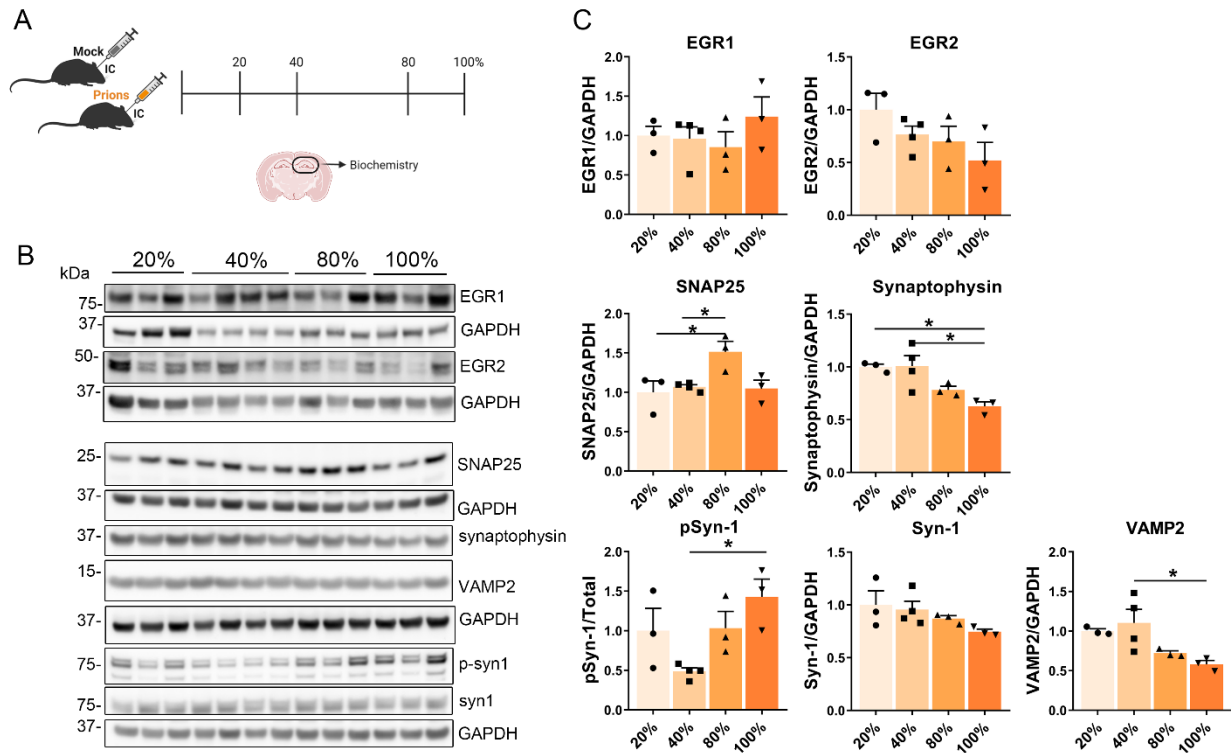
**Figure S4. Additional IEGs and synaptic proteins evaluated in a longitudinal study of the prion-infected hippocampus *in vivo*.** (A) A schematic summary shows the four timepoints used in this study. (B, C) Western blot and quantification of IEGs and pre-synaptic proteins. *n* = 3 - 4 mice per group. One-way ANOVA and Tukey HSD post-hoc test; *P ≤ 0.05.
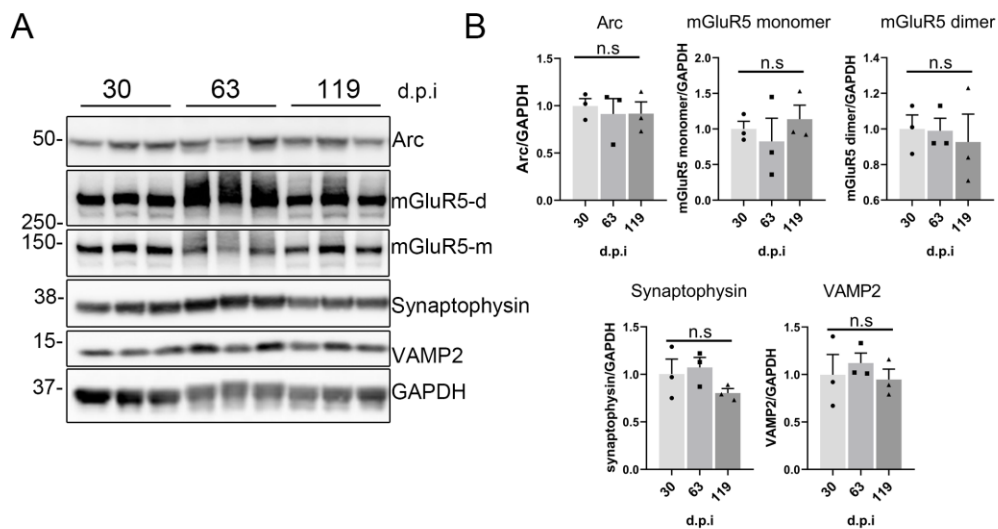
**Figure S5. Hippocampal Arc and mGluR5 are not altered following inoculation of WT mice with uninfected brain (mock).** (A, B) Western blot and quantification of Arc, mGluR5, VAMP2, and synaptophysin. *n* = 3 mice per group. One-way ANOVA and Tukey HSD post-hoc test; *P ≤ 0.05.

# References

Crain, J. M., M. Nikodemova and J. J. Watters (2013). "Microglia express distinct M1 and M2 phenotypic markers in the postnatal and adult central nervous system in male and female mice." J Neurosci Res **91**(9): 1143-1151.

Jang, E., S. Lee, J. H. Kim, J. H. Kim, J. W. Seo, W. H. Lee, K. Mori, K. Nakao and K. Suk (2013). "Secreted protein lipocalin-2 promotes microglial M1 polarization." FASEB J **27**(3): 1176-1190.

Kobayashi, K., S. Imagama, T. Ohgomori, K. Hirano, K. Uchimura, K. Sakamoto, A. Hirakawa, H. Takeuchi, A. Suzumura, N. Ishiguro and K. Kadomatsu (2013). "Minocycline selectively inhibits M1 polarization of microglia." Cell Death Dis **4**: e525.

Ly, L. V., A. Baghat, M. Versluis, E. S. Jordanova, G. P. Luyten, N. van Rooijen, T. van Hall, P. A. van der Velden and M. J. Jager (2010). "In aged mice, outgrowth of intraocular melanoma depends on proangiogenic M2-type macrophages." J Immunol **185**(6): 3481-3488.

Maung, R., M. M. Hoefer, A. B. Sanchez, N. E. Sejbuk, K. E. Medders, M. K. Desai, I. C. Catalan, C. C. Dowling, C. M. de Rozieres, G. A. Garden, R. Russo, A. J. Roberts, R. Williams and M. Kaul (2014). "CCR5 knockout prevents neuronal injury and behavioral impairment induced in a transgenic mouse model by a CXCR4-using HIV-1 glycoprotein 120." J Immunol **193**(4): 1895-1910.