Supplementary Material

Aggregate Trends of Apolipoprotein E on Cognition in Transgenic Alzheimer's Disease Mice

Supplementary Table 1. List of articles, sample size and group details, details on treatment descriptions, and details on original experimental methods.

Citation	Year	Mouse Genotypes Studied	Mouse Sample Sizes by Genotype	Isoform Used	Mouse Sample Sizes by Genotype and Treatment	Does this treatment increase or decrease ApoE levels?	Was the treatment meant to have a positive or negative effect on the mouse?	Treatment Description (green = positive effect, yellow = no treatment, red = negative effect)	Morris Water Maze Description
[1]	2015	KO, KI (2,3,4)	KO (5xFAD): 18 KI (E2FAD): 18 KI (E3FAD): 18 KI (E4FAD): 18	Human	N/A	N/A	N/A	N/A	"Acquisition trials (training) consisted of 4 trials (maximum 1 min) a day for 5 consecutive days with escape latency recorded for each trial. Reference memory was assessed on the sixth day in a one trial test for time spent in the target quadrant and the number of times the original area of the platform was crossed."
[2]	2014	KI (3,4)	KI (apoe3): 24 KI (apoe4): 24	Human	treated KI (apoE3): 12 untreated KI (apoE3): 12 treated KI (apoE4): 12 untreated KI (apoE4): 12	INCREASE, "Bexarotene induces an increase in ABCA1 and ABCG1 levels, which is expected to increase the lipidation of apoE4 and thus to have a beneficial effect, compensating for the decreased lipidation of native apoE4."	POSITIVE, "Bexarotene improves cognition in murine models of Alzheimer's disease"	"Bexarotene or DDW (control) were administered to 4-month-old apoE3 and apoE4 mice by oral gavage daily for 10 d."	The behavioral tests were initiated 10 d after the beginning of the bexarotene treatment. The mice were administered either DDW or bexarotene daily throughout this testing period. For the Morris water maze test, mice were placed in a 140 cm circular pool with the water rendered opaque with milk powder. A 10 cm circular platform submerged 1 cm below the surface of the water was placed at a fixed position. The mice were subjected to 4 trials per day for 4 d such that, for each trial, the mice were placed in 1 of equally spaced locations along the perimeter of the pool. The intertrial interval was 30 min and the location of the platform was unchanged between days. The mice were introduced to the arena from four random locations, the order of which was unchanged between days. The performance of the mice was monitored by measuring the time they took to reach the platform. Measurements were performed using the computerized video-assisted HVS water maze system (HVS Image)."
[3]	2014	WT, KI (3,4)	WT: 7 KI (apoE3-KI): 18 KI (apoE4-KI): 39	Human	untreated WT: 7 untreated KI (apoE3-KI): 9 treated KI (apoE3-KI): 9 untreated KI (apoE4-KI): 23 treated KI (apoE4-KI): 16	N/A, direct interaction with apoe unclear	POSITIVE, "Inhibitory Interneuron Progenitor Transplantation Restores Normal Learning and Memory in ApoE4 Knock-In Mice without or with Aβ Accumulation"	"Female apoE4-KI and apoE3-KI mice at 14 months of age and apoE4-KI/hAPPFAD mice at 10 months of age were anesthetized with 80 µl of ketamine (10 mg/ml) and xylazine (5 mg/ml) in saline solution and maintained on 0.8–1.0% isoflurane (Henry Schein). Concentrated GFP+ MGE cell suspensions (~600 cells/nl) were loaded into ~60 µm tip diameter, 30° beveled glass micropipette needles. Bilateral	"Behavioral tests were performed for MGE cell-transplanted and control-transplanted mice at 70–80 d after transplantation (DAT). All mice were singly housed during behavioral tests. The Morris water maze (MWM) test was conducted in a pool (122 cm in diameter) with room temperature water (22–23°C) with a 10 cm2 platform submerged 1.5 cm below the surface of opaque water during hidden trials. Mice were trained to locate the hidden platform over four trials per day on hidden platform days 1–5 (HD1–5), where HD0 was the first trial on the first day, with a maximum of 60 s per trial. Each memory trial was conducted for 60 s in the absence of the platform at 24, 72, and 120 h after the final learning session. Memory was assessed as the

								rostral and caudal stereotaxic sites were drilled and coordinates used for hilar transplantation.	percentage of time spent in the target quadrant that contained the platform during the learning trials compared with the average percentage of time spent in the nontarget quadrants. For visible trials, a black and white-striped mast (15 cm high) marked the platform location. The platform location and room arrangement remained constant throughout the assay with the exception of moving the platform during the visible trials. Speed was calculated by distance traveled divided by trial duration. Performance was objectively monitored using EthoVision video-tracking software (Noldus Information Technology).
[4]	2009	WT, KI (4)	WT (C57BL/6): 24 KI ((GFAP)-ApoE4): 14 KI ((GFAP)-ApoE4): 14	Human	untreated WT (C57BL/6): 24 untreated KI ((GFAP)-ApoE4): 14 treated KI ((GFAP)-ApoE4): 14	INCREASE, "The GFAP(Glial Fibrillary Acidic Protein) promoter [in the transgenic mice] drives the expression of ApoE cDNA in glia, primarily in astrocytes"	POSITIVE, "Spatial memory and temporal memory tests showed a trend in improving cognitive function in ApoE4 mice fed selective mitochondrial antioxidants acetyl-L-Carnitine and R-Lipoic acid."	"Seven-month-old ApoE4 transgenic mice were randomly divided into two groups (n=4 per group): control and treated (0.2% ALCAR in drinking water and 0.15% dexlipotam, a tris-salt of LA, which is equal to 0.1% LA) as described by our group elsewhere. Wild-type C57BL/6 mice without treatment were used as controls."	"The Morris water maze task tests spatial memory by requiring mice to find a submerged platform in a pool of water using external visual cues as described previously. The time required for an individual mouse to find the platform was measured using a digital camera and a computer system to record movement (Columbus Instruments, VideoMex-V). Trials (4 consecutive days, 4 trials per day) were with the same hidden platform location, but with varied start locations. On day 5, the platform was removed from the pool for a probe test, (60 sec) and the time spent at the actual site where the platform was previously located was recorded. On day 6, the time required to reach a visible platform was measured to determine visual function and motor ability. In the reversal test, the platform was moved to the opposite quadrant of the previous test (4 trials/day and 120 s/trial)."
[5]	2016	KO, KI (3)	KO (bEKO): 22 KO (ApoE KO): 16 KI (ApoE3/E3): 22	Human	treated KO (bEKO): 22 untreated KO (ApoE KO): 16 untreated KI (ApoE3/E3): 22	DECREASE in brain, "bEKO mice have greatly reduced brain ApoE" N/A in plasma, "Plasma ApoE levels are normal in the bEKO mouse"	POSITIVE, "the bEKO mice did not have the learning and memory impairment observed in ApoE KO mice."	"The bEKO (brain ApoE knock-out) mouse was generated as the result of the random integration of a human ApoE expression cassette containing an inadvertent mutation. The site of transgenic integration has an expression profile that is restricted to peripheral tissues. To generate the bEKO mice, the transgenic mouse line was bred to homozygosity and then backcrossed to ApoE knock-outs. ApoE3-targeted replacement mice were used as a control. Male mice were used for performing immunohistochemistry, electrophysiology, and biochemistry; both sexes were used for behavioral experiments."	"Mice were trained for 7 d to find a hidden platform in a 120-cm-diameter tube of cloudy water at 21°C. The platform was 10 cm in diameter and 1 cm below the water surface. Each day, mice underwent three trials, during which they were placed into the water at a pseudorandom start point and given 60 s to find the platform, guided by large cues on the wall. Mice that did not find the platform within 60 s were guided to the platform by hand. Mice were then given 5 s on the platform before being returned to their holding cage. On the eighth day, mice were tested with a probe trial in which the platform was removed and they were allowed to swim for 60 s. On the ninth day, mice were tested on a visual version on the task, in which the platform was moved to the opposite side of the pool and made visible with a flag. One male ApoE KO mouse failed the visual probe task and was removed from the analysis. Mouse movements were recorded and analyzed using HVS water maze software (HVS Image)."

[6]	2002	WT, KO	WT (C57BL/6J): 60 KO (C57BL/6Jtm1Unc): 56	N/A	N/A	N/A	N/A	N/A	"The water maze consisted of a circular pool (1.6 m in diameter and 60 cm deep) filled to a depth of 55 cm with water rendered opaque by addition of skim milk powder, and maintained at 16°C. FA square Plexiglas platform (10×10 cm), 0.5 cm below water level, was left in the same location (∼0.5 m in from the side) for the duration of each experiment. Latency, distance and swimming path to find the platform were recorded with a video camera connected to a computerized system (HVS Image, UK). Each mouse was given a block of four trials/day ranging from five to eight consecutive days, depending on the experiment. Each of the four cardinal points (North, West, East and South) were used as the starting location once within each block. Mice were placed in the pool facing the wall and were allowed to swim for a maximal time of 2 min. If a mouse did not find the platform within 2 min, it was placed on it for 15 s. The inter-trial intervals ranged between 10 and 15 min."
[7]	2012	WT, KO	WT: 50 KO (APOE KO): 40	N/A	treated WT: 30 untreated WT: 20 treated KO: 20 untreated KO: 20	N/A, "EtOH-induced memory alteration might be due to the involvement of GABAergic, opioid, and cholinergic systems"	NEGATIVE, "We conclude that high EtOH and AcH impair spatial memory in mice"	"intraperitoneal (i.p.) injection of EtOH (20%, w/v) 5 min before the RAM and MWM on the test day 4."	"A circular water tank (120 cm in diameter and 50 cm in height, 30 cm depth; maintained at 25 ± 2 °C) was filled with water made opaque using liquid milk. A clear Plexiglas escape platform (12 cm in diameter) was placed 1 cm below the water surface. The maze was divided by imaginary lines into four equal-size quadrants 1 to 4, and the platform was placed in the middle of each quadrant. The platform was moved every day to a chosen position, but was kept in that location for all 4 trials on the same day. The acquisition phase began following the habituation trials on day 1, which consisted of 4 trials per day for 4 days (16 trials, 30-min inter-trial interval). The latency to reach the platform within 120 s and allow 10 s to remain on the platform was recorded using a stop-watch. Mice failing to find the platform within 120 s were given a latency score of 120 s. Latencies were calculated as the mean from all training trials performed each day and then measured by the index [(trials − trial1)/trial1].On the 5th day, subjects received a probe trial in the non-EtOH state, in which the platform was removed from the pool. During this trial, mice were released from the quadrant 1 start point and were allowed to swim freely for 120 s. The time spent in the target quadrant (quadrant 4) was recorded to assess the retention of spatial memory."
[8]	2018	WT, KO	WT: 24 KO (ApoE−/−): 26	N/A	treated WT: 16 untreated WT: 8 treated KO (ApoE−/−): 18 untreated KO (ApoE−/−): 8	N/A, direct interaction with apoe unclear	POSITIVE, "Low Phytanic Acid-Concentrated DHA Prevents Cognitive Deficit and Regulates Alzheimer Disease Mediators in an ApoE−/− Mice Experimental Model"	"ApoE−/− mice were fed a high-fat diet. Wild-type C57BL/6 mice were fed a normal chow diet. Both compositions of DHA–PhA (PhA:50 and PhA:1000) were added to the fat diet (refined olive oil) at 10%."	"Spatial learning and memory were assessed using the Morris Water Maze (MWM) as previously described in detail. Basically, the maze was a circular pool (diameter 122 cm, height 40 cm) filled with 23 ± 1 °C water, located in a room with visible external cues, and monitored by a video camera above the apparatus. A hidden escape platform (diameter 10 cm and height 12 cm) was submerged 1 cm below the water surface in one of the four equal imaginary quadrants. From day 1 to 5 (learning curve), the animals were trained to find the escape platform, with 4 trials per day, a time limit of 60 s per trial, and a 4–5 min interval between trials (their escape latencies were recorded for each trial). To assess

									reference memory (probe trial), 24 h after the last learning day, one trial without platform was carried out for 60 s with a novel start position in the maze to ensure that the mice remembered the goal location rather than a specific swim path. An experimenter blind to the treatment scored the latency time to reach the target site (the previous platform location) and the time spent within a 10 cm target annulus around the former platform location.
[9]	1998	WT, KO, KI (3,4)	WT: 118 KO (APOE KO): 130 KI (NSE-apoE3): 68 KI (NSE-apoE4): 80	Human	N/A	N/A	N/A	N/A	"The ability of mice to locate a hidden platform submerged in a pool (61 cm in diameter) filled with opaque water (24°C) was tested in two blocks (separated by a 2-h interval) per day for 4 days. Each block consisted of two consecutive trials. The platform location was changed daily, and the starting point at which the mouse was placed into the water was changed for each trial. Mice that failed to find the platform within 120 sec were put on it for 15 sec. On day 5, the ability of the mice to locate a clearly visible platform was tested to exclude differences in vision, swim speed, and motivation. Because the time required to reach the hidden platform (latency) depends on path length as well as swim speed, all three parameters were recorded with an EthoVision video tracking system (Noldus Instruments, Sterling, VA) set to analyze two images per second. Because swim speeds did not differ significantly among age- and sex-matched mice of the different genotypes analyzed in this study, latencies were used here to illustrate differences in water maze performance."
[10]	2011	WT, KI (4)	WT (C57): 20 KI (hApoE4): 20	Human	treated WT (C57): 10 untreated WT (C57): 10 treated KI (hApoE4): 10 untreated KI (hApoE4): 10	N/A, direct interaction with apoe unclear	POSITIVE, "Long-term salicylamine supplementation did not significantly alter body weight or survival, but protected against the development of age-related deficits in spatial working memory in 12–14-month-old ApoE4 mice. "	"At 4 months of age, wild-type and ApoE4 were randomly assigned to receive either regular drinking water, or drinking water supplemented with 1 g/L SA. Animals were generally housed with one or two of their litter mates of the same gender, with large litters being divided as evenly as possible between regular drinking water and SA supplementation groups. All animals received a defined L-amino acid diet supplemented with choline and iron."	"Mouse spatial learning and reference memory were assessed using the Morris hidden platform water maze. Mice were trained to use external visual clues to find a hidden platform within the pool that remained in the same position for all nine of the training days. Each training day consisted of 4 trials, with the mice released from each of four different starting positions randomized in order each day and the time to reach the platform (escape latency) measured. All animals of the cohort completed the trial for the same start position before beginning the trials from the next start position. If an animal failed to find the platform in 60 s, latency was scored as 60 s, and the animal was gently guided to the platform. All animals were allowed to remain on the platform for 10 s before being removed to a warming cage. After the 4th trial of the 9th training day, the ability of the mice to remember the platform location was assessed in a probe trial by removing the platform and allowing the mouse to freely swim for 60 s. The percent time spent in the quadrant where the platform previously was positioned was then measured."
[11]	2017	WT, KI (4)	WT: 15 KI (APOE4): 30	Human	untreated WT: 15 treated KI (APOE4): 15 untreated KI (APOE4): 15	N/A, direct interaction with apoe unclear	POSITIVE, "Rapamycin rescues vascular, metabolic and learning deficits in apolipoprotein E4	"WT mice were fed with control diet (WT-control), whereas APOE4 transgenic mice were fed with either control diet containing only microencapsulating materials or	"Spatial memory was assessed using the Morris water maze paradigm. Mice (N = 15 per group) were pre-screened for neurodevelopmental deficits and were admitted into the study only if they exhibited intact vision, swimming, and climbing abilities and had no other overt sensorimotor deficits as determined by a

							transgenic mice with pre-symptomatic Alzheimer's disease"	with diet supplemented with microencapsulated rapamycin at 14 mg per kg food, which is roughly equivalent to 2.24 mg/kg/mouse/day based on the assumption that an average mouse weights 30 g and consumes 5 g of food per day. Diet was given for six months."	battery of neurobehavioral tasks performed before testing. Experimenters were blind with respect to genotype and treatment. Briefly, mice were subjected to a series of four trials in which they were released into a light-colored tank filled with opaque water whitened by the addition of non-toxic paint at 24.0 ± 1.0°C. Their task was to locate a 12 × 12 cm submerged platform (1 cm below the water surface) by utilizing visual cues. The water tank was surrounded by opaque dark panels with black-and-white geometric designs, as well as with different geometric designs placed at four locations at the inner edge of the pool 10 cm above the edge of the water to serve as internal cues. Animals were guided to the platform if they failed to locate it within 60 s, and they were required to remain on the platform for 15 to 20 s. During the course of testing, animals were monitored daily and their weights recorded weekly. Performance was recorded by a computer-based video tracking system (Water 2020, HVS Image, Buckingham, UK). Data were analyzed offline by using HVS Image and processed with Microsoft Excel."
[12]	2003	WT, KI (4)	WT: 5 KI (apoE4): 5	Human	N/A	N/A	N/A	N/A	"Briefly, the ability of mice to locate a hidden platform submerged in a pool (122 cm in diameter) filled with opaque water (22°C) was determined in two sessions (2.5 h apart) per day for 5 days. Each session consisted of three consecutive trials. The platform location was constant for each mouse; the starting point at which the mouse was placed into the water was changed for each trial. On days 6–8, the ability of the mice to locate a visible platform was tested to exclude differences in vision, swim speed, and motivation. Decreases in the time it took the mice to reach the hidden platform (latencies) and decreasing path lengths were used as putative measures of spatial learning. On the mornings of days 3, 5, and 7, a probe trial (platform removed) was performed, and the time the mice spent in the quadrant where the platform was previously located was recorded as a measure of memory retention."

[13]	2020	WT, KO	WT (C57BL/6 APOE+/+): 20 KO (APOE−/−): 20	N/A	treated WT (C57BL/6 APOE+/+): 20 treated KO (APOE−/−): 20	N/A, "Axonal injury results in long-term neurological deficits in traumatic brain injury (TBI) patients. Apolipoprotein E (ApoE) has been reported to activate intracellular adaptor protein Disabled-1 (Dab1) phosphorylation via its interaction with ApoE receptors. The Dab1 pathway acts as a regulator of axonal outgrowth and growth cone formation in the brain. We hypothesized that ApoE may alleviate axonal injury and regulate axonal regeneration via the Dab1 pathway after TBI."	NEGATIVE, "Traumatic axonal injury (TAI) is involved in almost all forms of brain trauma, especially traumatic brain injury (TBI), which results in long-term disability."	"The CCI (Controlled cortical impact) model was produced by the TBI-0310 TBI Model system (Precision Systems and Instrumentation, USA), as previously described. Each mouse was anesthetized with an induction gas mixture (3% isoflurane with 1 L/min 100% oxygen). Briefly, a 5-mm left lateral craniotomy centered at 1.0 mm lateral to the midline and 3.0 mm anterior to lambda was performed. The CCI injury was produced using a pneumatic cylinder with a 3-mm diameter flat-tip impounder at an impact velocity of 6.0 m/s, a dwell time of 40 ms, and a cortical contusion depth of 0.6 mm. The body temperature of each mouse was maintained at 36-37°C throughout the duration of the surgery."	"Morris water maze (MWM): The MWM was used to evaluate cognitive function post-CCI beginning at 15 days postinjury to allow for the recovery of motor deficits. The apparatus consisted of a white pool 150 cm in diameter and 40 cm deep. Visible cues were positioned on the walls of the tank and around the room. A goal platform 8 cm in diameter was positioned 1 cm below the surface of the water (hidden platform). After five sets of hidden platform trials, two sets of visible platform trials were performed. The maximum time allotted to reach the platform was 90 s. Performance in the hidden and visible platform trials was quantified as latency to reach the platform in seconds."
[14]	2013	WT, KI (4)	WT (rmTBIs): 196 KI (rmTBIs APOE4): 50	Human	treated WT (rmTBIs): 123 untreated WT (rmTBIs): 73 treated KI (rmTBIs APOE4): 50	N/A, "Long-term cognitive deficits were associated with increased astrocytosis but not tau phosphorylation or amyloid β (by ELISA); plaques or tangles (by immunohistochemistry); or brain volume loss or changes in white matter integrity (by MRI). "	NEGATIVE, "Mice subjected to rmTBI daily or weekly but not biweekly or monthly had persistent cognitive deficits as long as 1 year after injuries."	The mouse rmTBI (repetitive mild traumatic brain injuries) model was used as previously described with important modifications. Briefly, mice (3-month-old males) were anesthetized for 45 seconds. Anesthetized mice were placed on a delicate task wiper. A 54g metal bolt was used to deliver the impact to the dorsal aspect of the skull. At impact, the mouse head readily penetrated the Kimwipe, resulting in a rotational acceleration of the head. Sham-injured age-matched control mice underwent anesthesia but not concussive injury.	"Spatial learning and memory were assessed using a MWM paradigm as previously described. Each mouse was subjected to a maximum of 2 series of 4 trials per day. For probe trials, mice were placed in the pool with the platform removed. The time that the animal swam in the target quadrant was recorded (maximum 60 seconds). For visible trials, the platform was marked by red tape and placed 0.5 cm above the water level. Swim speeds were measured by Any Maze software (Stoeling, Wood Dale, IL). When mice underwent repeat MWM testing, 2 to 3 months or 6 months after their final injury, the platform was moved to a different quadrant than that used previously."
[15]	2016	WT, KO	WT (C57BL/6): 10 KO (ApoE-KO): 20	N/A	untreated WT (C57BL/6): 10 treated KO (ApoE-KO): 10 untreated KO (ApoE-KO): 10	N/A, "These findings suggested that cognitive impairment of ApoE-KO mouse might associate with tau pathology and 7,8-DHF could activate AKT and then phosphorylate its downstream molecule to inhibit expression of	POSITIVE, "7,8-Dihydroxyflavone Ameliorates Cognitive Impairment by Inhibiting Expression of Tau Pathology in ApoE-Knockout Mice"	"7,8-DHF was purchased from TCI company (Tokyo, D1916) and dissolved at 100 mg/ml concentration in 85% saline with 10% dimethylsulfoxide and 5% tweeen-20 (Solarbio, T8220), Akt (pan; C67E7; #4691), phospho-Akt (Ser473; D9E) XP (#4060), phospho-GSK-3β (Ser9; 5B3; #9323) were all	"After intervention for 25 weeks, MWM tests, which is commonly thought to be related with hippocampal-dependent spatial learning and memory, were carried on to assess behavioral performance of ApoE-KO mice and protective effects of 7,8-DHF on cognitive decline. The experiment was performed as previously described. A 120 cm diameter tank was filled with water with non-toxic milk powder dissolved in it. The pool was divided equally into four quadrants: northeast (NE), southeast (SE), southwest (SW), and northwest (NW). The circular

						abnormal tau, meanwhile, 7,8-DHF could reduce the expression of active-AEP and then inhibit production of truncated tau N368."		rabbit monoclonal antibodies and purchased from Cell Signaling. GSK-3β Rat mAb (#272536), Legumain/Asparaginyl Endopeptidase (AEP) Sheep pAb (AF2058) were purchased from R&D System. Phosphor-Tau (S396) Rabbit mAb (ab109390), PHF1 Rabbit mAb (ab184951), BDNF Rabbit mAb (EP1293; ab108383), TrkB Rabbit pAb (ab33655), and phospho-TrkB Rabbit pAb (Y816; ab75173) were all purchased from Abcam. Tau N368 rabbit antibody was a gift from Prof. Ye of Emory University, USA.After 7 days acclimatization period, all mice were fed with western type diet purchased from HFK Bioscience Company (Beijing, China, H10141) for 25 weeks. All the mice were randomly divided into three groups. The first group was normal group containing 10 C57BL/6 wild-type mice. The second group was cognitive impairment model group with 10 ApoE-KO mice in it. The third group was intervention group in which ApoE-KO mice were treated with 7,8-DHF chronically at the dose of 5 mg/kg daily by oral administration for 25 weeks while the mice in other two groups were given vehicles daily. During the experiment, all the mice were measured weight and monitor health status every week. All experimental researches were conducted at the same phase during the day."	platform was 10 cm in diameter located in the center of NE quadrant, and was submerged 1.5 cm below the surface of water. Several visual cues were placed in the room as spatial reference for mice to locate the invisible platform, and experimenter remained stationary in a fixed location. After 5 days of acquisition trials, the platform was removed and mice were placed in the SW quadrant, opposite to the former platform position and the probe trial underwent. During the whole trials, all mice were maintained on their western type diet and oral administrated by 7,8-DHF or vehicle. Behavioral parameters (latency; percentage of time and distance in NE quadrant; the number of mouse crossing over the position of the platform) were recorded and evaluated with AVTAS software."
[16]	2016	WT, KO, KI (4)	WT: 26 KO (ApoE-/-): 12 KI (apoe4): 16	Human	treated WT: 14 untreated WT: 12 treated KO (ApoE-/-): 6 untreated KO (ApoE-/-): 6 treated KI (apoe4): 8 untreated KI (apoe4): 8	INCREASE in plasma DECREASE in hippocampus	NEGATIVE, "ApoE protects against high-fat (HF) diet induced neurodegeneration by its role in the maintenance of the integrity of the blood-brain barrier"	"At 12 months of age, 48 female mice were randomly assigned to either a standard rodent chow diet (3.3% fat, ssniff Spezialdiäten GmbH, Soest, Germany: CTRL), or a high fat cholesterol enhanced diet (19% butter, 0.5% cholate, 1.25% cholesterol: HF) and fed for the remainder of the experiments."	"The MWM was used to assess spatial learning and memory. The mouse was placed at different starting positions in a circular pool (diameter 104 cm) that was filled with water (21–22°C, made opaque by adding milk powder). The mouse was trained to find the platform (diameter 8 cm) which was submerged 1 cm below the water surface and located in the north-east quadrant of the pool by using distant visual cues. The visual cues were present on the four walls surrounding the pool at a distance of 0.5 m. During all trials, the observer was present in the room and always located at the same position (behind a curtain surrounding the set-up)."

[17]	2014	KO	KO (apoe3): 22 KO (apoe4): 22	Human	N/A	N/A	N/A	N/A	"We used MWM to test spatial learning and memory function as described previously. Briefly, MWM tank was divided into four quadrants with four starting locations. The water temperature was maintained at 24+/- 1.0 C."
[18]	2002	WT, KO	WT: 16 KO (ApoE KO): 16	N/A	treated WT: 16 treated KO (ApoE KO): 16	N/A, direct interaction with apoe unclear	NEGATIVE, "Radiation adversely affected spatial working memory in the KO mice, but had no discernible effect in the WT mice as assessed 180 d after irradiation"	"Animals were placed in an acrylic holder and irradiated with a 2 Gy dose of 600 MeV/amu iron particles, whole body irradiation, using the Alternating Gradient Synchrotron at the Brookhaven National Laboratories. A fluence of 3 × 106 iron nuclei/cm2 was chosen to mimic the total HZE exposure (all > He ions) for a 2-year mission to Mars). Sham irradiated animals were positioned in the holder but received no HZE particle radiation."	"The Morris Water Maze test was used to assess spatial reference and working memory. The starting position of the mouse was varied for each of the 4 daily trials. If a mouse failed to locate the platform within the maximum trial period of 60 s, it was led to and placed on the platform for 10 s. At the completion of 7 training sessions (one session per day), the mice received a second task with different visual cues and a different position of submerged platform for 3 days. The time taken to find the platform was recorded for each trial. The daily time mean for the four trials was used for statistical analysis."
[19]	1997	KO	KO (apoE KO): 6 KO (heterozygous): 7	N/A	N/A	N/A	N/A	N/A	"A pool (white sidewalls: 140 cm diameter) was filled with warm water (26+/- 1 C), made opaque by the addition of chalk. A platform (8 cm diameter) was situated 5 mm below the surface of the water, invisible for the animal."
[20]	2016	KI (3,4)	KI (apoE3): 34 KI (apoE4): 34	Human	treated KI (apoE3): 17 untreated KI (apoE3): 17 treated KI (apoE4): 17 untreated KI (apoE4): 17	N/A, treatment modulates GABA	POSITIVE, "enhancing GABA signaling by PB treatment in aged apoE4-KI mice before and during behavioral tests rescues learning and memory deficits"	"PB (Sigma-Aldrich) was prepared in 0.9% sterile saline at 5 mg/ml. Mice were administered 20 mg/kg by intraperitoneal injection for 28 d (4 weeks), 2 weeks before (every morning) and during (every afternoon) behavioral tests or 50 mg/kg for 42 d (6 weeks) and discontinued for 2 weeks or 5 months before behavioral tests."	"All mice were singly housed during Morris water maze (MWM) test, which was conducted in a pool (122 cm diameter) with room temperature water (22–23°C) with a 10-cm-wide square platform submerged 1.5 cm below the surface of opaque water during hidden trials. Mice were trained to locate the hidden platform over 4 trials per day for 5 hidden days (HD)1–5, where HD0 is the first trial on the first day, with a maximum of 60 s per trial. Each memory trial (probe trial) was conducted for 60 s in the absence of the platform at 24, 72, and 120 h after the final learning session. Memory was assessed as percentage of time spent in the target quadrant that contained the platform during the learning trials compared with the average of time spent in the nontarget quadrants. For visible trials, a black-white striped mast (15 cm high) marked the platform location. The platform location and room arrangement remained constant throughout the assay with the exception of moving the platform during the visible trials. Speed was calculated by distance traveled divided by trial duration. Performance was objectively monitored using EthoVision video-tracking software (Noldus Information Technology)."
[21]	2013	KI (3,4)	KI (apoE3-TR): 21 KI (apoE4-TR): 24	Human	N/A	N/A	N/A	N/A	"hidden-platform version of the Morris water maze task."

[22]	2016	KI (4)	KI (E4FADF): 16	Human	treated KI (E4FADF): 8 untreated KI (E4FADF): 8	N/A, "ApoE levels were unaffected by EGF treatment"	POSITIVE, "EGF (epidermal growth factor) prevents cognitive deficits in E4FADF mice"	"Six month old E4FADF mice were administered EGF (epidermal growth factor) (Shenandoah, 300 µg/kg/wk) or vehicle control (water) by intraperitoneal injection (i.p.) until 8.5 months."	"Morris water maze (MWM) was conducted as described, with slight modifications in three phases. The circular pool was 120 cm in diameter and 50 cm tall, and the circular escape platform was 10 cm in diameter. The pool was filled with water containing non-toxic tempera paint (maintained at 25 °C) to 10 cm below the top rim and divided into equal-sized imaginary quadrants. Extramaze cues were placed in the four corners for spatial orientation. A single mouse was in the pool for each testing phase/session. MWM testing was comprised of three phases. (a) Visual Cue phase. Mice were trained over the course of 2 days to locate a flagged hidden platform (60s trial time, four trials each day with a 20 min inter-trial interval (ITI)). (b) Acquisition phase. After 2 days, mice were trained for 5 days (60s trial time, four trials each day with a 20 min ITI) to locate the position of the hidden platform (remains on the hidden platform for >2 s). During the visual cue and acquisition phases the mouse's entry quadrant varied but the platform location remained constant. Latency to find the platform (s) was measured. (c) Probe trial. 1 h following the final acquisition trial, a single 60s probe trial was conducted with the platform removed. The latency to the target area (i.e., where platform was located during acquisition phase) and the time spent in the target quadrant were calculated."
[23]	2014	KI (3,4)	KI (apoE3-fKI): 89 KI (apoE4-fKI): 117	Human	untreated KI (apoE3-fKI): 48 treated KI (apoE3-fKI/GFAP-Cre): 41 untreated KI (apoE4-fKI): 75 treated KI (apoE4-fKI/GFAP-Cre): 42	DECREASE, "After deleting APOE from astrocytes of apoE3-fKI/GFAP-Cre and apoE4-fKI/GFAP-Cre mice, apoE protein levels were reduced to ~20% of those seen in the cortex and hippocampus of apoE3-fKI and apoE4-fKI mice "	NEGATIVE, "Apolipoprotein E4 Produced in GABAergic Interneurons Causes Learning and Memory Deficits in Mice"	"To generate mice with a conditional deletion of the human APOE gene, homozygous apoE3-fKI (apoE3/3) and apoE4-fKI (apoE4/4) mice were crossbred with GFAP-Cre transgenic mice [B6.Cg-Tg(GFAP-cre)8Gtm], Synapsin 1-Cre (Syn-1-Cre) transgenic mice [B6.Cg-Tg(Syn1-cre)671Jxm/J], or Dlx-Cre transgenic mice [Tg(I12b-cre)]. These lines generated mice that were heterozygous for apoE3 or apoE4 and positive for GFAP-Cre, Syn-I-Cre, or Dlx-Cre. These mice were further crossbred with homozygous apoE3-fKI or apoE4-fKI mice to generate mice that were homozygous for apoE3 or apoE4 and positive for GFAP-Cre (apoE-fKI/GFAP-Cre), Syn-I-Cre (apoE-fKI/Syn-1-Cre), or Dlx-Cre (apoE-fKI/Dlx-Cre). Littermates that were negative for GFAP-Cre, Syn-I-Cre, or Dlx-Cre were used as controls. For generation of the apoE-fKI/Syn-I-Cre line, only female Syn-I-Cre mice were used for breeding purposes because	"Due to the large sample sizes, there were three separate Morris water maze (MWM) test cohorts. Each cohort contained littermate controls. Since control mice of apoE3-fKI and apoE4-fKI showed no significant difference across three cohorts and the conclusion was the same if we used pooled data or data from individual cohorts, we presented the pooled data for easier and more relevant comparisons. The MWM was performed as described previously. A platform (15 cm in diameter) was located in a water maze pool (diameter 122 cm) that was filled with opaque water (18–20°C). The platform was submerged 1.5 cm from the surface during the hidden platform session and marked with a black-and-white-striped mast (15 cm high) during the cued training sessions. The platform location was constant during the hidden platform session (northwest quadrant) and was altered between the remaining quadrants during the cued training sessions. Only female mice at 17 months of age (10–25 mice per group) were used. Mice were trained to locate the hidden platform (hidden days 1–5) in two daily sessions separated by at least 2.5 h. Each session consisted of two trials 15 min apart, each lasting 60 s. Entry points were changed semirandomly between trials, but were repeated in the same order each day. Escape latency is noted as the time taken to locate the hidden platform. Swim speed is defined as the path length to the platform divided by latency. In the probe trials 24, 72, and 120 h after the last hidden platform training, the performance of each mouse was monitored for 60 s with an EthoVision video-tracking system (Noldus Information Technology). For the probe trials, the hidden platform was removed, and the entry point

								germline recombination has been reported in the progeny of male Syn-I-Cre mice. To characterize Cre-recombinase expression, we crossbred Syn-1-Cre and Dlx-Cre transgenic mice with a Cre-reporter mouse line [Gt(ROSA)26Sortm6(CAG-ZsGreen1)Hze]."	remained constant at a 180° angle opposite from the original platform location. Performance in the probe trials was analyzed by comparing the percentage of time spent in the target quadrant to the average of percentage time spent in all other three quadrants. Visible platform tests were performed after the last probe trial and consisted of one trial/platform location. Visible platform locations were quadrants that were not used for hidden platform training. Time between visible platform trials was 2 h."
[24]	2014	KI (2,3,4)	KI (E2): 12 KI (E3): 12 KI (E4): 12	Human	N/A	N/A, "Our results show that plasma and brain apoE levels, cortical cholesterol, and spatial memory are all regulated by isoform-dependent interactions between apoE and LDLR."	N/A	N/A	"Spatial Learning and Memory in the Water Maze (Days 8-15). The water maze consisted of a circular pool (diameter 140 cm), filled with opaque water (white chalk added, 24°C) divided conceptually into four quadrants. Mice were first trained to locate an "escape" platform (plexiglass circle, 6 cm radius) submerged 2 cm below the surface of the water, by the use of a cue (a colored cylinder, 2.5 cm radius, 8 cm height) during the "Visible" trials (days 8-9). Mice were given two sessions per day (separated by three hours) consisting of two trials each (separated by 10 minutes). The location of the platform was moved for each session between the four quadrants to avoid procedural biases in task learning. Subsequent to the "Visible Platform" trials, mice were trained to locate the platform sans cue during the "Hidden Platform" trails, which required the mice to rely on extra-maze cues for spatial reference and orientation. E
[25]	2017	KI (3,4)	KI (E3): 16 KI (E4): 16	Human	treated KI (E3): 8 untreated KI (E3): 8 treated KI (E4): 8 untreated KI (E4): 8	N/A, "Significantly upregulated by injury in both genotypes were mRNA expression and protein level of ABCA1 transporter and APOJ, but not APOE."	NEGATIVE, "Traumatic brain injury (TBI) is strongly linked to an increased risk of developing dementia, including chronic traumatic encephalopathy and possibly Alzheimer's disease (AD)."	"Mice at 3 mo of age were randomly assigned to either sham or controlled cortical impact (CCI) experimental group and initially were handled for 2 days (5 min per day). Following surgical procedures, mice were allowed to recover for 3 days before starting behavioral testing. Following induction of anesthesia with 5% isoflurane, the mouse was moved to the stereotaxic frame, where the head was secured, core body temperature maintained at 37°C using a heating pad and anesthesia continued with 1.5% isoflurane. The head was shaven, surgical site sterilized with two separate iodine - alcohol washes, a 50% mixture of bupivacaine and lidocaine applied to the surgical site and ophthalmic ointment applied to the eyes. The scalp was opened with a midline incision exposing the dorsal aspect of the skull and	"Spatial navigational learning and memory retention were assessed using Morris water maze (MWM) as described previously; with testing performed on days 6–12 post-injury. Briefly, in a circular pool of water (diameter 122 cm, height 51 cm, temperature 21 ± 1°C), we measured the ability of mice to form a spatial relationship between a safe but invisible platform (submerged 1 cm below the water level; 10 cm in diameter) and several visual extra maze cues surrounding the pool of water. On day 6 post-injury, mice received a habituation trial, during which the animals were allowed to explore the pool of water without the platform present. Beginning the next day, they received four daily hidden platform training (acquisition) trials with 5-min inter-trial intervals for five consecutive days (days 7–11 post-injury). The platform remained in the center of one of the four quadrants of the pool (target quadrant). Animals were allowed 60 s to locate the platform and 20 s to remain there. Mice that failed to find the platform were lead to the platform by the experimenter and allowed to rest there for 20 s. Performance was recorded using Any-maze software (Stoelting Co.) during all trials. During the acquisition trials, escape latency (time to reach the platform) was subsequently used to analyze and compare the performance between all groups."

								the skull leveled. A 4.5 mm diameter craniotomy was performed over the left parietal cortex using a dental drill. Once the bone flap was removed, mice in the CCI group received a single impact at 1.0 mm depth with a 3.0 mm diameter metal tip onto the cortex (3 m/s, 100 ms dwell time; Impact One, Leica). Sham mice received identical anesthesia and craniotomy, but did not receive impact and are considered negative controls."	
[26]	2012	KI (3,4)	KI (apoE3-KI): 20 KI (apoE4-KI): 20	Human	N/A	N/A	N/A	N/A	"The water maze pool (diameter 122 cm) contained opaque water (22–23°C) with a platform 10 cm in diameter. The platform was submerged 1.5 cm from the surface during the hidden platform sessions and marked with a black-and-white-striped mast (15 cm high) during the cued training sessions. Mice at 12 or 16 months of age were trained to locate the hidden platform (hidden days 1–5) and the cued platform (visible days 1–3) in two daily sessions spaced by 3.5 hours, each consisting of two 60-second trials (hidden and cued training) with a 15 min interval. The platform location remained constant throughout the hidden platform sessions but was changed for each cued platform session. Entry points were changed semi-randomly between trials. Escape latency is noted as the time taken to locate the hidden platform. Swim speed is assessed as the path length to the platform divided by latency. 24 and 72 hours after the last hidden platform training, we performed a 60-second probe trial with the platform removed. Entry points for the probe trial were in the northwest quadrant, and the target quadrant was the southeast quadrant. Performance was monitored with an EthoVision video-tracking system (Noldus Information Technology)."
[27]	2013	KI (3,4)	KI (apoE3): 7 KI (apoE4): 7	Human	N/A	N/A	N/A	N/A	
[28]	2013	KI (3,4)	KI (apoE3): 26 KI (apoE4): 26	Human	treated KI (apoE3): 13 untreated KI (apoE3): 13 treated KI (apoE4): 13 untreated KI (apoE4): 13	N/A, "CNF1 decreased the levels of beta amyloid accumulation and interleukin-1β expression in the hippocampus"	POSITIVE, "data suggest that the pharmacological modulation of Rho GTPases by CNF1 can improve memory performances in an animal model of Alzheimer's disease via a control of neuroinflammation and a rescue of systemic energy homeostasis."	"An Escherichia coli protein toxin, named Cytotoxic Necrotizing Factor 1 (CNF1), was obtained from the 392 ISS strain (kindly provided by V. Falbo, Rome, Italy) and purified essentially as previously described with few modifications in the procedure. For all experiments, a concentration of 0.1 nM CNF1 was used."	"Mice were trained in the MWM task to locate a hidden escape platform in a circular pool. The apparatus consisted of a large circular water tank (1.00 m diameter, 50 cm height) with a transparent round escape platform (10 cm2). The pool was virtually divided into four equal quadrants identified as north, east, northwest, southeast, and southwest. The tank was filled with tap water at a temperature of 22±2°C up to 0.5 cm above the top of the platform and the water was made opaque with milk. The platform was placed in the tank in a fixed position (in the middle of the south-east quadrant). The pool was placed in a large room with a number of intra- (squares, triangles, circles and star) and extra-maze visual. After the training, each mouse was tested for 4 trials a day, for 4 consecutive days with an inter-trial interval of 30 min (Acquisition phase). A video camera was placed above the center of the pool and connected to a video-tracking

									system: Ethovision 3.1© (Noldus Information Technology B.V., Wageningen, Netherlands). Mice were released facing the wall of the pool from one of following starting points: North, East, South, or West and allowed to search for up to 60 s for the platform. If a mouse did not find the platform, it was gently guided to it and allowed to remain there for 15 s. Reference memory was assessed with one trial (Probe trial), on the fifth day, 24 h after the last acquisition trial, using one starting point for all the mice. Mice were allowed to search for up to 30 s for the platform. The latency to find the hidden platform was used as a measure of learning. The average swim speeds, were also analyzed. All experimental sessions were carried out between 09.00 and 15.00 h."
[29]	2013	KI (2,3,4)	KI (apoE2): 324 KI (apoE3): 308 KI (apoE4): 348	Human	N/A	N/A, "The effects of BDE-209 depend on age and apoE genotype."	N/A, "The effects of BDE-209 depend on age and apoE genotype."	"The day of delivery was designated as postnatal day 0 (PND0). BDE-209 (decabromodiphenyl ether) was administered on PND10. On PND30, the offspring were separated from the dam and housed in plastic cages containing 2–4 animals of the same sex. The animal room was maintained at a temperature of 22 ± 2 °C, a relative humidity of 50 ± 10%, and a 12-h light/dark automatic light cycle (light: 0800–2000 h). All animals were allowed free access to food (Panlab rodent chow, Barcelona, Spain) and tap water. A maximum of 2–3 animals from each litter and sex were assigned to one of the different experimental stages at 4 months, 12 months, or BDNF determination."	"The apparatus consisted of a circular pool (diameter: 1 m; height: 60 cm), virtually divided in four quadrants. An escape platform (10 cm diameter) was located 1 cm below the water surface. To acquire the task (localize the hidden platform), animals performed 2 trials per day for 10 days (60 min inter-trial interval). During each trial, mice were allowed to swim for a maximum of 90 s to find the hidden platform. If the animal failed to find the platform it was directly placed on it by the experimenter. Mice were maintained on the platform for 30 s. The starting position was changed for each trial (four different positions available; none of them was placed in the target quadrant). To avoid proximal cues and prevent non-spatial learning strategies, an internal mobile wall was added to the maze and rotated between trials. The retention of the task was assessed by probe trials consisting of 60 s free swim in the absence of the escape platform. Four probe trials were performed during the acquisition period (sessions 3, 5, 8 and 10) 1 h before the training trials, in order to evaluate memory along the learning process. Seventy-two hours after the last training session another probe trial was performed in order to evaluate long-term retention. Animal performance was recorded by a video camera (Sony CCD-IRIS model) placed above the maze. Data were analyzed by the video-tracking program Etho-Vision© (Noldus Information Technologies, Wageningen, The Netherlands)."
[30]	2019	KI (3,4)	treated KI (ApoE3): 20 treated KI (ApoE4): 20	Human	treated KI (ApoE3): 10 untreated KI (ApoE3): 10 treated KI (ApoE4): 10 untreated KI (ApoE4): 10	N/A, "Sirt3 (sirtuin 3) may mediate the neuroprotection of ketones by increasing neuronal energy metabolism in ApoE4 transgenic mice."	POSITIVE, "Ketones improved learning and memory abilities of ApoE4 mice but not ApoE3 mice."	"ApoE3 mice and ApoE4 (10-11 animals/ group) were treated with ketones or control saline by daily subcutaneous injections from 9 months of age (ketones, beta-hydroxybutyrate (BHB): 600 mg/kg/day; acetoacetate (ACA): 600 mg/kg/day; ACA: 150 mg/kg/day)."	"Spatial learning was assessed by the Morris Water Maze (MWM) task adapted for mice. Briefly, each mouse was introduced into the circular pool and allowed to swim. The time (escape latency) required to reach the platform located in northeast quadrant, as well as the swimming speed was recorded in each trial. Once the mouse located the platform, it was permitted to remain on it for 10 seconds. If the mouse did not locate the platform within 120 seconds, it was placed on the platform for 10 seconds. The mouse was given four trials per day for 4 days with an inter-trial interval of 20 minutes. Each trial was initiated by randomly placing an animal in one of the four starting locations. Escape latency and swimming speed were collected and

									analyzed using EthoVision® 3.1 tracking software (Noldus Information Technology Inc., Leesburg, VA). On the 5th day, a single probe trial was carried out. In this trial, the platform was removed and each mouse was placed from southwest quadrant of the pool and allowed to swim for 120 seconds. The time spent in the target quadrant (northeast) was collected and calculated using EthoVision® 3.1 tracking software."
[31]	2019	KI (3,4)	KI (ApoE3): 11 KI (ApoE4): 11	Human	N/A	N/A	N/A	N/A	"Spatial learning was assessed by the Morris water maze (MWM) task as described previously. We labeled all mice with series number randomly. The person who performed these water maze tests was blinded to the number assignment. Briefly, each mouse was introduced into a circular pool and allowed to swim freely. The time (escape latency) required to reach the platform located in northeast quadrant, as well as the swimming speed was recorded in each trial. Once the mouse located the platform, it was permitted to stay on it for 10 seconds. If the mouse did not locate the platform within 120 seconds, it was placed on the platform for 10 seconds. The mouse was given four trials per day for 4 days with an inter-trial interval of 20 minutes. Each trial was initiated by randomly placing a mouse in one of the four starting locations. Escape latency and swimming speed were collected and analyzed using EthoVision® 3.1 tracking software (Noldus Information Technology Inc., Leesburg, VA). On the 5th day, a single probe trial was carried out. In this trial, the platform was removed and each mouse was placed from southwest quadrant of the pool and allowed to swim for 120 seconds. The time spent in the target quadrant (northeast) was collected and calculated using EthoVision® 3.1 tracking software."

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