

## References

1. Kandel, E. R., Dudai, Y. & Mayford, M. R. The molecular and systems biology of memory. *Cell* **157**, 163–186 (2014).
2. Citri, A. & Malenka, R. C. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology* **33**, 18–41 (2008).
3. Scoville, W. B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* **20**, 11–21 (1957).
4. Squire, L. R. & Zola, S. M. Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. U. S. A.* **93**, 13515–13522 (1996).
5. Rosenbaum, R. S., Gilboa, A. & Moscovitch, M. Case studies continue to illuminate the cognitive neuroscience of memory. *Ann. N. Y. Acad. Sci.* **1316**, 105–33 (2014).
6. Morris, R. G., Garrud, P., Rawlins, J. N. & O'Keefe, J. Place navigation impaired in rats with hippocampal lesions. *Nature* **297**, 681–683 (1982).
7. Kim, J. J. & Fanselow, M. S. Modality-specific retrograde amnesia of fear. *Science* **256**, 675–677 (1992).
8. Phillips, R. G. & LeDoux, J. E. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav. Neurosci.* **106**, 274–285 (1992).
9. Strange, B. a, Witter, M. P., Lein, E. S. & Moser, E. I. Functional organization of the hippocampal longitudinal axis. *Nat. Publ. Gr.* **15**, 655–669 (2014).
10. Bannerman, D. M. *et al.* Regional dissociations within the hippocampus - Memory and anxiety. *Neurosci. Biobehav. Rev.* **28**, 273–283 (2004).
11. Moser, E., Moser, M. B. & Andersen, P. Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *J. Neurosci.* **13**, 3916–3925 (1993).
12. Fanselow, M. S. & Dong, H.-W. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* **65**, 7–19 (2010).
13. Smith, D. M. & Bulkin, D. a. The form and function of hippocampal context representations. *Neurosci. Biobehav. Rev.* **40**, 52–61 (2014).
14. Nadel, L., Hupbach, A., Gomez, R. & Newman-Smith, K. Memory formation, consolidation and transformation. *Neurosci. Biobehav. Rev.* **36**, 1640–5 (2012).
15. McGaugh, J. L. Time-dependent processes in memory storage. *Science* **153**, 1351–1358 (1966).
16. Leuner, B., Falduo, J. & Shors, T. J. Associative Memory Formation Increases the Observation of Dendritic Spines in the Hippocampus. *J. Neurosci.* **23**, 659–665 (2003).
17. Restivo, L., Vetere, G., Bontempi, B. & Ammassari-Teule, M. The formation of recent and remote memory is associated with time-dependent formation of dendritic spines in the hippocampus and anterior cingulate cortex. *J. Neurosci.* **29**, 8206–14 (2009).
18. Abel, T. *et al.* Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. *Cell* **88**, 615–626 (1997).
19. Bourtochouladze, R. *et al.* Different Training Procedures Recruit Either One or Two Critical Periods for Contextual Memory Consolidation, Each of Which Requires Protein Synthesis and PKA. *Learn. Mem.* **5**, 365–374 (1998).

20. Igaz, L. M., Vianna, M. R. M., Medina, J. H. & Izquierdo, I. Two time periods of hippocampal mRNA synthesis are required for memory consolidation of fear-motivated learning. *J. Neurosci.* **22**, 6781–6789 (2002).
21. Barrientos, R. M. *et al.* Memory for context is impaired by injecting anisomycin into dorsal hippocampus following context exploration. *Behav. Brain Res.* **134**, 299–306 (2002).
22. Lonergan, M. E., Gafford, G. M., Jarome, T. J. & Helmstetter, F. J. Time-dependent expression of arc and Zif268 after acquisition of fear conditioning. *Neural Plast.* **2010**, 8–11 (2010).
23. Remaud, J. *et al.* Anisomycin injection in area CA3 of the hippocampus impairs both short-term and long-term memories of contextual fear. *Learn. Mem.* **21**, 311–315 (2014).
24. Wang, H., Hu, Y. & Tsien, J. Z. Molecular and systems mechanisms of memory consolidation and storage. *Prog. Neurobiol.* **79**, 123–35 (2006).
25. Wiltgen, B. J. & Tanaka, K. Z. Systems consolidation and the content of memory. *Neurobiol. Learn. Mem.* **106**, 365–371 (2013).
26. Lee, S.-H. *et al.* Synaptic Protein Degradation Underlies Destabilization of Retrieved Fear Memory. *Science (80-. )*. **319**, 1253–1257 (2008).
27. Sol Fustiñana, M., de la Fuente, V., Federman, N., Freudenthal, R. & Romano, A. Protein degradation by ubiquitin-proteasome system in formation and labilization of contextual conditioning memory. *Learn. Mem.* **21**, 478–87 (2014).
28. Nader, K., Schafe, G. E. & Le Doux, J. E. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* **406**, 722–6 (2000).
29. Rao-Ruiz, P. *et al.* Retrieval-specific endocytosis of GluA2-AMPA receptors underlies adaptive reconsolidation of contextual fear. *Nat. Neurosci.* **14**, 1302–8 (2011).
30. Lopez, J., Gamache, K., Schneider, R. & Nader, K. Memory retrieval requires ongoing protein synthesis and NMDA receptor activity-mediated AMPA receptor trafficking. *J. Neurosci.* **35**, 2465–75 (2015).
31. Acheson, D. T., Gresack, J. E. & Risbrough, V. B. Hippocampal dysfunction effects on context memory: Possible etiology for posttraumatic stress disorder. *Neuropharmacology* **62**, 674–685 (2012).
32. Maren, S., Phan, K. L. & Liberzon, I. The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nat. Rev. Neurosci.* **14**, 417–28 (2013).
33. Abeles, M. *Corticomics: neural circuits of the cerebral cortex*. (Cambridge: CUP, 1991).
34. Braitenberg, V. & Schüz, A. *Cortex: Statistics and Geometry of Neuronal Connectivity*. (Springer, 1998).
35. Johansen, J. P., Cain, C. K., Ostroff, L. E. & LeDoux, J. E. Molecular mechanisms of fear learning and memory. *Cell* **147**, 509–24 (2011).
36. Atsak, P., Roozendaal, B. & Campolongo, P. Role of the endocannabinoid system in regulating glucocorticoid effects on memory for emotional experiences. *Neuroscience* **204**, 104–116 (2012).
37. Ramón y Cajal, S. La fine structure des centres nerveux. The croonian lecture. *Proc. R. Soc. London* 43–468 (1894).
38. Hebb, D. O. *The Organization of Behavior*. (John Wiley, 1949).

39. Bliss, T. V & Lomo, T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* **232**, 331-56 (1973).
40. Bliss, T. V & Collingridge, G. L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361**, 31-39 (1993).
41. Shors, T. J. & Matzel, L. D. Long-term potentiation: what's learning got to do with it? *Behav. Brain Sci.* **20**, 597-614; discussion 614-655 (1997).
42. Morris, R. G. M. *et al.* Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **358**, 773-86 (2003).
43. Ito, M. Bases and implications of learning in the cerebellum--adaptive control and internal model mechanism. *Prog. Brain Res.* **148**, 95-109 (2005).
44. Whitlock, J. R., Heynen, A. J., Shuler, M. G. & Bear, M. F. Learning induces long-term potentiation in the hippocampus. *Science* **313**, 1093-7 (2006).
45. Nabavi, S. *et al.* Engineering a memory with LTD and LTP. *Nature* **511**, 348-352 (2014).
46. Morgado-Bernal, I. Learning and memory consolidation: linking molecular and behavioral data. *Neuroscience* **176**, 12-9 (2011).
47. Schafe, G. E., Nader, K., Blair, H. T. & LeDoux, J. E. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *Trends Neurosci.* **24**, 540-546 (2001).
48. Goosens, K. A. & Maren, S. Long-term potentiation as a substrate for memory: evidence from studies of amygdaloid plasticity and Pavlovian fear conditioning. *Hippocampus* **12**, 592-9 (2002).
49. Chapman, P. F., Ramsay, M. F., Krezel, W. & Knevet, S. G. Synaptic plasticity in the amygdala: comparisons with hippocampus. *Ann. N. Y. Acad. Sci.* **985**, 114-24 (2003).
50. Südhof, T. C. & Rizo, J. Synaptic vesicle exocytosis. *Cold Spring Harb. Perspect. Biol.* **3**, a005637 (2011).
51. Fioravante, D. & Regehr, W. G. Short-term forms of presynaptic plasticity. *Curr. Opin. Neurobiol.* **21**, 269-274 (2011).
52. Catterall, W. A., Leal, K. & Nanou, E. Calcium channels and short-term synaptic plasticity. *J. Biol. Chem.* **288**, 10742-9 (2013).
53. Lüscher, C. & Malenka, R. C. NMDA Receptor-Dependent Long-Term Potentiation and Long-Term Depression (LTP / LTD). *Cold Spring Harb. Perspect. Biol.* **4**, 1-16 (2012).
54. Chater, T. E. & Goda, Y. The role of AMPA receptors in postsynaptic mechanisms of synaptic plasticity. *Front. Cell. Neurosci.* **8**, 1-14 (2014).
55. Silva, A. J., Stevens, C. F., Tonegawa, S. & Wang, Y. Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice. *Science* **257**, 201-6 (1992).
56. Silva, A. J., Paylor, R., Wehner, J. M. & Tonegawa, S. Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science* **257**, 206-11 (1992).
57. Mayford, M. *et al.* Control of memory formation through regulated expression of a CaMKII transgene. *Science* **274**, 1678-1683 (1996).
58. Silva, a J. *et al.* Impaired learning in mice with abnormal short-lived plasticity. *Curr. Biol.* **6**, 1509-1518 (1996).

59. Weeber, E. J. *et al.* A role for the beta isoform of protein kinase C in fear conditioning. *J. Neurosci.* **20**, 5906–5914 (2000).
60. Bozon, B. *et al.* MAPK, CREB and zif268 are all required for the consolidation of recognition memory. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **358**, 805–14 (2003).
61. Lee, Y.-S. & Silva, A. J. The molecular and cellular biology of enhanced cognition. *Nat. Rev. Neurosci.* **10**, 126–140 (2009).
62. Kandel, E. R. The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. *Mol. Brain* **5**, 14 (2012).
63. Gal-Ben-Ari, S. *et al.* Consolidation and translation regulation. *Learn. Mem.* **19**, 410–22 (2012).
64. Miyashita, T., Kubik, S., Lewandowski, G. & Guzowski, J. F. Networks of neurons, networks of genes: an integrated view of memory consolidation. *Neurobiol. Learn. Mem.* **89**, 269–84 (2008).
65. Alberini, C. M. Transcription factors in long-term memory and synaptic plasticity. *Physiol. Rev.* **89**, 121–45 (2009).
66. Czerniawski, J. *et al.* The importance of having Arc: expression of the immediate-early gene Arc is required for hippocampus-dependent fear conditioning and blocked by NMDA receptor antagonism. *J. Neurosci.* **31**, 11200–11207 (2011).
67. Sutton, M. a. & Schuman, E. M. Dendritic Protein Synthesis, Synaptic Plasticity, and Memory. *Cell* **127**, 49–58 (2006).
68. Richter, J. D. & Klann, E. Making synaptic plasticity and memory last: mechanisms of translational regulation. *Genes Dev.* **23**, 1–11 (2009).
69. Mitsushima, D., Ishihara, K., Sano, A., Kessels, H. W. & Takahashi, T. Contextual learning requires synaptic AMPA receptor delivery in the hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 12503–12508 (2011).
70. Plant, K. *et al.* Transient incorporation of native GluR2-lacking AMPA receptors during hippocampal long-term potentiation. *Nat. Neurosci.* **9**, 602–604 (2006).
71. Wiltgen, B. J. *et al.* A role for calcium-permeable AMPA receptors in synaptic plasticity and learning. *PLoS One* **5**, (2010).
72. Miguez, P. V. *et al.* PKMzeta maintains memories by regulating GluR2-dependent AMPA receptor trafficking. *Nat. Neurosci.* **13**, 630–634 (2010).
73. Kwapis, J. L., Jarome, T. J., Loneragan, M. E. & Helmstetter, F. J. Protein kinase Mzeta maintains fear memory in the amygdala but not in the hippocampus. *Behav. Neurosci.* **123**, 844–850 (2009).
74. Sala, C. & Segal, M. Dendritic spines: the locus of structural and functional plasticity. *Physiol. Rev.* **94**, 141–88 (2014).
75. Caroni, P., Donato, F. & Muller, D. Structural plasticity upon learning: regulation and functions. *Nat. Rev. Neurosci.* **13**, 478–90 (2012).
76. Holtmaat, A. & Svoboda, K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat. Rev. Neurosci.* **10**, 647–658 (2009).
77. Lamprecht, R. The actin cytoskeleton in memory formation. *Prog. Neurobiol.* **117**, 1–19 (2014).
78. Padamsey, Z. & Emptage, N. Two sides to long-term potentiation: a view towards reconciliation. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **369**, 20130154 (2014).
79. Morgan, S. L. & Teyler, T. J. Electrical stimuli patterned after the theta-rhythm induce multiple forms of LTP. *J. Neurophysiol.* **86**, 1289–1296 (2001).

80. Zakharenko, S. S., Zablow, L. & Siegelbaum, S. a. Visualization of changes in presynaptic function during long-term synaptic plasticity. *Nat. Neurosci.* **4**, 711-717 (2001).
81. Bayazitov, I. T., Richardson, R. J., Fricke, R. G. & Zakharenko, S. S. Slow presynaptic and fast postsynaptic components of compound long-term potentiation. *J. Neurosci.* **27**, 11510-11521 (2007).
82. Yang, Y. & Calakos, N. Presynaptic long-term plasticity. *Front. Synaptic Neurosci.* **5**, 1-22 (2013).
83. Holderith, N. *et al.* Release probability of hippocampal glutamatergic terminals scales with the size of the active zone. *Nat. Neurosci.* **15**, 988-97 (2012).
84. Michel, K., Müller, J. A., Opreşoreanu, A.-M. & Schoch, S. The presynaptic active zone: A dynamic scaffold that regulates synaptic efficacy. *Exp. Cell Res.* **335**, 157-164 (2015).
85. Alberini, C. M. Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci.* **28**, 51-6 (2005).
86. Da Silva, W. C. *et al.* Inhibition of mRNA synthesis in the hippocampus impairs consolidation and reconsolidation of spatial memory. *Hippocampus* **18**, 29-39 (2008).
87. Mamiya, N. *et al.* Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory. *J. Neurosci.* **29**, 402-13 (2009).
88. Suzuki, A. *et al.* Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* **24**, 4787-4795 (2004).
89. Tronson, N. C. & Taylor, J. R. Molecular mechanisms of memory reconsolidation. *Nat. Rev. Neurosci.* **8**, 262-75 (2007).
90. Lee, J. L. C., Everitt, B. J. & Thomas, K. L. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* **304**, 839-43 (2004).
91. Von Herten, L. S. J. & Giese, K. P. Memory reconsolidation engages only a subset of immediate-early genes induced during consolidation. *J. Neurosci.* **25**, 1935-42 (2005).
92. Taubenfeld, S. M., Milekic, M. H., Monti, B. & Alberini, C. M. The consolidation of new but not reactivated memory requires hippocampal C/EBPbeta. *Nat. Neurosci.* **4**, 813-8 (2001).
93. Lee, J. L. C. & Hynds, R. E. Divergent cellular pathways of hippocampal memory consolidation and reconsolidation. *Hippocampus* **23**, 233-244 (2013).
94. Silva, A. J., Smith, A. M. & Giese, K. P. Gene targeting and the biology of learning and memory. *Annu. Rev. Genet.* **31**, 527-46 (1997).
95. Nguyen, P. V., Abel, T., Kandel, E. R. & Bourtchouladze, R. Strain-dependent differences in LTP and hippocampus-dependent memory in inbred mice. *Learn. Mem.* **7**, 170-9 (2000).
96. Schimanski, L. A. & Nguyen, P. V. Multidisciplinary approaches for investigating the mechanisms of hippocampus-dependent memory: a focus on inbred mouse strains. *Neurosci. Biobehav. Rev.* **28**, 463-83 (2004).
97. Wehner, J. M., Sleight, S. & Upchurch, M. Hippocampal protein kinase C activity is reduced in poor spatial learners. *Brain Res.* **523**, 181-7 (1990).
98. Bowers, B. J. *et al.* Protein and molecular characterization of hippocampal protein kinase C in C57BL/6 and DBA/2 mice. *J. Neurochem.* **64**, 2737-46 (1995).

99. Paylor, R., Baskall-Baldini, L., Yuva, L. & Wehner, J. M. Developmental differences in place-learning performance between C57BL/6 and DBA/2 mice parallel the ontogeny of hippocampal protein kinase C. *Behav. Neurosci.* **110**, 1415–25 (1996).
100. Fordyce, D. E., Clark, V. J., Paylor, R. & Wehner, J. M. Enhancement of hippocampally-mediated learning and protein kinase C activity by oxiracetam in learning-impaired DBA/2 mice. *Brain Res.* **672**, 170–176 (1995).
101. Burgoyne, R. D. & Haynes, L. P. Sense and specificity in neuronal calcium signalling. *Biochim. Biophys. Acta* (2014).
102. West, A. E. & Greenberg, M. E. Neuronal activity-regulated gene transcription in synapse development and cognitive function. *Cold Spring Harb. Perspect. Biol.* **3**, a005744– (2011).
103. Fields, R. D., Lee, P. R. & Cohen, J. E. Temporal integration of intracellular Ca<sup>2+</sup> signaling networks in regulating gene expression by action potentials. *Cell Calcium* **37**, 433–42 (2005).
104. Simms, B. A. & Zamponi, G. W. Neuronal voltage-gated calcium channels: structure, function, and dysfunction. *Neuron* **82**, 24–45 (2014).
105. Pietrobon, D. Calcium channels and migraine. *Biochim. Biophys. Acta* **1828**, 1655–65 (2013).
106. Nimmervoll, B., Flucher, B. E. & Obermair, G. J. Dominance of P/Q-type calcium channels in depolarization-induced presynaptic fm dye release in cultured hippocampal neurons. *Neuroscience* **253**, 330–340 (2013).
107. Ermolyuk, Y. S. *et al.* Differential triggering of spontaneous glutamate release by P/Q-, N- and R-type Ca<sup>2+</sup> channels. *Nat. Neurosci.* **16**, 1754–63 (2013).
108. Sutton, K. G., McRory, J. E., Guthrie, H., Murphy, T. H. & Snutch, T. P. P/Q-type calcium channels mediate the activity-dependent feedback of syntaxin-1A. *Nature* **401**, 800–4 (1999).
109. Ferrari, M. D., Klever, R. R., Terwindt, G. M., Ayata, C. & van den Maagdenberg, A. M. J. M. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol.* **14**, 65–80 (2015).
110. Van den Maagdenberg, A. M. J. M. *et al.* A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. *Neuron* **41**, 701–10 (2004).
111. Van den Maagdenberg, A. M. J. M. *et al.* High cortical spreading depression susceptibility and migraine-associated symptoms in Ca(v)2.1 S218L mice. *Ann. Neurol.* **67**, 85–98 (2010).
112. Vecchia, D., Tottene, A., van den Maagdenberg, A. M. J. M. & Pietrobon, D. Abnormal cortical synaptic transmission in CaV2.1 knockin mice with the S218L missense mutation which causes a severe familial hemiplegic migraine syndrome in humans. *Front. Cell. Neurosci.* **9**, 8 (2015).
113. Tottene, A. *et al.* Enhanced Excitatory Transmission at Cortical Synapses as the Basis for Facilitated Spreading Depression in CaV2.1 Knockin Migraine Mice. *Neuron* **61**, 762–773 (2009).
114. Adams, P. J. *et al.* Contribution of calcium-dependent facilitation to synaptic plasticity revealed by migraine mutations in the P/Q-type calcium channel. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 18694–18699 (2010).
115. Chanda, M. L. *et al.* Behavioral evidence for photophobia and stress-related ipsilateral head pain in transgenic Cacna1a mutant mice. *Pain* **154**, 1254–62 (2013).

116. Langford, D. J. *et al.* Coding of facial expressions of pain in the laboratory mouse. *Nat. Methods* **7**, 447–449 (2010).
117. Kors, E. E. *et al.* Delayed cerebral edema and fatal coma after minor head trauma: role of the CACNA1A calcium channel subunit gene and relationship with familial hemiplegic migraine. *Ann. Neurol.* **49**, 753–60 (2001).
118. Stam, A. H. *et al.* Early seizures and cerebral oedema after trivial head trauma associated with the CACNA1A S218L mutation. *J. Neurol. Neurosurg. Psychiatry* **80**, 1125–9 (2009).
119. Allen Institute. Cacna1a: Allen Brain Atlas: Mouse Brain (<http://mouse.brain-map.org/gene/show/12071>)
120. Ow, S. Y. *et al.* iTRAQ underestimation in simple and complex mixtures: ‘the good, the bad and the ugly’. *J. Proteome Res.* **8**, 5347–55 (2009).
121. Karp, N. A. *et al.* Addressing accuracy and precision issues in iTRAQ quantitation. *Mol. Cell. Proteomics* **9**, 1885–97 (2010).
122. Gillet, L. C. *et al.* Targeted data extraction of the MS/MS spectra generated by data-independent acquisition: a new concept for consistent and accurate proteome analysis. *Mol. Cell. Proteomics* **11**, O111.016717 (2012).
123. Schubert, O. T. *et al.* building high quality assay libraries for targeted analysis of SWATH MS data. *Nat. Protoc.* **10**, 426–441 (2015).
124. Mortazavi, A., Williams, B. A., McCue, K., Schaeffer, L. & Wold, B. Mapping and quantifying mammalian transcriptomes by RNA-Seq. *Nat. Methods* **5**, 621–8 (2008).
125. Marioni, J. C., Mason, C. E., Mane, S. M., Stephens, M. & Gilad, Y. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. *Genome Res.* **18**, 1509–17 (2008).
126. Bloom, J. S., Khan, Z., Kruglyak, L., Singh, M. & Caudy, A. A. Measuring differential gene expression by short read sequencing: quantitative comparison to 2-channel gene expression microarrays. *BMC Genomics* **10**, 221 (2009).
127. ‘t Hoen, P. A. C. *et al.* Deep sequencing-based expression analysis shows major advances in robustness, resolution and inter-lab portability over five microarray platforms. *Nucleic Acids Res.* **36**, e141 (2008).
128. Takahashi, H., Lassmann, T., Murata, M. & Carninci, P. 5’ end-centered expression profiling using cap-analysis gene expression and next-generation sequencing. *Nat. Protoc.* **7**, 542–61 (2012).
129. Aitken, S. *et al.* Transcriptional Dynamics Reveal Critical Roles for Non-coding RNAs in the Immediate-Early Response. *PLoS Comput. Biol.* **11**, e1004217 (2015).
130. Mandillo, S. *et al.* Reliability, robustness, and reproducibility in mouse behavioral phenotyping: a cross-laboratory study. *Physiol. Genomics* **34**, 243–255 (2008).
131. Chesler, E. J., Wilson, S. G., Lariviere, W. R., Rodriguez-Zas, S. L. & Mogil, J. S. Influences of laboratory environment on behavior. *Nat. Neurosci.* **5**, 1101–1102 (2002).
132. Balcombe, J. P., Barnard, N. D. & Sandusky, C. Laboratory routines cause animal stress. *Contemp. Top. Lab. Anim. Sci.* **43**, 42–51 (2004).
133. Hurst, J. L. & West, R. S. Taming anxiety in laboratory mice. *Nat. Methods* **7**, 825–826 (2010).
134. Krackow, S. *et al.* Consistent behavioral phenotype differences between inbred mouse strains in the IntelliCage. *Genes, Brain Behav.* **9**, 722–731 (2010).

135. Loos, M. *et al.* Sheltering Behavior and Locomotor Activity in 11 Genetically Diverse Common Inbred Mouse Strains Using Home-Cage Monitoring. *PLoS One* **9**, e108563 (2014).
136. Loos, M. *et al.* Within-strain variation in behavior differs consistently between common inbred strains of mice. *Mamm. Genome* (2015). doi:10.1007/s00335-015-9578-7
137. Maroteaux, G. *et al.* High-throughput phenotyping of avoidance learning in mice discriminates different genotypes and identifies a novel gene. *Genes, Brain Behav.* **11**, 772–784 (2012).
138. Remmelink, E. *et al.* A 1-night operant learning task without food-restriction differentiates among mouse strains in an automated home-cage environment. *Behav. Brain Res.* **283**, 53–60 (2015).
139. Seigers, R. *et al.* Cognitive impact of cytotoxic agents in mice. *Psychopharmacology (Berl)*. 17–37 (2014). doi:10.1007/s00213-014-3636-9
140. Kramvis, I., Mansvelter, H. D., Loos, M. & Meredith, R. Hyperactivity, perseveration and increased responding during attentional rule acquisition in the Fragile X mouse model. *Front. Behav. Neurosci.* **7**, 172 (2013).
141. Urbach, Y. K. *et al.* Automated phenotyping and advanced data mining exemplified in rats transgenic for Huntington’s disease. *J. Neurosci. Methods* **234**, 38–53 (2014).
142. Squire, L. R. & Knowlton, B. J. Memory, hippocampus, and brain systems. *Cogn. Neurosci.* 825–837 (1995).
143. Youn, J. *et al.* Finding the right motivation: Genotype-dependent differences in effective reinforcements for spatial learning. *Behav. Brain Res.* **226**, 397–403 (2012).
144. Upchurch, M. & Wehner, J. M. Differences between inbred strains of mice in Morris water maze performance. *Behav. Genet.* **18**, 55–68 (1988).
145. Holmes, A., Wrenn, C. C., Harris, A. P., Thayer, K. E. & Crawley, J. N. Behavioral profiles of inbred strains on novel olfactory, spatial and emotional tests for reference memory in mice. *Genes, Brain, Behav.* **1**, 55–69 (2002).
146. André, J. M., Cordero, K. A. & Gould, T. J. Comparison of the performance of DBA/2 and C57BL/6 mice in transitive inference and foreground and background contextual fear conditioning. *Behav. Neurosci.* **126**, 249–57 (2012).
147. Schimanski, L. A. & Nguyen, P. V. Impaired fear memories are correlated with subregion-specific deficits in hippocampal and amygdalar LTP. *Behav. Neurosci.* **119**, 38–54 (2005).
148. Otto, T., Eichenbaum, H., Wiener, S. I. & Wible, C. G. Learning-related patterns of CA1 spike trains parallel stimulation parameters optimal for inducing hippocampal long-term potentiation. *Hippocampus* **1**, 181–92 (1991).
149. Nguyen, P. V., Duffy, S. N. & Young, J. Z. Differential maintenance and frequency-dependent tuning of LTP at hippocampal synapses of specific strains of inbred mice. *J. Neurophysiol.* **84**, 2484–93 (2000).
150. Izquierdo, I. & McGaugh, J. L. Behavioural pharmacology and its contribution to the molecular basis of memory consolidation. *Behav. Pharmacol.* **11**, 517–34 (2000).
151. Li, K. W. *et al.* Proteomics analysis of rat brain postsynaptic density. Implications of the diverse protein functional groups for the integration of synaptic physiology. *J. Biol. Chem.* **279**, 987–1002 (2004).
152. Counotte, D. S. *et al.* Changes in molecular composition of rat medial prefrontal cortex synapses during adolescent development. *Eur. J. Neurosci.* **32**, 1452–60 (2010).



153. Klemmer, P. *et al.* Proteomics, ultrastructure, and physiology of hippocampal synapses in a fragile X syndrome mouse model reveal presynaptic phenotype. *J. Biol. Chem.* **286**, 25495–504 (2011).
154. Li, K. W. *et al.* Quantitative proteomics and protein network analysis of hippocampal synapses of CaMKIIalpha mutant mice. *J. Proteome Res.* **6**, 3127–33 (2007).
155. Meyer-Arendt, K. *et al.* IsoformResolver: A peptide-centric algorithm for protein inference. *J. Proteome Res.* **10**, 3060–75 (2011).
156. Reiter, L. *et al.* Protein identification false discovery rates for very large proteomics data sets generated by tandem mass spectrometry. *Mol. Cell. Proteomics* **8**, 2405–17 (2009).
157. Tusher, V. G., Tibshirani, R. & Chu, G. Significance analysis of microarrays applied to the ionizing radiation response. *Proc. Natl. Acad. Sci. U. S. A.* **98**, 5116–5121 (2001).
158. Ruano, D. *et al.* Functional gene group analysis reveals a role of synaptic heterotrimeric G proteins in cognitive ability. *Am. J. Hum. Genet.* **86**, 113–25 (2010).
159. Bernardinelli, Y., Muller, D. & Nikonenko, I. Astrocyte-synapse structural plasticity. *Neural Plast.* **2014**, 232105 (2014).
160. Verbich, D., Prenosil, G. A., Chang, P. K.-Y., Murai, K. K. & McKinney, R. A. Glial glutamate transport modulates dendritic spine head protrusions in the hippocampus. *Glia* **60**, 1067–77 (2012).
161. Goudriaan, A. *et al.* Specific glial functions contribute to schizophrenia susceptibility. *Schizophr. Bull.* **40**, 925–35 (2014).
162. Cijssouw, T. *et al.* Munc18-1 redistributes in nerve terminals in an activity- and PKC-dependent manner. *J. Cell Biol.* **204**, 759–75 (2014).
163. Jahn, R. & Fasshauer, D. Molecular machines governing exocytosis of synaptic vesicles. *Nature* **490**, 201–7 (2012).
164. Schlüter, O. M., Schmitz, F., Jahn, R., Rosenmund, C. & Südhof, T. C. A complete genetic analysis of neuronal Rab3 function. *J. Neurosci.* **24**, 6629–6637 (2004).
165. Rao-Ruiz, P. *et al.* Time-dependent changes in the mouse hippocampal synaptic membrane proteome after contextual fear conditioning. *Hippocampus* (2015). doi:10.1002/hipo.22432
166. Ménard, C., Valastro, B., Martel, M.-A., Martinoli, M.-G. & Massicotte, G. Strain-related variations of AMPA receptor modulation by calcium-dependent mechanisms in the hippocampus: contribution of lipoxygenase metabolites of arachidonic acid. *Brain Res.* **1010**, 134–43 (2004).
167. Zilles, K., Wu, J., Crusio, W. E. & Schwegler, H. Water maze and radial maze learning and the density of binding sites of glutamate, GABA, and serotonin receptors in the hippocampus of inbred mouse strains. *Hippocampus* **10**, 213–25 (2000).
168. Wöllert, T. *et al.* Myosin5a tail associates directly with Rab3A-containing compartments in neurons. *J. Biol. Chem.* **286**, 14352–61 (2011).
169. Rudolf, R., Bittins, C. M. & Gerdes, H.-H. The role of myosin V in exocytosis and synaptic plasticity. *J. Neurochem.* **116**, 177–91 (2011).
170. Andrieux, A. *et al.* The suppression of brain cold-stable microtubules in mice induces synaptic defects associated with neuroleptic-sensitive behavioral disorders. *Genes Dev.* **16**, 2350–64 (2002).

171. Ertunc, M. *et al.* Fast synaptic vesicle reuse slows the rate of synaptic depression in the CA1 region of hippocampus. *J. Neurosci.* **27**, 341–54 (2007).
172. Lvov, A., Chikvashvili, D., Michaelevski, I. & Lotan, I. VAMP2 interacts directly with the N terminus of Kv2.1 to enhance channel inactivation. *Pflugers Arch.* **456**, 1121–36 (2008).
173. Jones, M. W., Peckham, H. M., Errington, M. L., Bliss, T. V & Routtenberg, A. Synaptic plasticity in the hippocampus of awake C57BL/6 and DBA/2 mice: interstrain differences and parallels with behavior. *Hippocampus* **11**, 391–6 (2001).
174. Walker, S. A. *et al.* Identification of a Ras GTPase-activating protein regulated by receptor-mediated Ca<sup>2+</sup> oscillations. *EMBO J.* **23**, 1749–60 (2004).
175. Yarwood, S., Bouyoucef-Cherchalli, D., Cullen, P. J. & Kupzig, S. The GAP1 family of GTPase-activating proteins: spatial and temporal regulators of small GTPase signalling. *Biochem. Soc. Trans.* **34**, 846–50 (2006).
176. Kupzig, S. *et al.* GAP1 family members constitute bifunctional Ras and Rap GTPase-activating proteins. *J. Biol. Chem.* **281**, 9891–900 (2006).
177. Krapivinsky, G., Medina, I., Krapivinsky, L., Gapon, S. & Clapham, D. E. SynGAP-MUPP1-CaMKII synaptic complexes regulate p38 MAP kinase activity and NMDA receptor-dependent synaptic AMPA receptor potentiation. *Neuron* **43**, 563–74 (2004).
178. Allen Institute. Rasal1: Allen Brain Atlas: Mouse Brain (<http://mouse.brain-map.org/gene/show/19178>)
179. Liu, Q. *et al.* CAPRI and RASAL impose different modes of information processing on Ras due to contrasting temporal filtering of Ca<sup>2+</sup>. *J. Cell Biol.* **170**, 183–90 (2005).
180. Oancea, E. & Meyer, T. Protein kinase C as a molecular machine for decoding calcium and diacylglycerol signals. *Cell* **95**, 307–18 (1998).
181. Violin, J. D., Zhang, J., Tsien, R. Y. & Newton, A. C. A genetically encoded fluorescent reporter reveals oscillatory phosphorylation by protein kinase C. *J. Cell Biol.* **161**, 899–909 (2003).
182. Craske, M. *et al.* Hormone-induced secretory and nuclear translocation of calmodulin: oscillations of calmodulin concentration with the nucleus as an integrator. *Proc. Natl. Acad. Sci. U. S. A.* **96**, 4426–31 (1999).
183. De Koninck, P. & Schulman, H. Sensitivity of CaM kinase II to the frequency of Ca<sup>2+</sup> oscillations. *Science* **279**, 227–30 (1998).
184. Giese, K. P. & Mizuno, K. The roles of protein kinases in learning and memory. *Learn. Mem.* **20**, 540–52 (2013).
185. Sot, B., Behrmann, E., Raunser, S. & Wittinghofer, A. Ras GTPase activating (RasGAP) activity of the dual specificity GAP protein Rasal requires colocalization and C2 domain binding to lipid membranes. *Proc. Natl. Acad. Sci. U. S. A.* **110**, 111–6 (2013).
186. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* **33**, 629–808 (2013).
187. Ophoff, R. A. *et al.* Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca<sup>2+</sup> channel gene CACNL1A4. *Cell* **87**, 543–52 (1996).
188. Pietrobon, D. & Moskowitz, M. A. Pathophysiology of migraine. *Annu. Rev. Physiol.* **75**, 365–91 (2013).

189. Tottene, A. *et al.* Familial hemiplegic migraine mutations increase Ca(2+) influx through single human CaV2.1 channels and decrease maximal CaV2.1 current density in neurons. *Proc. Natl. Acad. Sci. U. S. A.* **99**, 13284–9 (2002).
190. Eikermann-Haerter, K. *et al.* Enhanced subcortical spreading depression in familial hemiplegic migraine type 1 mutant mice. *J. Neurosci.* **31**, 5755–5763 (2011).
191. Kors, E. E. *et al.* Expanding the phenotypic spectrum of the CACNA1A gene T666M mutation: a description of 5 families with familial hemiplegic migraine. *Arch. Neurol.* **60**, 684–8 (2003).
192. Karner, E., Delazer, M., Benke, T. & Bösch, S. Cognitive functions, emotional behavior, and quality of life in familial hemiplegic migraine. *Cogn. Behav. Neurol.* **23**, 106–11 (2010).
193. Karner, E. *et al.* Long-term Outcome of Cognitive Functions, Emotional Behavior, and Quality of Life in a Family With Familial Hemiplegic Migraine. *Cogn. Behav. Neurol.* **25**, 85–92 (2012).
194. Freilinger, T. *et al.* A novel mutation in CACNA1A associated with hemiplegic migraine, cerebellar dysfunction and late-onset cognitive decline. *J. Neurol. Sci.* **300**, 160–163 (2011).
195. Le Pira, F. *et al.* Memory disturbances in migraine with and without aura: A strategy problem? *Cephalalgia* **20**, 475–478 (2000).
196. Calandre, E. P., Bembibre, J., Arnedo, M. L. & Becerra, D. Cognitive disturbances and regional cerebral blood flow abnormalities in migraine patients: their relationship with the clinical manifestations of the illness. *Cephalalgia* **22**, 291–302 (2002).
197. Kalaydjian, a., Zandi, P. P., Swartz, K. L., Eaton, W. W. & Lyketsos, C. How migraines impact cognitive function: Findings from the Baltimore ECA. *Neurology* **68**, 1417–1424 (2007).
198. Suhr, J. a. & Seng, E. K. Neuropsychological functioning in migraine: Clinical and research implications. *Cephalalgia* **32**, 39–54 (2012).
199. Lu, Y. M. *et al.* Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. *J. Neurosci.* **17**, 5196–5205 (1997).
200. Bohbot, V. D. *et al.* Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. *Neuropsychologia* **36**, 1217–1238 (1998).
201. Wang, D. *et al.* Genetic enhancement of memory and long-term potentiation but not CA1 long-term depression in NR2B transgenic rats. *PLoS One* **4**, 1–8 (2009).
202. Matus-Amat, P., Higgins, E. a, Barrientos, R. M. & Rudy, J. W. The role of the dorsal hippocampus in the acquisition and retrieval of context memory representations. *J. Neurosci.* **24**, 2431–2439 (2004).
203. Moses, S. N., Cole, C., Driscoll, I. & Ryan, J. D. Differential contributions of hippocampus, amygdala and perirhinal cortex to recognition of novel objects, contextual stimuli and stimulus relationships. *Brain Res. Bull.* **67**, 62–76 (2005).
204. Han, X. *et al.* Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. *Cell Stem Cell* **12**, 342–353 (2013).
205. Saxe, M. D. *et al.* Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 17501–17506 (2006).

206. Jolas, T. *et al.* Long-term potentiation is increased in the CA1 area of the hippocampus of APP(swe/ind) CRND8 mice. *Neurobiol. Dis.* **11**, 394–409 (2002).
207. D'Hooge, R. *et al.* Neurocognitive and psychotiform behavioral alterations and enhanced hippocampal long-term potentiation in transgenic mice displaying neuropathological features of human alpha-mannosidosis. *J. Neurosci.* **25**, 6539–6549 (2005).
208. Müller, L., Tokay, T., Porath, K., Köhling, R. & Kirschstein, T. Enhanced NMDA receptor-dependent LTP in the epileptic CA1 area via upregulation of NR2B. *Neurobiol. Dis.* **54**, 183–193 (2013).
209. Taverna, F. *et al.* Defective place cell activity in nociceptin receptor knockout mice with elevated NMDA receptor-dependent long-term potentiation. *J. Physiol.* **565**, 579–591 (2005).
210. Olesen, J. & Jørgensen, M. B. Leao's spreading depression in the hippocampus explains transient global amnesia. A hypothesis. *Acta Neurol. Scand.* **73**, 219–20 (1986).
211. Strupp, M. *et al.* Diffusion-weighted MRI in transient global amnesia: elevated signal intensity in the left mesial temporal lobe in 7 of 10 patients. *Ann. Neurol.* **43**, 164–70 (1998).
212. Collingridge, G. L., Peineau, S., Howland, J. G. & Wang, Y. T. Long-term depression in the CNS. *Nat. Rev. Neurosci.* **11**, 459–473 (2010).
213. Goh, J. J. & Manahan-Vaughan, D. Synaptic depression in the CA1 region of freely behaving mice is highly dependent on afferent stimulation parameters. *Front. Integr. Neurosci.* **7**, 1 (2013).
214. Gonzalez, J., Morales, I. S., Villarreal, D. M. & Derrick, B. E. Low-frequency stimulation induces long-term depression and slow onset long-term potentiation at perforant path-dentate gyrus synapses in vivo. *J. Neurophysiol.* **111**, 1259–73 (2014).
215. Antunes, M. & Biala, G. The novel object recognition memory: Neurobiology, test procedure, and its modifications. *Cogn. Process.* **13**, 93–110 (2012).
216. Eikermann-Haerter, K. *et al.* Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. *J. Clin. Invest.* **119**, 99–109 (2009).
217. Klychnikov, O. I. *et al.* Quantitative cortical synapse proteomics of a transgenic migraine mouse model with mutated CaV2.1 calcium channels. *Proteomics* **10**, 2531–2535 (2010).
218. De Fusco, M. *et al.* Haploinsufficiency of ATP1A2 encoding the Na<sup>+</sup>/K<sup>+</sup> pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat. Genet.* **33**, 192–6 (2003).
219. Dichgans, M. *et al.* Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet* **366**, 371–7
220. Vecchia, D. & Pietrobon, D. Migraine: a disorder of brain excitatory-inhibitory balance? *Trends Neurosci.* **35**, 507–20 (2012).
221. De Vries, B., Frants, R. R., Ferrari, M. D. & van den Maagdenberg, A. M. J. M. Molecular genetics of migraine. *Hum. Genet.* **126**, 115–32 (2009).
222. Vecchia, D., Tottene, A., van den Maagdenberg, A. M. J. M. & Pietrobon, D. Mechanism underlying unaltered cortical inhibitory synaptic transmission in contrast with enhanced excitatory transmission in CaV2.1 knockin migraine mice. *Neurobiol. Dis.* **69**, 225–34 (2014).

223. Riedel, G. Glutamate receptor function in learning and memory. *Behav. Brain Res.* **140**, 1–47 (2003).
224. Nakazawa, K. Requirement for Hippocampal CA3 NMDA Receptors in Associative Memory Recall. *Science* **297**, 211–218 (2002).
225. Bevilacqua, L. R., Medina, J. H., Izquierdo, I. & Cammarota, M. Memory consolidation induces N-methyl-D-aspartic acid-receptor- and Ca<sup>2+</sup>/calmodulin-dependent protein kinase II-dependent modifications in alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor properties. *Neuroscience* **136**, 397–403 (2005).
226. Morris, R. G. M. NMDA receptors and memory encoding. *Neuropharmacology* **74**, 32–40 (2013).
227. Dilekoz, E. *et al.* Migraine mutations impair hippocampal learning despite enhanced long-term potentiation. *J. Neurosci.* **35**, 3397–402 (2015).
228. Deacon, R. M. J. Assessing nest building in mice. *Nat. Protoc.* **1**, 1117–9 (2006).
229. Weyer, S. W. *et al.* APP and APLP2 are essential at PNS and CNS synapses for transmission, spatial learning and LTP. *EMBO J.* **30**, 2266–80 (2011).
230. Deacon, R. M. J. & Rawlins, J. N. P. T-maze alternation in the rodent. *Nat. Protoc.* **1**, 7–12 (2006).
231. Blasi, F. *et al.* Recognition memory impairments after subcortical white matter stroke in mice. *Stroke* **45**, 1468–1473 (2014).
232. Aarts, E. *et al.* The light spot test: measuring anxiety in mice in an automated home-cage environment. *Behav. Brain Res.* **294**, 123–130 (2015).
233. Akkerman, S., Prickaerts, J., Steinbusch, H. W. M. & Blokland, A. Object recognition testing: Statistical considerations. *Behav. Brain Res.* **232**, 317–322 (2012).
234. Jirkof, P. Burrowing and nest building behavior as indicators of well-being in mice. *J. Neurosci. Methods* **234**, 139–146 (2014).
235. Sharma, S., Rakoczy, S. & Brown-Borg, H. Assessment of spatial memory in mice. *Life Sci.* **87**, 521–36 (2010).
236. Harrison, F. E., Hosseini, a. H. & McDonald, M. P. Endogenous anxiety and stress responses in water maze and Barnes maze spatial memory tasks. *Behav. Brain Res.* **198**, 247–251 (2009).
237. Hansen, J. M., Hauge, A. W., Ashina, M. & Olesen, J. Trigger factors for familial hemiplegic migraine. *Cephalalgia* **31**, 1274–1281 (2011).
238. Gil-Gouveia, R., Oliveira, A. G. & Martins, I. P. Assessment of cognitive dysfunction during migraine attacks: a systematic review. *J. Neurol.* **262**, 654–665 (2015).
239. Popoli, M., Yan, Z., McEwen, B. S. & Sanacora, G. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat. Rev. Neurosci.* **13**, (2011).
240. Lauritzen, M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain* **117** ( Pt 1), 199–210 (1994).
241. Donnet, A. Transient Global Amnesia Triggered by Migraine in a French Tertiary-Care Center: An 11-Year Retrospective Analysis. *Headache* **55**, 853–9 (2015).
242. Deacon, R. M. J. & Rawlins, J. N. P. Hippocampal lesions, species-typical behaviours and anxiety in mice. *Behav. Brain Res.* **156**, 241–249 (2005).
243. Deacon, R. M. J., Croucher, A. & Rawlins, J. N. Hippocampal cytotoxic lesion effects on species-typical behaviours in mice. *Behav. Brain Res.* **132**, 203–213 (2002).

244. Law, C. W., Chen, Y., Shi, W. & Smyth, G. K. voom: Precision weights unlock linear model analysis tools for RNA-seq read counts. *Genome Biol.* **15**, R29 (2014).
245. Robinson, M. D., McCarthy, D. J. & Smyth, G. K. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics* **26**, 139–40 (2010).
246. Anders, S. & Huber, W. Differential expression analysis for sequence count data. *Genome Biol.* **11**, R106 (2010).
247. Rapaport, F. *et al.* Comprehensive evaluation of differential gene expression analysis methods for RNA-seq data. *Genome Biol.* **14**, R95 (2013).
248. Vries, B. De *et al.* RNA expression profiling in brains of familial hemiplegic migraine type 1 knock-in mice. *Cephalalgia* **34**, 174–82 (2014).
249. Wellcome Trust Sanger Institute. Mouse Genomes Project - Query SNPs, indels or SVs ([http://www.sanger.ac.uk/sanger/Mouse\\_SnpViewer/rel-1410](http://www.sanger.ac.uk/sanger/Mouse_SnpViewer/rel-1410))
250. Keane, T. M. *et al.* Mouse genomic variation and its effect on phenotypes and gene regulation. *Nature* **477**, 289–94 (2011).
251. Gao, Z. *et al.* Cerebellar Ataxia by Enhanced CaV2.1 Currents Is Alleviated by Ca<sup>2+</sup>-Dependent K<sup>+</sup>-Channel Activators in Cacna1aS218L Mutant Mice. *J. Neurosci.* **32**, 15533–15546 (2012).
252. Tedford, H. W. & Zamponi, G. W. Direct G protein modulation of Cav2 calcium channels. *Pharmacol. Rev.* **58**, 837–62 (2006).
253. Weiss, N., Sandoval, A., Felix, R., Van den Maagdenberg, A. & De Waard, M. The S218L familial hemiplegic migraine mutation promotes deinhibition of Ca(v)2.1 calcium channels during direct G-protein regulation. *Pflugers Arch.* **457**, 315–26 (2008).
254. Rumpel, S., LeDoux, J., Zador, A. & Malinow, R. Postsynaptic receptor trafficking underlying a form of associative learning. *Science* **308**, 83–8 (2005).
255. Rosenberg, T. *et al.* The roles of protein expression in synaptic plasticity and memory consolidation. *Front. Mol. Neurosci.* **7**, 86 (2014).
256. Alberini, C. M. & Ledoux, J. E. Memory reconsolidation. *Curr. Biol.* **23**, R746–R750 (2013).
257. Barnes, P., Kirtley, A. & Thomas, K. L. Quantitatively and qualitatively different cellular processes are engaged in CA1 during the consolidation and reconsolidation of contextual fear memory. *Hippocampus* **22**, 149–71 (2012).
258. Brebner, K. *et al.* Nucleus accumbens long-term depression and the expression of behavioral sensitization. *Science* **310**, 1340–3 (2005).
259. Langmead, B., Trapnell, C., Pop, M. & Salzberg, S. L. Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. *Genome Biol.* **10**, R25 (2009).
260. Faulkner, G. J. *et al.* A rescue strategy for multimapping short sequence tags refines surveys of transcriptional activity by CAGE. *Genomics* **91**, 281–288 (2008).
261. De Hoon, M.J., Bertin, N., Chalk, A. M. in *Cap Anal. Gene Expr. Sci. Decod. Gene Transcr.* 101–121 (Pan Stanford Publishing Pte. Ltd, Yokohama, 2010).
262. Pardo, L. M. *et al.* Regional differences in gene expression and promoter usage in aged human brains. *Neurobiol. Aging* **34**, 1825–36 (2013).
263. Sandelin, A. *et al.* Mammalian RNA polymerase II core promoters: insights from genome-wide studies. *Nat. Rev. Genet.* **8**, 424–436 (2007).

264. Hubbard, T. *et al.* The Ensembl genome database project. *Nucleic Acids Res.* **30**, 38–41 (2002).
265. Quinlan, A. R. & Hall, I. M. BEDTools: a flexible suite of utilities for comparing genomic features. *Bioinformatics* **26**, 841–2 (2010).
266. Arner, E. *et al.* Transcribed enhancers lead waves of coordinated transcription in transitioning mammalian cells. *Science* (80-. ). **347**, 1–8 (2015).
267. Tullai, J. W. *et al.* Immediate-early and delayed primary response genes are distinct in function and genomic architecture. *J. Biol. Chem.* **282**, 23981–23995 (2007).
268. Okaty, B. W., Sugino, K. & Nelson, S. B. A quantitative comparison of cell-type-specific microarray gene expression profiling methods in the mouse brain. *PLoS One* **6**, 1–10 (2011).
269. Wang, J., Duncan, D., Shi, Z. & Zhang, B. WEB-based GENE SeT AnaLYsis Toolkit (WebGestalt): update 2013. *Nucleic Acids Res.* **41**, 77–83 (2013).
270. Tarca, A. L. *et al.* A novel signaling pathway impact analysis. *Bioinformatics* **25**, 75–82 (2009).
271. Sato, S. *et al.* A mammalian homolog of *Drosophila melanogaster* transcriptional coactivator intersex is a subunit of the mammalian Mediator complex. *J. Biol. Chem.* **278**, 49671–4 (2003).
272. Ögren, S. O. *et al.* The role of 5-HT<sub>1A</sub> receptors in learning and memory. *Behav. Brain Res.* **195**, 54–77 (2008).
273. Yu, J. *et al.* MTMR4 attenuates transforming growth factor beta (TGF-beta) signaling by dephosphorylating R-smads in endosomes. *J. Biol. Chem.* **285**, 8454–8462 (2010).
274. Bae, J. J. *et al.* Increased transforming growth factor- $\beta$ 1 modulates glutamate receptor expression in the hippocampus. *Int. J. Physiol. Pathophysiol. Pharmacol.* **3**, 9–20 (2011).
275. Arendt, K. L. *et al.* Retinoic Acid and LTP Recruit Postsynaptic AMPA Receptors Using Distinct SNARE-Dependent Mechanisms. *Neuron* 442–456 (2015). doi:10.1016/j.neuron.2015.03.009
276. Jurado, S. *et al.* LTP Requires a Unique Postsynaptic SNARE Fusion Machinery. *Neuron* **77**, 542–558 (2013).
277. Stern, C. M. & Mermelstein, P. G. Caveolin regulation of neuronal intracellular signaling. *Cell. Mol. Life Sci.* **67**, 3785–3795 (2010).
278. Andero, R., Dias, B. G. & Ressler, K. J. A role for Tac2, Nk<sub>1</sub>B, and Nk<sub>3</sub> receptor in normal and dysregulated fear memory consolidation. *Neuron* **83**, 444–54 (2014).
279. Gkika, D. *et al.* TRP channel-associated factors are a novel protein family that regulates TRPM8 trafficking and activity. *J. Cell Biol.* **208**, 89–107 (2015).
280. Tao, J. *et al.* MiR-207/352 regulate lysosomal-associated membrane proteins and enzymes following ischemic stroke. *Neuroscience* **305**, 1–14 (2015).
281. Hall, J., Thomas, K. L. & Everitt, B. J. Cellular imaging of zif268 expression in the hippocampus and amygdala during contextual and cued fear memory retrieval: selective activation of hippocampal CA1 neurons during the recall of contextual memories. *J. Neurosci.* **21**, 2186–93 (2001).
282. Sowa, G. Novel insights into the role of caveolin-2 in cell- and tissue-specific signaling and function. *Biochem. Res. Int.* **2011**, (2011).
283. Scherer, P. E. *et al.* Cell-type and Tissue-specific Expression of Caveolin-2. *J. Biol. Chem.* **272**, 29337–29346 (1997).

284. Gaudreault, S. B., Chabot, C., Gratton, J. P. & Poirier, J. The Caveolin Scaffolding Domain Modifies 2-Amino-3-hydroxy-5-methyl-4-isoxazole Propionate Receptor Binding Properties by Inhibiting Phospholipase A2 Activity. *J. Biol. Chem.* **279**, 356–362 (2004).
285. Sase, S., Stork, O., Lubec, G. & Li, L. Contextual fear conditioning modulates hippocampal AMPA-, GluN1- and serotonin receptor 5-HT1A-containing receptor complexes. *Behav. Brain Res.* **278**, 44–54 (2015).
286. Massicotte, G. Modification of glutamate receptors by phospholipase A2: its role in adaptive neural plasticity. **57**, 1542–1550 (2000).
287. Keeffe, B. A. O., Cilia, S., Maiyar, A. C., Vaysberg, M. & Firestone, G. L. The serum- and glucocorticoid-induced protein kinase-1 ( Sgk-1 ) mitochondria connection: Identification of the IF-1 inhibitor of the F(1) F(0)-ATPase as a mitochondria-specific binding target and the stress-induced mitochondrial localization of endogeno. *Biochimie* **95**, 1258–1265 (2013).
288. Fortpied, J., Maliekal, P., Vertommen, D. & Van Schaftingen, E. Magnesium-dependent phosphatase-1 is a protein-fructosamine-6-phosphatase potentially involved in glycation repair. *J. Biol. Chem.* **281**, 18378–18385 (2006).
289. Cai, Z. *et al.* Role of RAGE in Alzheimer’s Disease. *Cell. Mol. Neurobiol.* (2015). doi:10.1007/s10571-015-0233-3
290. Yan, D. *et al.* Effects of Advanced Glycation End Products on Calcium Handling in Cardiomyocytes. *Cardiology* **129**, 75–83 (2014).
291. Gant, J. C. *et al.* Reversal of Aging-Related Neuronal Ca<sup>2+</sup> Dysregulation and Cognitive Impairment by Delivery of a Transgene Encoding FK506-Binding Protein 12.6/1b to the Hippocampus. *J. Neurosci.* **35**, 10878–10887 (2015).
292. Hanley, J. G. Endosomal sorting of AMPA receptors in hippocampal neurons. *Biochem. Soc. Trans.* **38**, 460–465 (2010).
293. Regehr, W. G. Short-term presynaptic plasticity. *Cold Spring Harb. Perspect. Biol.* **4**, 1–19 (2012).
294. Castillo, P. E. Presynaptic LTP and LTD of excitatory and inhibitory synapses. *Cold Spring Harb. Perspect. Biol.* **4**, (2012).
295. Parsons, M. J. *et al.* Using hippocampal microRNA expression differences between mouse inbred strains to characterise miRNA function. *Mamm. Genome* **19**, 552–560 (2008).
296. Lenselink, A. M. *et al.* Strain Differences in Presynaptic Function: Proteomics, Ultrastructure and Physiology of Hippocampal Synapses in DBA/2J and C57Bl/6J mice. *J. Biol. Chem.* **290**, 15635–45 (2015).
297. Lu, Y. & Wehner, J. M. Enhancement of contextual fear-conditioning by putative (??)-??-amino- 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulators and N-methyl-D-aspartate (NMDA) receptor antagonists in DBA/2J mice. *Brain Res.* **768**, 197–207 (1997).
298. Fioravante, D. *et al.* Protein kinase C is a calcium sensor for presynaptic short-term plasticity. *Elife* **3**, e03011 (2014).
299. Kreft, M., Bak, L. K., Waagepetersen, H. S. & Schousboe, A. Aspects of astrocyte energy metabolism, amino acid neurotransmitter homeostasis and metabolic compartmentation. *ASN Neuro* **4**, 187–199 (2012).
300. Coleman, D. L. & Kuzava, J. E. Genetic regulation of malic enzyme activity in the mouse. *J. Biol. Chem.* **266**, 21997–22002 (1991).



301. Inyushin, M. *et al.* Potassium channel activity and glutamate uptake are impaired in astrocytes of seizure-susceptible DBA/2 mice. *Epilepsia* **51**, 1707–1713 (2010).
302. Alonso, I. *et al.* Motor and cognitive deficits in the heterozygous leaner mouse, a Cav2.1 voltage-gated Ca<sup>2+</sup> channel mutant. *Neurobiol. Aging* **29**, 1733–1743 (2008).
303. Takahashi, E., Niimi, K. & Itakura, C. Age-related spatial and nonspatial short-term memory in Cav2.1c1 mutant mice, Rolling Nagoya. *Behav. Brain Res.* **204**, 241–245 (2009).
304. Takahashi, E. & Niimi, K. Spatial learning deficit in aged heterozygous Cav2.1 channel mutant mice, rolling mouse Nagoya. *Exp. Gerontol.* **44**, 274–279 (2009).
305. Mallmann, R. T. *et al.* Ablation of CaV2.1 Voltage-Gated Ca<sup>2+</sup> Channels in Mouse Forebrain Generates Multiple Cognitive Impairments. *PLoS One* **8**, e78598 (2013).
306. Lee, Y.-S. Genes and signaling pathways involved in memory enhancement in mutant mice. *Mol. Brain* **7**, 43 (2014).
307. Silva, A. J. Molecular and cellular cognitive studies of the role of synaptic plasticity in memory. *J. Neurobiol.* **54**, 224–37 (2003).
308. Earls, L. R. *et al.* Dysregulation of presynaptic calcium and synaptic plasticity in a mouse model of 22q11 deletion syndrome. *J. Neurosci.* **30**, 15843–15855 (2010).
309. Reymann, K. G. & Frey, J. U. The late maintenance of hippocampal LTP: Requirements, phases, ‘synaptic tagging’, ‘late-associativity’ and implications. *Neuropharmacology* **52**, 24–40 (2007).
310. Pineda, V. V. *et al.* Removal of G(ialpha1) constraints on adenylyl cyclase in the hippocampus enhances LTP and impairs memory formation. *Neuron* **41**, 153–63 (2004).
311. Garcia-Alvarez, G. *et al.* Impaired spatial memory and enhanced long-term potentiation in mice with forebrain-specific ablation of the Stim genes. *Front. Behav. Neurosci.* **9**, 1–12 (2015).
312. Josselyn, S. A. Continuing the search for the engram: examining the mechanism of fear memories. *J. Psychiatry Neurosci.* **35**, 221–8 (2010).
313. Mayford, M. The search for a hippocampal engram. *Philos. Trans. R. Soc. B Biol. Sci.* **369**, 20130161–20130161 (2013).
314. Schmidt, B., Marrone, D. F. & Markus, E. J. Disambiguating the similar: The dentate gyrus and pattern separation. *Behav. Brain Res.* **226**, 56–65 (2012).
315. Malenka, R. C. Synaptic plasticity in the hippocampus: LTP and LTD. *Cell* **78**, 535–8 (1994).
316. Smith, D. M. & Mizumori, S. J. Y. Hippocampal place cells, context, and episodic memory. *Hippocampus* **16**, 716–29 (2006).
317. Maren, S. Seeking a Spotless Mind: Extinction, Deconsolidation, and Erasure of Fear Memory. *Neuron* **70**, 830–845 (2011).
318. Takahashi, E., Niimi, K. & Itakura, C. Subthreshold pharmacological and genetic approaches to analyzing CaV2.1-mediated NMDA receptor signaling in short-term memory. *Eur. J. Pharmacol.* **645**, 113–8 (2010).
319. Niimi, K. *et al.* Blockade of Cav2.1-mediated NMDA receptor signaling disrupts conditioned fear extinction. *Behav. Brain Res.* **259**, 45–9 (2014).
320. Moseley, A. E. *et al.* Deficiency in Na,K-ATPase alpha isoform genes alters spatial learning, motor activity, and anxiety in mice. *J. Neurosci.* **27**, 616–626 (2007).

321. Pohlmann-Eden, B. *et al.* The relevance of neuropsychiatric symptoms and cognitive problems in new-onset epilepsy – Current knowledge and understanding. *Epilepsy Behav.* **51**, 199–209 (2015).
322. Peroutka, S. J. What turns on a migraine? A systematic review of migraine precipitating factors. *Curr. Pain Headache Rep.* **18**, 454 (2014).
323. Shyti, R. *et al.* Stress hormone corticosterone enhances susceptibility to cortical spreading depression in familial hemiplegic migraine type 1 mutant mice. *Exp. Neurol.* **263**, 214–20 (2015).
324. Loebel, A., Le Bé, J.-V., Richardson, M. J. E., Markram, H. & Herz, A. V. M. Matched pre- and post-synaptic changes underlie synaptic plasticity over long time scales. *J. Neurosci.* **33**, 6257–66 (2013).
325. MacDougall, M. J. & Fine, A. The expression of long-term potentiation: reconciling the preists and the postivists. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **369**, 20130135 (2014).
326. Middei, S., Ammassari-Teule, M. & Marie, H. Synaptic plasticity under learning challenge. *Neurobiol. Learn. Mem.* **115**, 108–115 (2014).