**a.** Transcriptional luciferase assay for the four SNPs in human neuroblastoma cell line SH-SY5Y, $F(4) = 7.87$, ***$p < 0.001$, posthoc analysis: $t_{pGL3-rs2660304} (4.482)$, ***$p < 0.001$, $r = 0.91$; $t_{rs2660304-rs2802535} (-4.57)$, ***$p < 0.001$, $r = 0.92$; $t_{rs2660304-rs1625579} (-4.57)$, ***$p < 0.001$, $r = 0.92$; $t_{pGL3-rs2660304} (1.65)$, ns$\;p = 0.4781$, $r = 0.64$, n: three experiments. **b.** Fold-change differences of MIR137 determined by qRT-PCR from **Fig. 1c**, separated by its individual lines, $W_{IN} = 65$, *$p = 0.0157$, $r = -0.40$, box plot shows, in ascending order, the lowest maximum value, the first quartile, median, third quartile and the highest maximum value, dots are outlier. **c.** Summary table of the human fibroblasts and their genotype alleles for the four disease-associated SNPs. First four are homozygous for common major alleles; the last two are homozygous for the minor alleles. **d.** Examples of successfully induced neurons before FACS. Left: bright field, middle: transduced cells, right: expression of the neuron-specific HSV-CamKII-mCherry construct. Scale bar: 100 μm. Before any iN experiments, cells were visually controlled for successful reprogramming. **e.** Relative microRNA levels in induced neurons from common major and minor allele SNPs determined by RT-qPCR, $t_{miR-9} (7.87) = -0.2$, ns$\;p = 0.8475$, $r = 0.07$, $t_{miR-19b} (8.28) = 0.12$, ns$\;p = 0.9047$, $r = 0.04$, $t_{miR-124} (13.89) = -0.16$, ns$\;p = 0.8773$, $r = 0.04$, box plot shows, in ascending order, the lowest maximum value, the first quartile, median, third quartile and the highest maximum value, dots are outlier, n: number of samples from at least two reprogramming, s.e.m.
Presynaptic target genes validation.

a. Summary table of putative in silico predicted miR-137 target genes involved in “synaptic transmission”.

Red: targets tested in this study. b. Luciferase assay results for additional putative miR-137 targets, light grey and dark orange: miR-137 binding site deletion construct (Δ), \( W_{\text{Calb1}} = 170, *p = 0.0180, r = -0.43; \)
\( t_{\text{CamK2}}(14.58) = -0.14, \text{ns} p = 0.8888, r = 0.04; F_{\text{Nrxn1}}(3, 80) = 13.89, *** p < 0.001; F_{\text{Stx8}}(3, 56) = 0.60, \text{ns} p = 0.6159; W_{\text{Stxbp5}} = 187, \text{ns} p = 0.4381, r = -0.13; F_{\text{Syn2a}}(3, 20) = 0.05, \text{ns} p = 0.9831; W_{\text{Syn2a}} = 201, \text{ns} p = 0.6326, r = 0.07; F_{\text{Syn2b}}(3, 74) = 0.72, \text{ns} p = 0.545; F_{\text{Synj1}}(3, 56) = 1.30, \text{ns} p = 0.2845; W_{\text{Synpr}} = 278, \text{ns} p = 0.1515, r = -
0.22; $W_{SYT9} = 121, ns p = 0.2983, r = -0.18; W_{Vamp1} = 119, ns p = 0.1786 r = -0.22; F_{Vamp2}(3, 81) = 3.92, *p = 0.0115; W_{Vamp7} = 172, ns p = 0.7637, r = -0.05. c. Example images of FM4–64 recording, white: induced neuron, green: FM4–64, arrow: terminal. ns: not significant, s.e.m.
miR-137<sub>OE</sub> validation and <i>in vivo</i> expression.
a–b. Relative miR-137 expression level determined by qRT-PCR. a. in HEK-293T cells, $T_x(2) = 44.89$, ***$p < 0.001$, $r = 1$; b. in primary cortical neuronal culture at DIV14, $T_y(3.97) = 4.48$, *$p = 0.0112$, $r = 0.91$, $n$: number of experiments. c. Additional examples of hippocampi tile-scans injected with the lentivirus expressing the ΔmiR-137OE or miR-137OE constructs, immunostained for mCherry (magenta) and the nuclei dye DAPI (blue). CA3: *Cornu Ammonis* region 3. Staining was reliably throughout this study. d. Immunostaining of ΔmiR-137OE or miR-137OE-transduced dentate gyrus for DAPI (blue), mCherry (magenta), glial fibrillary acidic protein (GFAP), and ionized calcium-binding adapter molecule (Iba1). This experiment was repeated in at least three different animals. Scale bars: 100 μm. s.e.m.
Supplementary Figure 4

Ultrastructural analysis for miR-137\textsubscript{OE} and \textit{ΔmiR}-137\textsubscript{OE}.

\textbf{a.} Ultrastructural images of the mossy fiber presynaptic terminals in \textit{ΔmiR}-137\textsubscript{OE} and miR-137\textsubscript{OE} mice. Black arrow: mCherry gold-particle. Orange arrows: gap within the vesicle pool in miR-137\textsubscript{OE} synapses, * active zone, scale bar: 100 nm.

\textbf{b.} Total number of vesicles for \textit{ΔmiR}-137\textsubscript{OE} (black, \(n = 84\)) and miR-137\textsubscript{OE} (orange, \(n = 112\)), \(W = 4294\), \(ns p = 0.2973\), \(r = -0.07\), box plot shows, in ascending order, the lowest maximum value, the first quartile, median, third quartile and the highest maximum value, dots are outlier, \(n\): number of analyzed synapses of at least three animals. \(ns\): not significant, s.e.m.
Supplementary Figure 5

Behavior analysis for miR-137OE and ΔmiR-137OE.

a–c. Equivalent levels of locomotion and a trend for anxiety in miR-137OE as measured by a. Open-field arena paradigm: margin distance: t(12.94) = -0.61, \( ns \ p = 0.5547, r = 0.17 \); margin time: t(12.20) = -1.89, \( ns \ p = 0.083, r = 0.48 \); center distance: t(13.83) = 2.55, \( * p = 0.023, r = 0.57 \); center time: t(12.20) = 1.89, \( ns \ p
= 0.083, r = 0.48; total distance: t(12.89) = 1.31, \( p = 0.2117, r = 0.34 \); horizontal activity: t(13.52) = 1.98, \( p = 0.0685, r = 0.47 \); vertical activity: t(13.15) = 1.36, \( p = 0.1952, r = 0.35 \); stereotype: t(13.87) = 2.13, \( p = 0.05167, r = 0.50 \). b. Light-dark box paradigm: Frequency of exploration: t(9.90) = 0.94, \( p = 0.3709, r = 0.29 \), time spend in light: t(11.88) = 0.60, \( p = 0.5585, r = 0.17 \). c. Elevated-plus maze paradigm. Panel from left to right: time spent in closed or open arm, no significant main effect, F(1, 26) = 2.09, \( p = 0.161 \), \( r = 0.29 \), time of entering did not differ between open-closed arm and the condition, F(1, 26) = 0.40, \( p = 0.535 \). Distance and velocity, \( t_{distance}(12.98) = 0.36 \), \( p = 0.7259, r = 0.10 \), \( t_{velocity}(12.97) = 0.35 \), \( p = 0.7298, r = 0.10 \). d. Nociception response, \( W = 20.5 \), \( p = 0.7471, r = −0.09 \). e. Freezing response after context and before cue in \%, t(41.97) = −1.20, \( p = 0.2381, r = 0.18 \). f. Thigmotaxis, percentage of the trail time and path that were spent in the defined thigmotaxis band (0.8) relative to the diameter of the pool, \( t_{time}(24.07) = −0.83 \), \( p = 0.4165, r = 0.17 \), \( t_{path}(25.57) = −0.15 \), \( p = 0.8838, r = 0.03 \). g. Three-chamber social interaction paradigm. Amount of time that the mouse spends to explore, left panel: new versus familiar mouse, F(2, 24) = 22.41, \( p < 0.001 \), right panel: mouse versus object, F(2, 24) = 45.5, \( p < 0.001 \). No significant difference for \( \Delta \)mir-137 OE and miR-137 OE in both experimental set-ups, \( F_{familiar \ mouse}(2, 48) = 2.41 \), \( p = 0.10 \) and \( F_{empty \ cage}(2, 48) = 2.86 \), \( p = 0.0673 \). Social paradigm for the familiar paradigm: for \( \Delta \)mir-137 OE: \( t_{familiar-middle}(−3.81) \), \( p = 0.0023 \), \( t_{familiar-new}(2.86) \), \( p = 0.0225 \), \( t_{middle-new}(6.67) \), \( p < 0.001 \); for miR137 OE: \( t_{familiar-middle}(−5.89) \), \( p < 0.001 \), \( t_{familiar-new}(3.44) \), \( p = 0.00574 \), \( t_{middle-new}(9.33) \), \( p < 0.001 \); for the empty paradigm for \( \Delta \)mir-137 OE: \( t_{empty-middle}(−6.06) \), \( p < 0.001 \), \( t_{empty-mouse}(3.35) \), \( p = 0.0718 \), \( t_{middle-mouse}(9.41) \), \( p < 0.001 \); for miR-137 OE: \( t_{empty-middle}(−4.03) \), \( p = 0.0013 \), \( t_{empty-mouse}(3.19) \), \( p = 0.0106 \), \( t_{middle-mouse}(7.22) \), \( p < 0.001 \). n: animals used for each experiment. ns: not significant, s.e.m.
Supplementary Figure 6

Sponge miR-137 and Sponge Control.
a. Additional ultrastructural images of the mossy fiber presynaptic terminals in Sponge\textsubscript{Control} and Sponge\textsubscript{miR-137} mice. Black arrow: gold-particle labeled GFP, * active zone, scale bar: 100 nm. b. Total vesicle number for Sponge\textsubscript{Control} (black, n = 50) and Sponge\textsubscript{miR-137} (blue, n = 43) mice in the presynaptic compartments at the mossy fiber synapse, $t(88.82) = -1.80$, ns $p = 0.0751$, $r = -0.19$, box plot shows, in ascending order, the lowest maximum value, the first quartile, median, third quartile and the highest maximum value, dots are outlier, n: number of analyzed synapses of at least three animals. c. Input-output curve estimated from fEPSP against the fiber volley amplitude at the mossy fiber-CA3 synapse in hippocampal slices from Sponge\textsubscript{Control} (black, n = 4) and Sponge\textsubscript{miR-137} (blue, n = 4), $F(1, 129) = 1.46$, ns $p = 0.229$, shaded area: 95% confidence interval, n: number of analyzed hippocampal slices from at least three animals. d. Open-field arena paradigm. Total distance: $t(16.5) = -0.72$, ns $p = 0.4809$, $r = 0.18$; time moving: $t(16.33) = -1.01$, ns $p = 0.3285$, $r = 0.24$; moves/counts: $t(17.51) = -0.88$, ns $p = 0.389$, $r = 0.21$; distance periphery: $t(16.37) = -0.18$, ns $p = 0.8617$, $r = 0.04$; time periphery: $t(16.19) = 2.62$, * $p = 0.0182$, $r = 0.55$; distance center: $t(12.89) = -2.80$, * $p = 0.0151$, $r = 0.62$; time center: $t(16.21) = -2.63$, * $p = 0.0182$, $r = 0.55$. e. Nociception response, $t(13.47) = 0.30$, ns $p = 0.7664$, $r = 0.08$. f. Freezing response after context and before cue in %, $t(17.12) = 0$, ns $p = 1$, $r = 0$, n: number of animals. ns: not significant, s.e.m.
Supplementary Figure 7

Endogenous expression of synaptic target genes and Syt1 restoration (miR-137-Syt1-Venus).
a–c. Endogenous target gene expression in the dentate gyrus and the mossy fiber-CA3 pathway of naïve C57BL/6 animals. a. Absolute endogenous mRNA levels measured by RT-qPCR. b–c. Endogenous protein levels of Cplx1, Nsf, Syn3 and Syt1 by b. western blot (cropped. Full-length blots are presented in Supplementary Fig. 9), and c. immunohistochemistry. Vibratome sections, immunolabeled against the mossy fiber pathway marker zinc transporter 3 (ZnT3, green), the target gene (magenta), and stained with nuclei dye DAPI (blue). Scale bar: 10 µm. The observation was repeated in at least three different animals. d. Additional ultrastructural images of the mossy fiber presynaptic terminal of ΔmiR-137OE-Venus (grey), miR-137OE-Venus (red), miR-137OE-Syt1-Venus (green), and ΔmiR-137OE-Syt1-Venus (purple) mice, black arrow: gold particles staining of Venus, red arrows: gap within the vesicle pool in miR-137OE-Venus, * active zone, scale bar: 100 nm. e. Total vesicle number for ΔmiR-137OE-Venus (grey, n=56), miR-137OE-Venus (red, n=53), miR-137OE-Syt1-Venus (green, n=56), and ΔmiR-Syt1-Venus (purple, n=58), $H(3) = 77.75$, ***$p < 0.001$. Multiple comparison two-tailed test after Kruskal-Wallis, *$p < 0.05$, box plot shows, in ascending order, the lowest maximum value, the first quartile, median, third quartile and the highest maximum value, dots are outlier. f. Nociception response measured by mean speed of movement during shock in (cm s$^{-1}$), $H(3) = 6.10$, ns$p = 0.1068$. ns: not significant, s.e.m.
Supplementary Figure 8

Syt1-KD and Syt1-KD\textsubscript{Control} in the DG-CA3 synapse and miR-137\textsubscript{OE} and ΔmiR-137\textsubscript{OE} at the entorhinal cortex-DG synapse.
a–c. Electrophysiological properties of Syt1 knockdown in acute hippocampal slices, black: Syt1-KD
brown: Syt1-shRNA. n: number of hippocampal slice preparation from at least 3 animal. a. LTP recording for Syt1-shRNA (n = 5) and Syt-1 control (n = 5), H(1) = 129.44 ***p < 0.001. Arrows: application of either high frequency stimulation or DCG-IV, embedded representative fEPSP traces, grey traces: baseline level before stimulation. Right bar chart: LTP magnitude calculated by averaging fEPSP amplitude during the last 10 min (50–60 min) recording, W = 2688, ***p < 0.001, r = −0.39. b. Input-output curve from fEPSP against the fiber volley amplitude at the mossy fiber-CA3 synapse from Syt1-shRNA (brown, n=5) and Syt-1 control (black, n=5), H(1) = 6.63, *p = 0.0100, shaded area: 95% confidence interval. c. fEPSP amplitude for 1 Hz sustained stimulation for Syt1-shRNA (n = 5) and Syt-1 control (black, n = 5), H(1) = 47.32, ***p < 0.001. Embedded: representative traces, grey traces: response to the 1st stimulation. d. BrdU incorporation in miR-137OE (orange) compared to ΔmiR-137OE (black) in the dentate gyrus, t(4.77) = −3.18, *p = 0.0264. Right panel: immunostaining for BrdU (green) and virus expression of mCherry (red), n: number of animals. b. LTP recording at the molecular layer of the dentate gyrus with stimulation of medial perforant path in miR-137OE and control ΔmiR-137OE, H(1) = 3.19, ns p = 0.0741, arrows: application of stimulation paradigm, right bar chart: LTP magnitude during the last 10 min (50–60 min) recording, W = 1528, ns p = 0.9285, r = −0.01. c. Input-output curve estimated from fEPSP against the fiber volley amplitude measured at a range of stimulus intensities at the molecular layer of the dentate gyrus in hippocampal slices from ΔmiR-137OE (black, n=12) and miR-137OE (orange, n = 14), F(1,66) = 0.91, ns p = 0.4543, shaded area: 95% confidence interval. n: number of analyzed hippocampal slices from at least three animals, ns: not significant, s.e.m.
Supplementary Figure 9
**Full-length western blot images.**
Samples were run on a 4–15% TGX SDS-gradient gel (Bio-Rad Laboratories). Molecular weight (M, in kDa): BLUEstain 2 Protein ladder, 5–245 kDa (Goldbio). Images were taken with the infrared imaging system from Odysee (Li-cor). This allows staining for two proteins at the same time on the same plot. Light-blue bands indicate oversaturation. a. for Fig. 2e, left and right panel show the same plot, but with adjustment of brightness and contrast; b. for Fig. 2d, the second and the fourth row are adjustment in brightness and contrast from the plots in the first and the third row, respectively; c. and d. for **Supplementary Fig. 7.** For Syt1, we always observed in varying intensity a band at ~75 kDa. This band is likely to be unstripped Nsf. We tried to optimize the stripping procedure, however we could never remove the strong signal band for Nsf completely. For consistency, we decided to stain always Syt1 after Nsf.
Supplementary Table 1: Primers

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**Promoter luciferase activity assay**

Rs2660304_5-MluI  GCG ACACGT tgtaagtaacatgtcaagaaatgatgagtgtg
Rs2660304_3-XhoI  CCG CTACAG gcaataacacagtcaatccgtattatccacc
Rs1198583_5-KpnI  GCG ACACGT gtgggtatcagaaatgtaattttgag
Rs1198583__3-XhoI  CCG CTACAG atctctctgctctgctctcc
Rs1625579_5-KpnI  GCG ACACGT gcctagcttatctgtaaattgtgagaaagcc
Rs1625579__3-XhoI  CCG CTACAG tctacctctctactttgagattatctacaacc
Rs2802535_5-MluI  GCG ACACGT tggaaacgagacatggccatagtgttaagc
Rs2802535__3-XhoI  CCG CTACAG tgcctctactctctctctcttacacttc