List of Supplementary material.

10 Supplementary Figures.

**Supplementary Figure 1.** R26-MetRS* mouse: a new mouse line enabling cell-type specific protein metabolic labelling in complex tissues *in vivo.*

**Supplementary Figure 2.** Scheme of GFP-MetRS*, BONCAT, decay of proteins in MetRS* and ANL-treated cells, diagram of mouse construct and PCR verification of GFP-MetRS* mouse.

**Supplementary Figure 3.** Expression of MetRS* in brain tissue.

**Supplementary Figure 4.** Cre-dependent nascent protein labelling in acute and organotypic hippocampal slices.

**Supplementary Figure 5.** Genetically-targeted protein labelling following *in vivo* administration of ANL.

**Supplementary Figure 6.** Workflow and data-processing of the study.

**Supplementary Figure 7.** Correlation and characterization of proteomes and characteristics of ANL-labelled proteins.

**Supplementary Figure 8.** Cell-type specific proteomics *in vivo*: Purkinje neurons (GAD2-Cre::R26-MetRS* cerebellum).

**Supplementary Figure 9.** Analysis of CaMK2a excitatory hippocampal proteome following exposure to an enriched environment.

**Supplementary Figure 10.** Full-length gels.

12 Supplementary Tables.

**Supplementary Table 1.** CaMK2a (standard cage) excitatory hippocampal proteome.

**Supplementary Table 2.** Gene ontology: CaMK2a (standard cage) excitatory hippocampal proteome.

**Supplementary Table 3.** Cell-type specific protein and gene markers

**Supplementary Table 4.** GAD2 proteome.

**Supplementary Table 5.** Gene ontology: GAD2 Purkinje neuron proteome.

**Supplementary Table 6.** Differentially expressed genes in CaMK2a (standard cage) vs GAD2 proteomes.

**Supplementary Table 7.** CaMK2a enriched environment excitatory hippocampal proteome.

**Supplementary Table 8.** Differentially expressed genes in CaMK2a-standard cage vs CaMK2a- enriched environment proteomes.

**Supplementary Table 9.** Gene ontology of differentially expressed genes in CaMK2a-standard cage vs CaMK2a-enriched environment proteomes.

**Supplementary Table 10.** Primers used for mouse genotyping.

**Supplementary Table 11.** Custom parameters used for MS analysis in MaxQuant and Perseus.

**Supplementary Table 12.** Full hippocampus, cerebellum and glia proteomes.
**Figure S8**

**a** Purified Proteins (KDa)

**b** Enriched proteins

**c** Purkinje neuron proteome ("unique" + enriched)

**d** Gene ontology (top 15 cellular Processes)

**e** Cell-type marker enrichment

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Nature Biotechnology: doi:10.1038/nbt.4016
Figure S9

a

b

Disease-related Regulated proteins

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Depression

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Autism

| Mfn2 |

Epilepsy

| SncA | Mfn2 |

Multiple sclerosis

| SncA | Mfn2 |

Bipolar disorder

| Mfn2 | Sod1 |

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