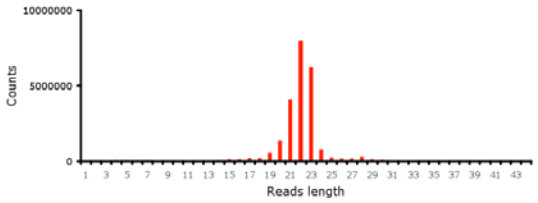
SUPPORTING ONLINE MATERIAL

Supplementary Figures

Figure S1

a



b

Sequence length statistics

Sequence range	% reads			
	Replicate 1	Replicate 2	Replicate 3	Replicate 4
0	0.03%	2.00%	0.41%	0.15%
1-17	3.42%	5.43%	3.25%	5.44%
18-26	89.48%	89.01%	90.69%	89.22%
27-44	5.09%	2.13%	3.76%	3.27%
Not attributed *	1.98%	1.43%	1.90%	1.92%

c

Sequence mapping statistics

Mapping to	% reads 18-26				
	Replicate 1	Replicate 2	Replicate 3	Replicate 4	Brain
Reference Genome					
Uniquely	31.61%	39.34%	49.93%	48.01%	-
Multiple	64.75%	56.58%	44.19%	46.26%	-
miRBase mature seq					
Uniquely	60.53%	75.04%	69.29%	59.84%	48.51%
Multiple	0.02%	0.06%	0.13%	0.02%	0.25%

Figure S1. Length distribution of sequenced reads and the respective length and mapping statistics per probe**. (a)** Length range of sequenced reads after trimming for the 3' adapter sequence and **(b)** proportion (in %) of these reads in three different nucleotide length classes. Vast majority of reads are found within 18-26 nt and only this class of reads has been tested further. **(c)** % of sequenced reads mapping against mouse genome (NCBI Assembly M37) and the known mouse miRNAome (miRBase, as of Dec 2010). Multiple mapping against mouse genome was set up to a threshold of 10.

Figure S2

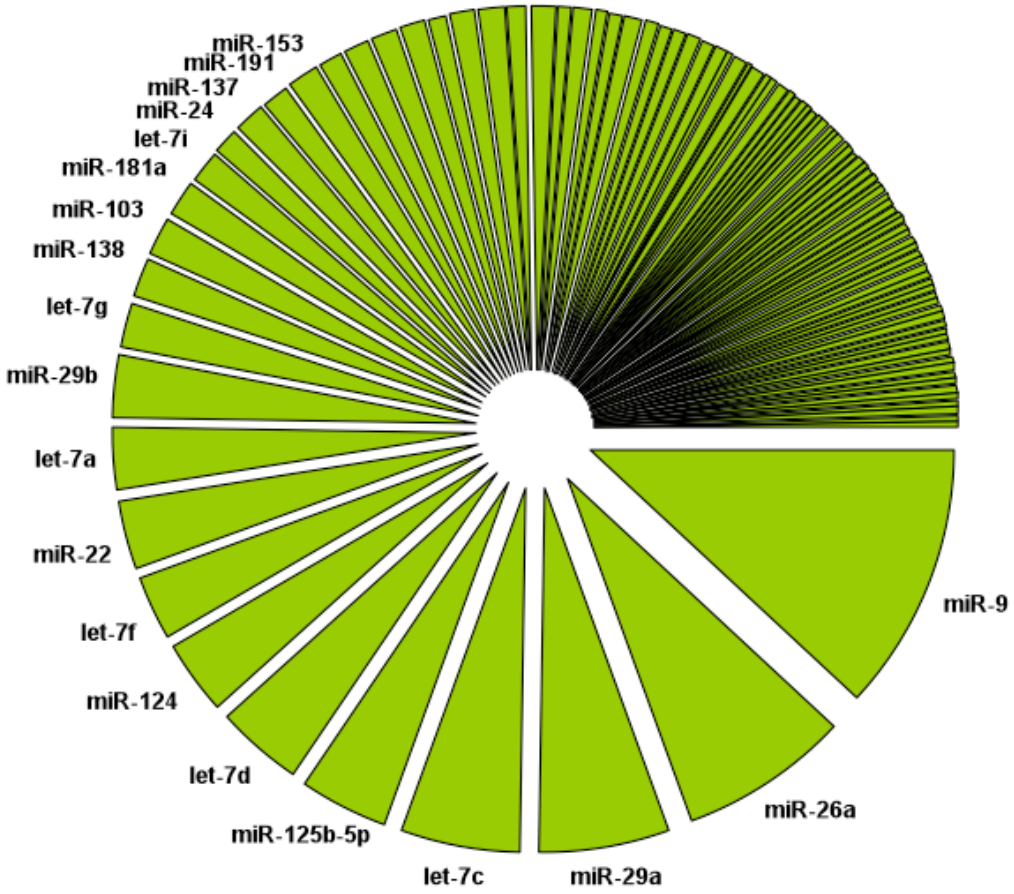
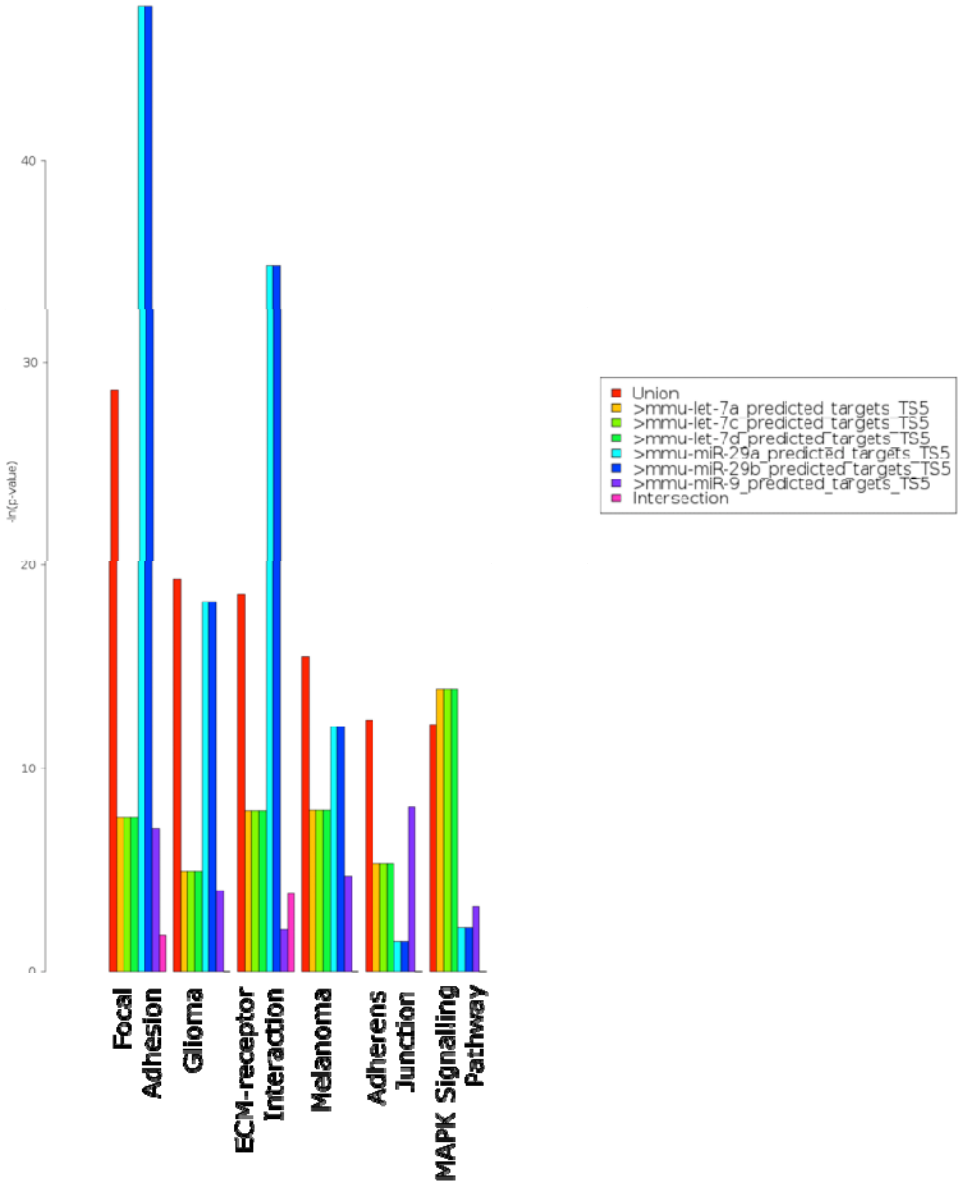


Figure S2. Distribution of miRNAs in mouse whole brain. Proportion of sequence counts per miRNA with respect to the total number of counts attributed to miRNAs in this tissue. Only names of miRNAs belonging to the top 20 ranked miRNAs are depicted. Massive parallel sequencing data from whole brain was obtained from previously published work (Chiang et al, 2010).

Figure S3

a



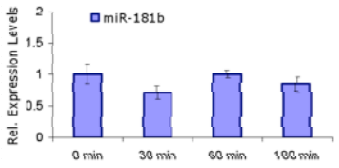
b

miR-181b Targets GO-Term Analysis

	Biological Process	p-value
1	regulation of gene expression	1.83E-19
2	regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	1.10E-18
3	regulation of macromolecule biosynthetic process	6.77E-18
4	regulation of transcription	7.03E-18
5	regulation of cellular biosynthetic process	1.35E-17

PANTHER Database > Biological Process

1	RNA metabolism	1.31E-17
2	transcription, initiation	1.10E-16
3	nucleoside, nucleotide and nucleic acid metabolism	1.70E-09
4	angiogenesis	1.40E-08
5	neurogenesis	8.03E-08



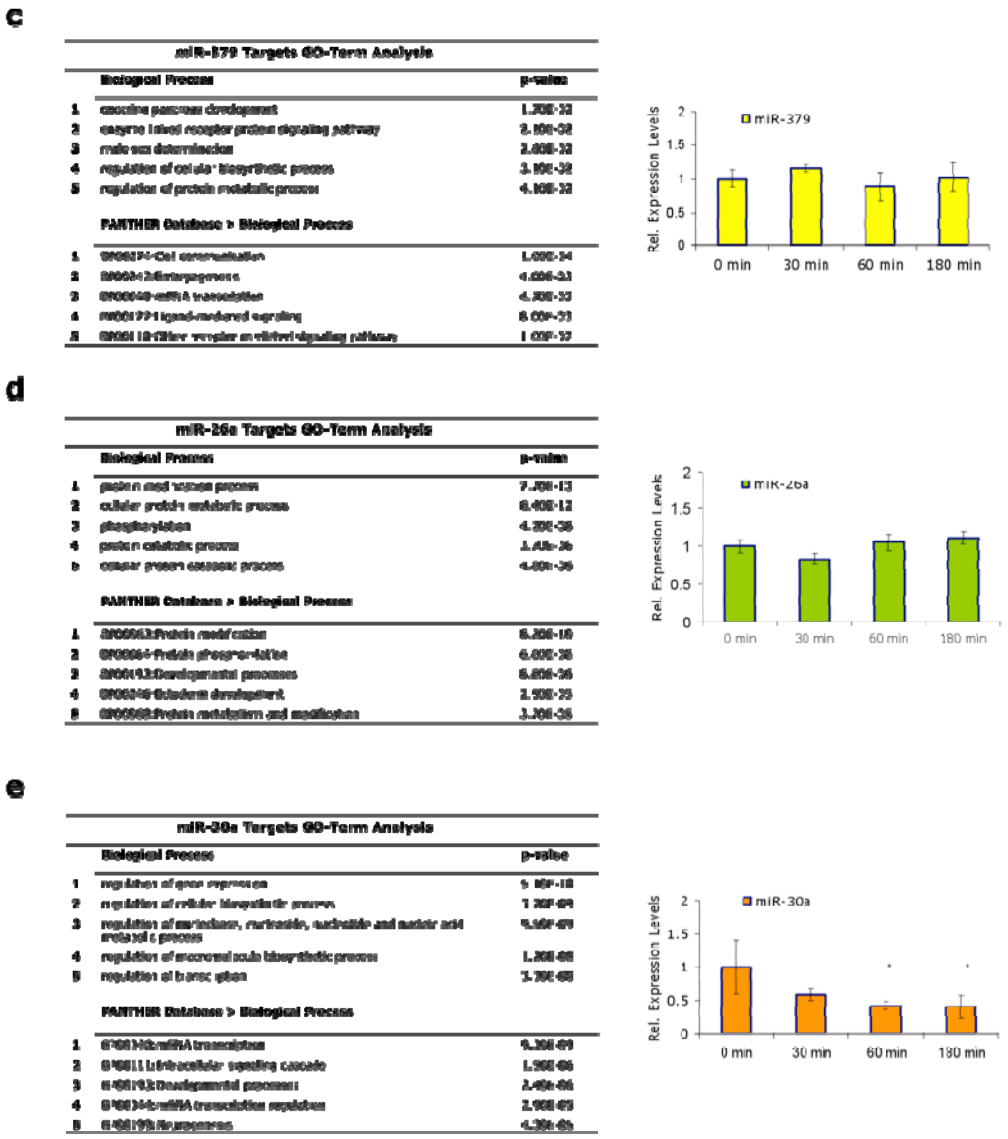


Figure S3. KEGG pathway and GO-term analysis of targets of other miRNAs tested in this study and respective expression levels after FC. **(a)** miRNAs found to be highly expressed both in hippocampus and whole brain are likely to control general cellular pathways in these tissues. (-ln(p-value)) represents the enrichment score for these pathways for each of the miRNAs tested. These miRNAs have been also previously shown to control key cellular processes such as cell cycle regulation or DNA methylation (Roush & Slack, 2008) (Takada et al, 2009) **(b-e)** GO-term analysis (left panel) and expression analysis 30-60-180 min after FC (right panel) for two miRNAs also enriched in hippocampus (b-c), a miRNA not enriched in hippocampus (d) and a miRNA whose targets depict like miR-34c enrichment in learning associated genes upregulated after FC (e). The last one is the only miRNA from those tested that like miR-34c responds to FC, however in a totally different way as miR-34c (compare Fig S4b), implying a different mode of regulatory control than miR-34c (n=4, $p < 0.05$).

Figure S4

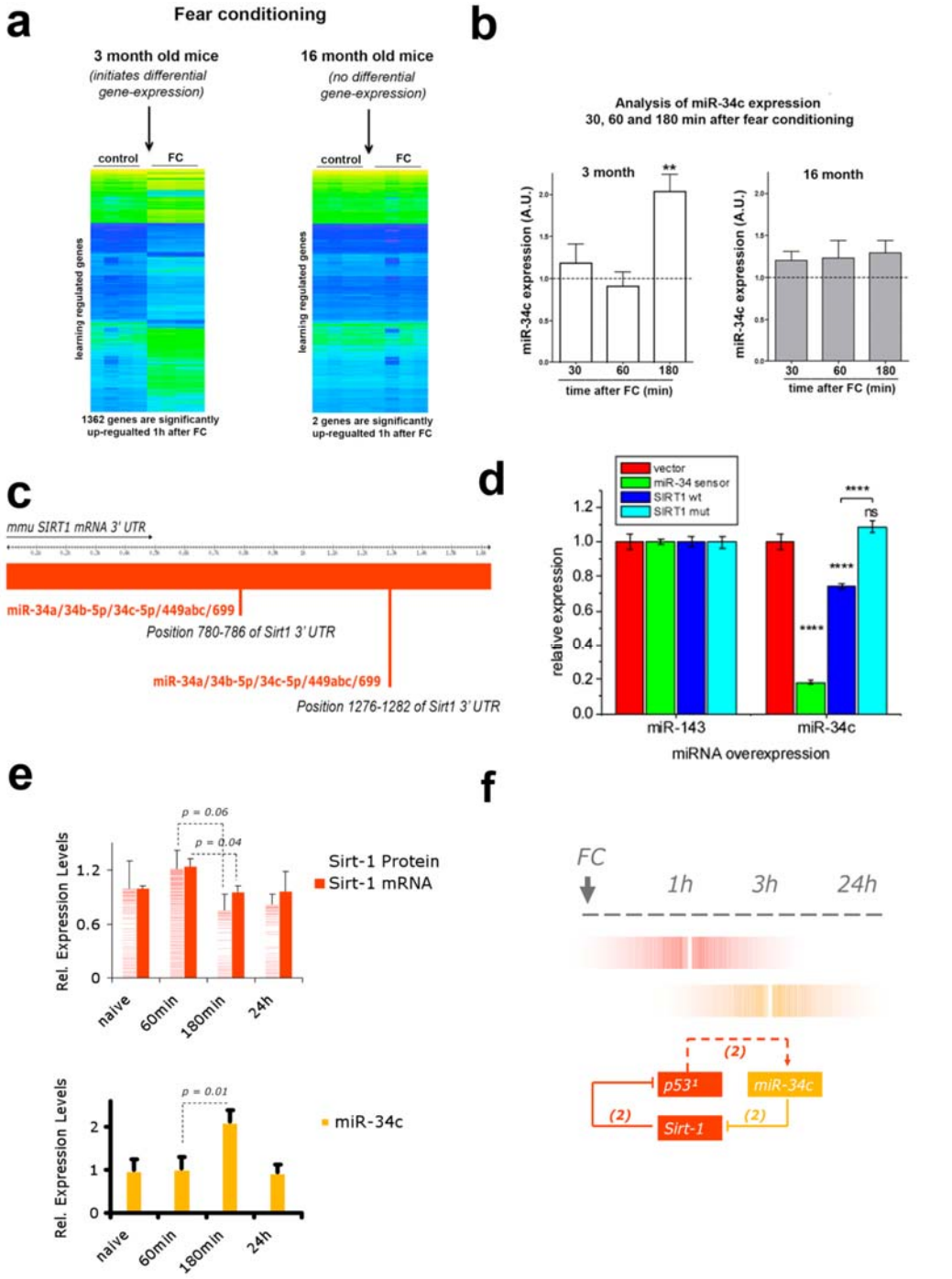


Figure S4. miR-34c is regulated during fear conditioning and its expression correlates with SIRT1 levels.

(a) Modified after (Peleg et al, 2010). In a recent work we identified 1362 hippocampal genes that are up-regulated in mice 60 min after exposure to contextual

fear conditioning, a commonly used paradigm for associative learning in rodents. Notably, miR-34c showed the highest grade of enrichment regarding predicted targets within the group of up-regulated learning associated genes (see Fig 2d). Two possible roles for miRNA involvement can be envisioned for the regulation of learning-induced gene-expression. The expression of miRNAs may decrease early after fear conditioning and thus contribute to the up-regulation of target genes 60 min after fear conditioning. Alternatively, miRNAs may increase at a later time-point after fear conditioning and thus help to restrict of the gene-expression response in order to prevent aberrant plasticity. **(b)** To address this question we decided to analyzed the expression profiles of miR-34c and other hippocampal miRNAs (see Fig. S3b-e), 30 min, 60 min and 180 min after fear conditioning. Interestingly, expression levels of miR-34c increased 3h after FC in 3-month old mice (n=4; p=0.01 relative to control, which is depicted as the line summarizing the expression levels in mice exposed to the same context but not receiving the footshock). This data suggests a possible feedback loop mechanism in the regulation of learning associated genes, as it has been already shown for this miRNA in other biological contexts (Yamakuchi et al, 2008). This is further supported by the fact that miR-34c levels did not increase upon fear conditioning in 16-month-old mice (n=4/group), in which the learning induced hippocampal gene-expression program is not initiated upon fear conditioning. **(c)** *Sirt1* is a confirmed target of the miR34 family (Yamakuchi et al, 2008). *Sirt1* is expressed in the hippocampus and essential for memory function (Michán et al, 2010). Sirt-1 mRNA incorporates in its 3'UTR two miRNA seeds for miR-34c and related miRNAs. Red lines depict the targeting positions. **(d)** Cortical neurons (DIV5+3) were co-transfected with the dual luciferase 3'UTR reporters and miRNA expression constructs. The 3'UTR of renilla contained two artificial miR-34 target sites or SIRT1 3'UTR (wild type or a mutant lacking both putative miR-34 seed regions). Relative expression was determined by normalizing the ratio of renilla and firefly luciferase activity to the effect of each miRNA on a control renilla-luciferase reporter (and miR-143 expressing vector). Statistical analysis using two-way ANOVA comparing miR-34c and miR-143 and SIRT1 wildtype and mutant (**** denotes $p < 0.001$; ns, not significant n=12).**(e)** mRNA and protein levels of SIRT1 60min, 180min and 24h after FC. Note, that the reduction in SIRT1 levels at 180 min corresponds to increase of miR-34c levels at that time point (n=4; *$P<0.05$). **(f)** Proposed mode of action for miR-34c after fear conditioning (FC). (1) Fear conditioning training leads to increased levels of p53 (Peleg et al, 2010). (2) p53 has been previously shown to activate expression of miR-34 family genes, which repress expression of SIRT1-1, SIRT1 deacetylates p53 and reduces p53 activity (Yamakuchi & Lowenstein, 2009). This data also indicates that the up-regulation of miR-34c observed in models for age-associated memory impairment and Alzheimer's disease (Fig.3a & Fig 4) may be the result of aberrant plasticity. Error bars indicate SEM.

Figure S5

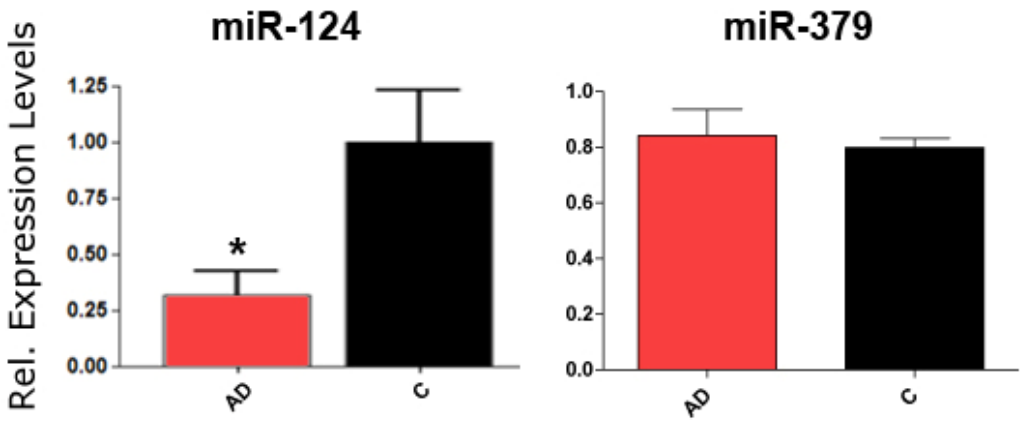


Figure S5: miRNA expression levels in AD patients (hippocampus) compared with aged match controls.

miRNA expression profiles for the AD patients (AD) and age matched controls (C) as presented in Fig. 4 for miR-124, a miR that has been implicated with learning and memory function and miR-379 (n=6,7; *P<0.05)

Figure S6

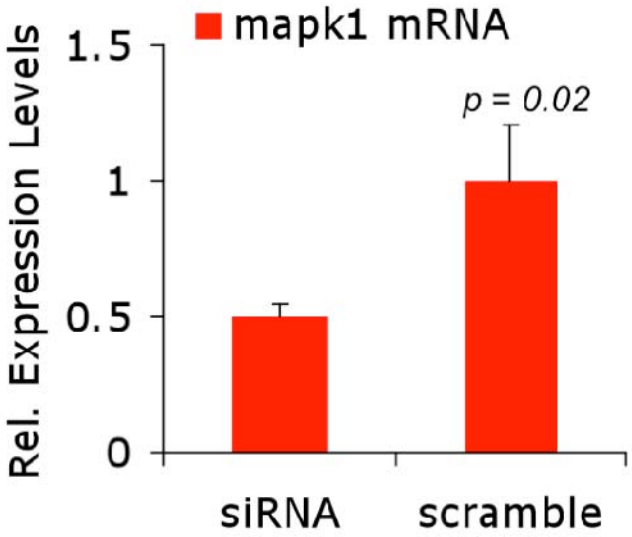


Figure S6: Microinjections of small RNA oligos into the hippocampus affects gene-expression.

To confirm transfection of hippocampal cells and successful action of oligos within our transfection protocol (see material & methods for details) we first employed a positive control. To this end we injected mice intra-hippocampally with a commercially available (Qiagen, Mm/Hs_MAPK1 control siRNA- Cat. No. 1027321) siRNA oligo against Mapk1. The function of this siRNA can be measured via reduction of mRNA Mapk1 mRNA levels. Notably, mice injected with MAPK1 control siRNA showed reduced hippocampal *mapk1* mRNA levels when compared with those treated with the negative control siRNA (scramble; AllStars Neg. Control siRNA, Cat No 1027281, Qiagen). This negative control siRNA has no homology to any known mammalian gene, it has been validated using Affymetrix GeneChip arrays and a variety of cell-based assays and shown to ensure minimal nonspecific effects on gene expression and phenotype. In addition, cloning experiments confirmed that it enters RISC {https://www.qiagen.com/products/genesilencing/allstarrnaicontrols/allstarsnegativecontrols.aspx}. This data confirmed that with our transfection protocol, oligos are able to enter the cell and get successfully incorporated within RISC.

Figure S7

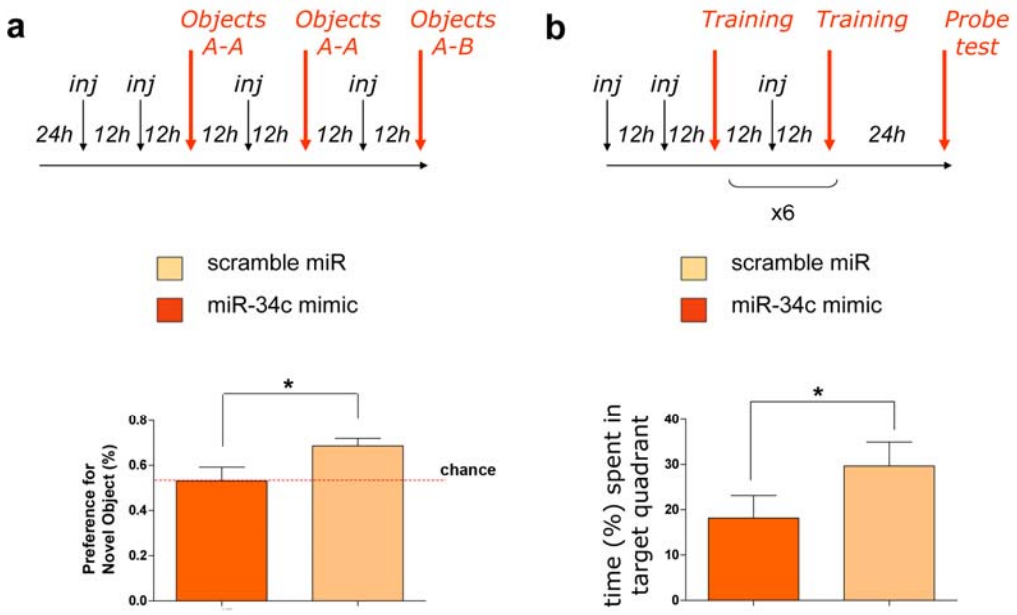


Figure S7: Intrahippocampal injection of miR-34c injections affects memory consolidation in the novel object recognition and water maze paradigm.

(a) Upper panel, Experimenal design for intrahippocampal administration of miR-34c mimic and the respective scramble miR during the training session in the novel object recognition paradigm (See supplemental material & methods for details). Lower panel shows that mice injected with miR-34c mimic show no preference for the novel object during a memory test suggesting impaired memory consolidation (n=5,8; p=0.03). (**b)** Experimental design for intrahippocampal administration of miR-34c mimic and the respective scramble miR during the training session of the Morris water maze paradigm (See supplemental material & methods for details). Injection has been repeated throughout all 8 training sessions. Lower panel shows the target preference during the probe test performed 24h after the last training session. Note that miR-34c mimic injected mice show impaired target preference indicative of impaired spatial memory consolidation (n=7,8,p=0.03)

Figure S8

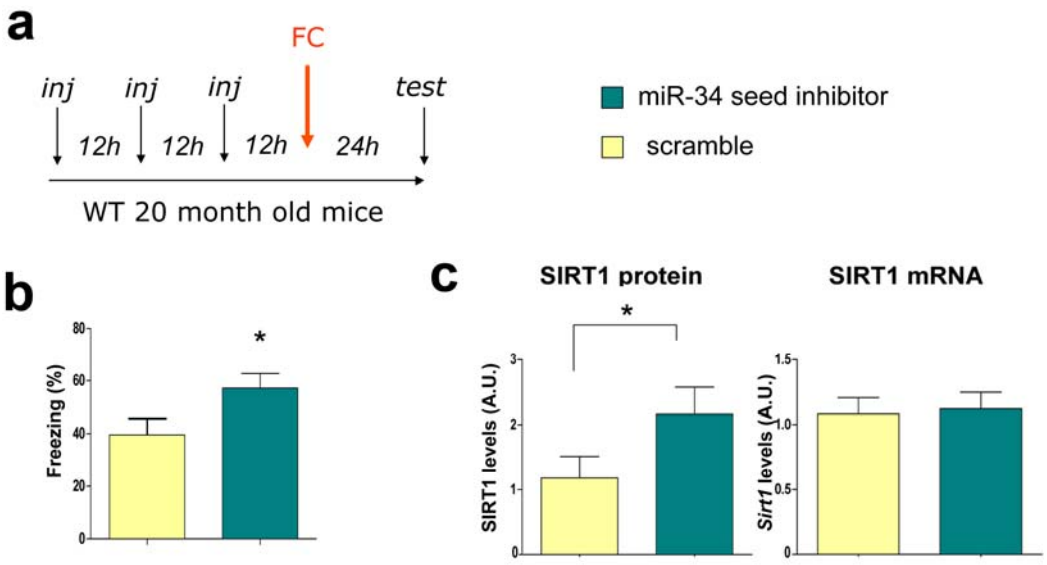


Figure S8. Targeting miR-34c seed enhances learning in 20-month-old wild type animals. (a) Experimental design. **(b)** Inhibiting miR-34c activity via intrahippocampal injection of miR34 seed inhibitor enhances associative memory as measured in the contextual fear conditioning paradigm in 20 month old animals (n=8,7 *P*=0.02**). (c)** miR-34 seed inhibitor treated 20-month-old mice show elevated SIRT1 protein levels **(**P=0.03) while *Sirt1* mRNA levels were unaffected (n=7 p3=0.04). FC; contextual fear conditioning. Error bars indicate SEM.

Figure S9

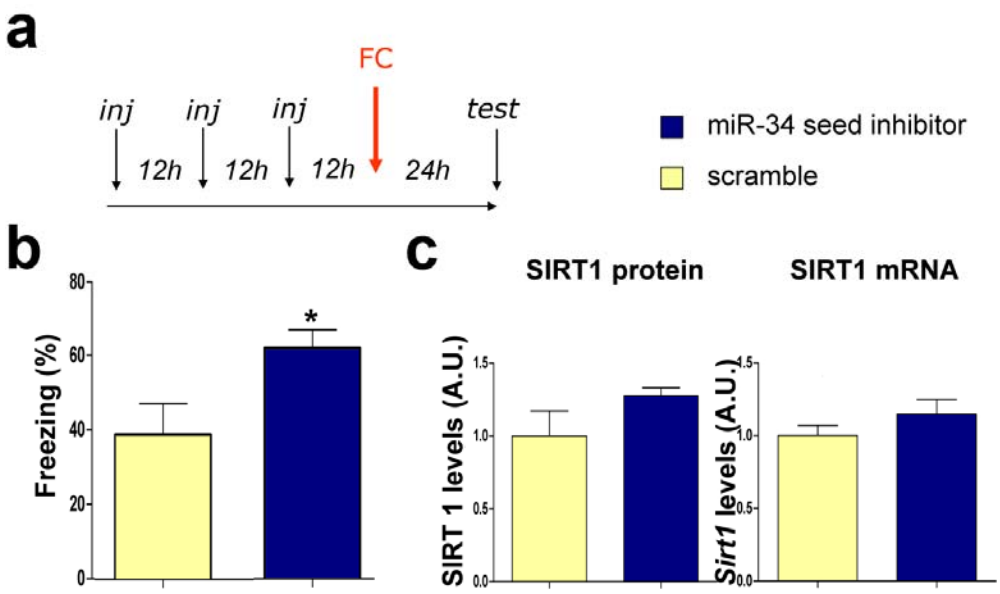


Figure S9. Targeting miR-34c seed enhances learning in 3-month-old wild type animals. (a) Experimental design. **(b)** Inhibiting miR-34c activity in 3-month-old wild type mice via intrahippocampal injection of miR34 seed inhibitor enhances associative learning as measured in the contextual fear conditioning paradigm (n=5,6 p=0.01). **(c)** In contrast to the effect observed in disease models were SIRT1 protein is down-regulated (See Fig 7 & Fig S7) inhibiting miR-34c activity does not have significant effects on SIRT1 protein in 3-month old mice, although there was a non-significant trend (n=6). This data suggests that the effect of miR34c on memory formation in young wild type mice involve other targets in addition to SIRT1. FC, contextual fear conditioning. Error bars indicate SEM.

Figure S10

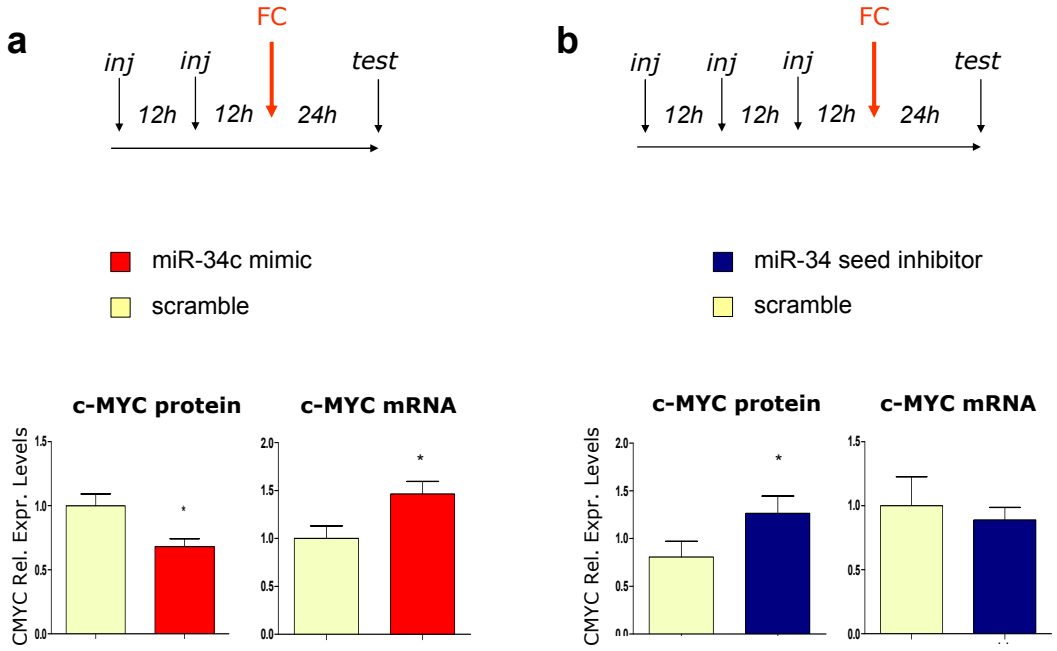


Figure S10. c-MYC expression levels get affected upon injection of miR-34c mimic and miR-34 seed inhibitors

Protein and mRNA levels of c-MYC under the injection plan used in this study (upper panels). Lower panels: **(a)** As in case of SIRT1, high miR-34c levels result in decrease of c-MYC protein levels (n=5, p=0.01). The inhibitory effect of miR-34c on translation is even bigger if we take into account the compensatory increase in the c-MYC mRNA levels (p=0.01). **(b)** Inhibition of miR-34 seed results in upregulation of c-MYC protein levels (n=5,6; p=0.04). Error bars indicate SEM.

Supplementary Materials and Methods

Contextual fear conditioning and other behavioral tests

To assess associative learning, the contextual fear conditioning paradigm was used. Behavior testing was performed as described previously (Peleg et al, 2010) employing TSE Systems apparatuses and software and Scan software (Clever Systems). Mice were single housed and habituated to the testing room at least 3 days before behaviour experiments. The training consisted of a single exposure to the conditioning context (3 min) followed by a single electric foot shock (0.7 mA, constant current, 2s) (Fear Conditioning-FC) and the memory test was performed 24h later (Test).

The water maze training was performed as described previously (Fischer et al, 2007). In brief, in a circular tank (diameter 1.2 m) filled with opaque water a platform (11x 11 cm) was submerged below the water's surface in the center of the target quadrant. Tracing the swimming pathway of the mice was performed using a video camera and the Videomot 2 software (TSE). Each training session included the following steps:

a) mice were placed into the maze subsequently from four random points of the tank and were allowed to search for the platform for 60 s. b) In case finding of the platform was unsuccessful mice were gently guided to it. c) Mice remained on the platform for 15 s. During the memory test (probe test) mice were left to swim in the maze for 60s with the platform removed. Time spent in the target quadrant (%) was employed to control for memory deficits in mice treated with the miRNA mimic compared with those injected with the scramble oligo.

For the novel object recognition test animals were placed in a plastic arena (100x100 cm, height 20 cm) for 5 min. The explorative behavior of the animals was recorded by a video camera and analyzed by the Videomot 2 software (TSE). During each training session (10min) that was performed on consecutive days mice were allowed to explore the field which in the first two sessions did not contain any object (habituation phase), the next two sessions contained two same objects (A-A), and in the last session (memory test/probe test) contained object A and a novel object B. Time spent exploring the novel object on that day (%) compared to the other was used quantify memory performance.

Hippocampal injections

We employed miRNA mimics (synthetic RNAs which mimic mature endogenous miRNAs after transfection) for mmu-miR-34c, mature miRNA sequence: 5' AGGCAGUGUAGUUAGCUGAUUGC (MSY0000381) (Qiagen, Hilden, Germany). For inhibition we employed the following inhibitors (chemically synthesized modified RNAs which specifically inhibit endogenous miRNA function after transfection into cells) (Qiagen) Anti-mmu-miR-34a (MIN0000542) 5' UGGCAGUGUCUUAGCUGGUUGU, Anti-mmu-miR-34b-5p (MIN0000382) 5' AGGCAGUGUAAUUAGCUGAUUGU, Anti-mmu-miR-34c (MIN0000381) (same sequence as the mimic). All used miRNA mimics and inhibitors were HPLC purified, for *in vivo* applications. For injections, miRNA mimics and inhibitors were diluted in PBS and the HiPerfect transfection reagent from Qiagen according to a modified protocol of that recommended by the manufacturer for cell transfections. In detail: Steril cold PBS (water can be also used) was added to the oligo tube to a final concentration of 100 μM for the mimic or 1mM for the inhibitor and mixed intensively and left at room temperature for 3 minutes. All handling was done under aseptic conditions. Mixture was transferred into to 0.2 ml tubes and 1,35 μl of the HP transfection reagent was added for each 10 μl of the mimic or inhibitor mix. The rest was aliquoted and kept in -80 for not longer than a month and was not frozen-defrozen more than once. Oligo-HP mix was mixed intensively for 1 minute and left at room temperature for 5min. Then it was warmed in the hand for 1 minute before injection. To confirm transfection of cells and successful action of oligos within our transfection protocol *in vivo*: i) different mice were injected as described above with synthesized control siRNA oligo from Qiagen (Mm/Hs_MAPK1 control siRNA- Cat. No. 1027321) against Mapk1 and compared with mice injected with a validated negative control siRNA (scramble) (AllStars Neg. Control siRNA, Cat No 1027281, Qiagen). This scramble oligo has no homology to any known mammalian gene, it has been validated using Affymetrix GeneChip arrays and a variety of cell-based assays and shown to ensure minimal nonspecific effects on gene expression and phenotype. In addition, cloning experiments confirmed that it enters RISC {https://www.qiagen.com/products/genesilencing/allstarrnaicontrols /allstarsnegativecontrols.aspx}. Reduction of mRNA levels of the target Mapk1 mRNA in the hippocampi of mice treated with the MAPK1 control siRNA compared

with those treated with the Neg. Control siRNA (scramble) confirmed that with the currently used transfection protocol, transfected oligos are able to enter the cell and get successfully incorporated within RISC (Fig S6). ii) Expression levels of the already experimentally established miR-34c target, SIRT1 were determined in mice hippocampi in comparison to mice treated with the scramble oligo and confirmed increased or reduced activity of miR-34c mimics and inhibitors, respectively (Fig 5, Fig 6, Fig 7). iii) In case of transfection with miR-34c mimics expression levels of the mature miR-34c oligo were determined, confirming the increase of the total amount of the active miR-34c oligo/miRNA in mouse hippocampi of injected mice 12h after the second injection, and immediately before FC (Fig 5a). Importantly, mock-transfected injected mice did not present any sign of increased toxicity of the transfection agent used.

For the miRNA target protection assays we used the miScript Target Protectors, which are single-stranded, modified RNAs that specifically interfere with the interaction of an miRNA with a single target, while leaving the regulation of other targets of the same miRNA unaffected (Qiagen). The design of the protectors of SIRT1 was as follows: i) miScript Target Protector mmu_Sirt1_34c_780nt for the binding site starting at position 780nt of the Sirt1 mRNA 3'UTR: Design for: AGATCTTCACCACAAATACTGCCAAGATGTGAATATGCAA. This target protector will hybridize to all transcripts of the same gene (Sirt1):NM_001159590, NM_001159589, NM_019812 (MTP0001486).ii) miScript Target Protector mmu_Sirt1_34c_1270nt for the binding site starting at position 1270nt of the Sirt1 mRNA 3'UTR: Design for: ACCCAGTTAGGACCATTACTGCCAGAGGAGAAAAGTATTA. This target protector will hybridize to all transcripts of the same gene (Sirt1):NM_001159590, NM_001159589, NM_019812 (MTP0001493). As control the Negative Control miScript Target Protector was used (MTP0000002-Qiagen), which has no homology to any known mammalian gene. Target protectors were used according to the above described transfection and injection scheme for mimics in a final concentration of 100 μM.

Real-time quantitative RT-PCR and western blot analysis

The optimized miRNA-specific primers used for each miRNA as well as for the endogenous control RNU6B (miScript Primer Assays, Qiagen) are as follows:

Mm_miR-34c_1 (MS00001442), Mm_miR-181b_1 (MS00006083) , Mm_miR-379_2 (MS00011942) , Mm_miR-26a_1 (MS00005929), Mm_miR-30a_1 (MS00011704), Hs_RNU6B_2 (MS00014000). PCR specificity was checked as described previously (Zovoilis et al, 2008). For Real-time quantitative RT–PCR of mRNAs, the LightCycler PCR Mix (Roche Applied Science) was used according to manufacturer's conditions with gene-specific primers and the respective UPL probes as follows: Sirt-1F: 5' CGTGGAGACATTTTTAATCAGGTA, Sirt-1R: 5' GCTTCATGATGGCAAGTGG , mouse UPL probe #104; Hprt-1F: 5' TCCTCCTCAGACCGCTTTT, HPRT-1 R: 5' CCTGGTTCATCATCGCTAATC mouse UPL probe #95. Forty five cycles of PCR amplification were performed as follows: denaturation at 95°C for 10s, annealing at 60°C for 30s and extension at 72°C for 10s. PCR assays were performed twice for each cDNA sample. Data were analysed with the LightCycler 480 software (Roche Applied Science). The relative quantification method was chosen to determine quantities based on a standard curve of serial dilutions of a control hippocampal cDNA. All quantities were further normalized to values of RNU6B and Hprt-1 for miRNA or mRNA quantification, respectively.

For Western bloting, in brief, 20 μg protein was loaded per lane of an SDS gel (consisting of a stacking gel 5% acrylamide and a running gel with 12% acrylamide concentration),it was run between 60-100V and then transferred in a wet-blot system (Mini Trans-Blot Cell, Bio-RAD) at 45-60V , 4 ˚C overnight onto a nitrocellulose membrane (Protran, o.2um, Whatman, Dassel, Germany). After transfer it was blocked in 5% milkpowder, while primary antibodies were incubated 0.5% milkpowder at 4 ˚C overnight, followed by three washes and incubation of with the respective fluorophore coupled secondary antibody (Li-COR Bioscienbces). Band intensity was determined in ratio to β-actin.

Massive parallel sequencing and mapping of small RNAs, annotation and quantification of miRNAs

The 3' adapter sequences were trimmed from the raw reads in 3 steps:
(3' adapter sequence “ATCTCGTATGCCGTCTTCTGCTTGT”)
1) The full adapter sequence was used, which permits to identify “inserts” of 25 nt or less.

2) If no adapter sequence was found, in successive steps the last base of the adapter was removed and the sequence was searched at the end of the reads. The minimum adapter size of 8 bases permits identifying inserts of up to 42 bases.
3) Finally the remaining reads were searched for not-exact matches of the adapter. The first 5 bases of the adapter were searched within the full reads sequences and at least 80% of the following bases must be identical to the adapter sequence (max 44 bp). After trimming of the adapter sequences, the inserts were sorted in separate files according to their lengths.

For estimating the proportion of sequenced small RNAs representing miRNAs, reads were firstly mapped against the Mus Musculus Full Genome (NCBI Assembly M37) using ELAND v2 (CASAVA Version 1.6.0 from Illumina) allowing up to 2 mismatches. From the respective output files, subsequent BED files were derived and the genomic intervals defined by each read were evaluated based on whether they map on a known miRNA genomic location or not (UCSC table browser miRNA track that shows microRNAs from the miRBase (www.mirbase.org) (Griffiths-Jones, 2010) (Fujita et al, 2010). In the latter case, the read was subtracted from the tested pool of reads. The total of the subtracted reads relative to the total number of mapped reads was used to determine the miRNA class proportion of sequenced reads and the number of the known miRNA precursor regions that are represented by at least one sequenced read in mouse hippocampus.For quantifying the reads that correspond to known mature miRNAs we used a more conservative and strict approach. Firstly, since multiple genomic locations may produce the same mature miRNA, reads were mapped not against the mouse genome but against all known mouse (mmu) mature miRNA sequences present in miRBase, which instead not show this type of redundancy. During mapping we allowed no mismatch and repressed multiple mapping reads (which due to the non-redundancy of the selected database, where almost absent). The exact Bowtie parameters were set as follows: -a , -v (allowed mismatches) to 0, -m to 1(repressed multiple mapping reads) with the rest parameters used at default values (Bowtie 0.12.7). Then, occurrences of each mature miRNA per replicate were summed and pooled resulting in the total sequence count number, that has been further used to determine the number and the approximate range of each miRNA in mouse hippocampus. Reads derived from whole mouse brain were

retrieved from (Chiang et al, 2010) but were mapped exactly as reads from hippocampus to define the respective miRNA range in this tissue. We defined for the top ranking miRNAs in hippocampus the relative to the brain read count number as follows: we first scaled for each miRNA the count numbers in hippocampus according to the total difference in read counts between the two libraries and then normalized it to the respective count number in brain. The output was then converted to the natural logarithm of this value. In all cases the mature sequences in miRbase for each miRNA were used as the diagnostic sequence for both libraries.

miRNA expression constructs and luciferase assay

For plasmid-based expression of miR-34c the precursor hairpin was PCR-amplified from mouse genomic DNA and cloned in the 3'UTR of mCherry driven by human ubiquitin C promoter in FUW plasmid (using 5'-gatgctagcacagcttggctgacgatttgct-3' and 5'-ataggcgcgccctatggctctgtcctcacca-3') as described previously (Edbauer et al, 2010). For dual luciferase assays (Promega) we modified psiCHECK2 vector (Promega) to express both renilla and firefly luciferase from human synapsin promoter for robust expression in neurons. We inserted either two artificial miR-34 targets sites 5'-cgcgccAGGCAGTGTAGTTAGCTGATTGgatccAGGCAGTGTAGTTAGCTGATTG-'3 or the mouse SIRT1 3'UTR (using 5'-ataggcgcgccactattgaagctgtccggattcagg-3' and 5'-atagaattccagtcattaaacggtctacaaaacatatgcc-3') in the 3'UTR of renilla luciferase. To generate a miR-34-resistant SIRT1 mutant, we removed both putative target sites for miR-34 (5'-atcttcaccacaaatactgccaa-3' and 5'-agttaggaccattactgcca-3', 7mer-1A seed match underlined) using PCR-mutagenesis. For dual luciferase assays, cortical neurons were cultured from embryonic day 19 rat embryos and transfected with luciferase-based miRNA-sensors together with miRNA overexpression constructs using Lipofectamine 2000 (Invitrogen) as described previously (Edbauer et al, 2010).

References

Chiang HR, Schoenfeld LW, Ruby JG, Auyeung VC, Spies N, Baek D, Johnston WK, Russ C, Luo S, Babiarz JE, Blelloch R, Schroth GP, Nusbaum C, Bartel DP (2010) Mammalian microRNAs: experimental evaluation of novel and previously annotated genes. *Genes Dev* **24:** 992-1009

Edbauer D, Neilson JR, Foster KA, Wang CF, Seeburg DP, Batterton MN, Tada T, Dolan BM, Sharp PA, Sheng M (2010) Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. *Neuron* **65:** 373-384

Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH (2007) Recovery of learning & memory after neuronal loss is associated with chromatin remodeling. *Nature* **447:** 178-182

Fujita PA, Rhead B, Zweig AS, Hinrichs AS, Karolchik D, Cline MS, Goldman M, Barber GP, Clawson H, Coelho A, Diekhans M, Dreszer TR, Giardine BM, Harte RA, Hillman-Jackson J, Hsu F, Kirkup V, Kuhn RM, Learned K, Li CH, Meyer LR, Pohl A, Raney BJ, Rosenbloom KR, Smith KE, Haussler D, Kent WJ (2010) The UCSC Genome Browser database: update 2011. *Nucleic Acids Res* **18**

Griffiths-Jones S (2010) miRBase: microRNA sequences and annotation. *Curr Protoc Bioinformatics* **12:** 1-10

Michán S, Li Y, Chou MM, Parrella E, Ge H, Long JM, Allard JS, Lewis K, Miller M, Xu W, Mervis RF, Chen J, Guerin KI, Smith LE, McBurney MW, ., Sinclair DA, Baudry M, de Cabo R, Longo VD (2010) SIRT1 is essential for normal cognitive function and synaptic plasticity. *J Neurosci* **30:** 9695-0707

Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Java S, Agis-Balboa RC, Cota P, Wittnam J, Gogul-Doering A, Opitz L, Salinas-Riester G, Dettenhofer M, KAng H, Farinelli L, Chen W, Fischer A (2010) Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science* **328:** 753-756

Roush S, Slack FJ (2008) The let-7 family of microRNAs. *Trends Cell Biol* **18:** 505-516

Takada S, Berezikov E, Choi YL, Yamashita Y, Mano H (2009) Potential role of miR-29b in modulation of Dnmt3a and Dnmt3b expression in primordial germ cells of female mouse embryos. *RNA* **15:** 1507-1514

Yamakuchi M, Ferlito M, Lowenstein CJ (2008) miR-34a repression of SIRT1 regulates apoptosis. *Proc Natl Acad Sci U S A* **105:** 13421-13426

Yamakuchi M, Lowenstein CJ (2009) MiR-34, SIRT1 and p53: the feedback loop. *Cell Cycle* **8:** 712-715

Zovoilis A, Nolte J, Drusenheimer N, Zechner U, Hada H, Guan K, Hasenfuss G, Nayernia K, Engel W (2008) Multipotent adult germline stem cells and embryonic stem cells have similar microRNA profiles. *Mol Hum Reprod* **14:** 521-52