Supplementary Material and Methods

Immunohistochemistry

Mice were sacrificed by cervical dislocation. Brains were removed and post-fixed in 4% PFA. After overnight cryoprotection in a 30% sucrose solution, brains were blocked in the coronal plane, frozen on dry ice, and sectioned at 50 µm on a cryostat. Sections at 100 µm intervals were stored in 1xPBS until processing. To reveal c-Fos expression levels in the brain, free-floating sections were incubated in 0.3% H_2O_2 in 1xPBS for 10 min. After a rinse in 1xPBS, sections were incubated in 5% normal goat serum in 1xPBS containing 0.25% TritonX-100 and a c-Fos antibody raised in rabbit (Santa Cruz, sc-52; 1:800/1:500) and left for overnight incubation (up to 96 hours) at room temperature (RT). Sections were washed with 1xPBS and incubated at RT for 1 h in biotinylated goat anti-rabbit secondary antibody (#65-6140, Invitrogen; 1:400). After a thorough rinse, the sections were incubated at RT for 1 h in avidin-biotin peroxidase complex (Vectastain ABC, Vector Laboratories; 1:800). To visualize the peroxidase labeling, sections were processed with a DAB/nickel substrate working solution (DAB Peroxidase Substrate, SK-4100; Vector Laboratories) for 7 min at RT. After rinsing with 1xPBS, sections were mounted on gelatin-coated slides, dehydrated, and coverslipped.

Sections were imaged using a Leica bright-field microscope at 10x magnification. Several brain regions were selected for analysis: prefrontal cortex (PFC), primary motor cortex (mCx), somatosensory cortex (ssCx), lateral septum (LS), paraventricular nucleus (PvN), hippocampus (CA1, CA3, and dentate gyrus (DG)), thalamus (Thal) and the basolateral nucleus of the amygdala (BLA). Each brain region of interest was identified using a standard mouse brain atlas

(*84*). c-Fos immunoreactive nuclei were counted using the threshold values in ImageJ software. Labelled cells were counted bilaterally, averaged and normalized to the size of area.

ECoG and video monitoring: surgery and analysis

Before surgery, animals were weighed and pre-operative analgesic treatment (buprenorphine, 0.05 mg/kg, s.c.) was applied. Mouse was transferred to the induction chamber where isoflurane anesthetic was applied (3% isoflurane/oxygene, flow 0.8 l/min). Animal was monitored and the depth of anesthesia was confirmed by checking paw pinch reflex. After induction of anesthesia, animal was transferred to the heating pad of the stereotaxic apparatus and its head was fixed. The same inhalation anesthetic was applied for maintenance of anesthesia (1.6 - 3.0% isoflurane/oxygene, flow 0.6 - 0.8 l/min). Skull of the mouse was exposed and cleaned from the remaining tissue. Subcutaneous pocket was made and filled with sterile saline. Two holes were made on the skull leaving intact dura mater: on cortex (anterior 2.2 mm, lateral left 1 mm) and on cerebellum (posterior 6 mm, lateral right 1 mm). Transmitter (ETA-F10; specification: https://www.datasci.com/products/implantable-telemetry/mouse-(miniature)/eta-f10) was inserted in the subcutaneous pocket. Two stainless steel screws were positioned in the holes and the wires from transmitter were tightly placed around the screws. Electrodes were fixed using dental cement (Tetric EvoFlow, Ivoclar vivadent). Skin was sutured and animal was transferred to the heating pad for recovery. Post-operative analgesic treatment was applied if needed (buprenorphine, 0.05 mg/kg, *s.c.*). Animal was transferred to the home cage, and they were daily checked and weighed. Video and ECoG recording started 7 days later.

For ECoG recordings, implanted animals in their home cages were placed on the DSI receiver board (www.datasci.com) in front of an infrared camera for 24-hvideo monitoring. 1 signal (sampling rate of 1000 Hz) and behavior was recorded synchronously for at least 24 h.

Analysis of EEG and video monitoring data

EEG and ECoG signal was visually inspected for abnormal activity and video records were checked for epileptic-like events by two observers. Visual inspection of ECoG (EEG) signal revealed spike-wave discharges (SWDs) with narrow peak frequency ~7 Hz as the potential pathological activity. Two types of epileptic-like events were found in behavioral analysis, called: twitches and jumps.

SWDs and behavioral epileptic-like events were time matched within time window of ± 10 s. Number of behavioral epileptic-like events accompanied with SWDs was further analyzed, by calculating the probability of concurrence. Probability of concurrence of SWDs >1.5 s duration and epileptic-like events were analyzed by calculating the probability of coincidence, a concurrence of the events without apparent causal connection. The program created in Python 3.6 was used to calculate the probability of coincidence (https://github.com/d-kovacevic/experiment_simulation/blob/master/simulate.py). Total number of behaviorally detected events (twiches or jumps) and SWD per mouse during 12-h recording intervals were entered in the program. The program randomly generated the same number of events (behavioral and ECoG(EEG)) during selected time range (12 h = 43200 s). The procedure was repeated 50000-times and the program calculated the probability of coincidence within ± 10s (delta_time = 10 s) for these two events. Probability of 0.05 was taken as the borderline for the connection. Data were expressed as the –log(probability) per group. Video and EEG recordings were always

time-matched using the light impulse detected as an additional channel in our EEG recording. Detected drift ranged from 1s to 6s over 24h. Thus, time window of 10s should compensate for this shift of the system.

Automated home cage observation and data analyses

Mice were transferred to specially designed automated home cages (PhenoTyper model 3000, Noldus Information Technology, Wageningen, The Netherlands). The PhenoTyper cages (L = 30 cm, W = 30 cm, H = 35 cm) were made of transparent Perspex walls with an opaque Perspex floor, covered with bedding material. Every cage was equipped with a water bottle, feeding station and a shelter with two entrances in one corner of the cage. In the opposite corner, the tube of a rewarder dispenser was inserted into the cage. Water was available *ad libitum* during the entire period and food was available *ad libitum* during the observation of spontaneous behavior. Mice were introduced in the cages in the second half of the subjective light phase (14:00–17:00 h). The behavior of mice was video-tracked for seven days (EthoVision HTP 2.1.2.0, based on EthoVision XT 4.1, Noldus Information Technology, Wageningen, The Netherlands) starting at the first subjective dark phase (19:00 h), as described in detail previously (*27, 28*). Resulting track files, containing X-Y coordinates of the center of gravity (COG) at a resolution of 15 images per second, were processed using AHCODA^{TM} analysis software (Synaptologics BV, Amsterdam, The Netherlands) to extract behavioral parameters. The first three days in the PhenoTyper were used for observation of spontaneous animal behavior. For assessment of spontaneous behavior 115 activity parameters were analyzed and divided in 6 categories: activity, dark-light ratio, habituation, kinematics, sheltering, phase transition, as described in detail previously (*28*). The last and first 10 min of each dark and light phase were not included in

summary statics to ensure that a potential asynchrony of the data streams and light regime in the testing facility would not affect these statistics.

Initial discrimination and reversal learning (CognitionWall DL/RL task)

CognitionWall DL/RL task is a 4 day continuously running task within the PhenoTyper developed for measuring the initial discrimination (DL) and reversal (RL) learning (*33*). This task started during the 3rd light phase (at 16:30 h), 15 mins after the CognitionWall was placed in the cage. The CognitionWall is a wall with three holes, placed in front of the reward food dispenser; dimensions of the wall were H = 25 cm, W = 17 cm, Ø of holes = 3.3 cm.

The DL phase was lasting for 2 days during which mice had to learn to earn their food (Dustless Precision Pellets, 14 mg, Bio-Serve) by going through the left hole of the CognitionWall. They were rewarded with a food pellet for every 5th correct choices. The RL started 48 h later when the rewarded hole was switched to the right hole. Again, every 5th entry through the correct hole (RL: right hole) was awarded with a food pellet. The rate at which a mouse gains a relative preference for the rewarded entrance is used as a measure of DL and RL. The parameter analyzed was the number of entries made in order to reach criterion. The criterion was 80% correct responses within the moving window size of 30 entries (i.e., 24 correct entries of the 30 last entries).

Avoidance learning (Shelter task)

The avoidance learning test (Shelter task) is developed to measure avoidance learning in high-throughput fashion (*27*). It is a 3 day continuously running test in the automated home-cage environment (PhenoTyper) enriched with a shelter with two entrances. The Shelter task initiated

after assessment of spontaneous behavior in the Phenotyper. During the first 4 days in the home-cage mice could freely enter the shelter. On the 4th day, initial preference for the left or the right entrance was defined by the system. On days 5 and 6, each time when mouse entered the shelter through the previously defined preferred entrance, bright illumination was automatically switched on in the shelter, but not when using the other entrance. During the day 7, the sanctioning was discontinued (bright illumination) and stability of the learned response was assessed. Avoidance learning was studied during the dark phase when shelter illumination is a stronger stimulus than during the light phase. The preference index (calculated as: [(number of entries through the preferred entrance) – (number of entries through non-preferred entrance)]/(total number of entries)) was considered as specific measure of cognitive aspects. A reduction in the preference index indicates that a mouse is establishing a specific association between its preferred entrance and the aversive stimulus. Aversion index (calculated as: [(time spent in the illuminated shelter after entering through the sanctioned entrance) – (time spent in the dark shelter after entering through the non-sanctioned entrance)]/(total time spent in shelter)) was the measure of light averseness.

Novelty-induced hypophagia

Mice were familiarized to a highly palatable snack (a few crumbs of cream cracker) placed into a familiar metal food cup in the home for three days prior to the testing day. On the testing day novelty-induced hypophagia was assessed by transferring mice to a novel clean cage with fresh bedding containing the metal cup with the familiar snack. The latency to start eating the snack was recorded manually. If a subject did not eat within 600 s, the maximum time was assigned.

Grip strength

Neuromuscular function was assessed by sensing the peak amount of force (N) mice applied in grasping a pull bar connected to a force meter (1027DSM Grip Strength Meter, Columbus Instruments, Columbus, OH, USA). Mice were allowed to grasp the pull bar 5 times with front paws only, followed by grasping 5 times with front and hind paws. The median of these five repetitions was taken as grip strength.

Elevated plus maze

We performed the elevated plus maze test as described in (*85*). Mice were introduced onto the center of an Elevated plus maze (EPM) facing a closed arm (arms 30 cm x 6 cm x 35 cm, length x width x height ([L x W x H]), elevated 50 cm above the ground). The EPM was illuminated with a single white fluorescent light bulb from above (open arms 70 lx, closed arm 30 lx) and exploratory behavior was video tracked for 5 min (Viewer 2, Biobserve GmbH, Bonn, Germany). The border between the center and arm entries was defined at 3 cm into each arm. Zone visits were analyzed using the elevated plus maze plugin of the tracking software, which was set to count zone visits if both the nose and body reference point had crossed the zone the zone border. The dependent measures were the number of open arm visits, time spent on the open arms and the first latency to explore an open arm. To counteract the detection of distance moved due to jitter of body reference point produced by grainy video signal, the track correction option was set to 1.

Open field

Mice were introduced into a corner of a white square open field (50 cm x 50 cm x 35 cm [l x W x H]) illuminated with a single white fluorescent light bulb from above (200 lx) and exploration was tracked for 10 min (Viewer 2, Biobserve GmbH, Bonn, Germany). The surface area was divided into nine equally sized squares, and the center square was used as center area. Zone visits to the center area were counted using the body reference point.

Dark-light box

Mice were introduced into the dark compartment (<10 lx; 25 cm x 25 cm x 30 cm, [L x W x H]) of a dark-light box system. 60 s later the motorized door opened providing access to an identical sized compartment which was brightly lit (~625 lx) and left open for 10 min. Visits to, and time spent in the light compartment were counted when the body reference point of a mouse protruded at least 2 cm into the light compartment away from the door.

Rotarod

Motor function and motor learning was evaluated using an accelerating rotarod (Roto-rod series 8, IITC Life Science, Woodland Hills, CA, USA). On day one, mice received two habituation trials of 120 s (acceleration from 0 to 20 rpm in 120 s) followed by 3 training trials (acceleration from 0 to 40 rpm in 180 s). On day 2, mice received 5 additional training trials. Previous observations indicated that mice never reached the maximum rpm programmed during habituation and training sessions. The maximum rpm reached in each trial was the dependent measure.

Barnes maze

The Barnes maze consists of a circular grey platform (Ø 120 cm) elevated 100 cm above the floor with 24 holes (Ø 4.5 cm) spaced at equal distance 5 cm away from the edge of the platform. One hole was designated as escape hole, and equipped with a cylindrical entrance (4.5 cm diameter x 5 cm depth) mounted underneath the maze providing access to an escape box (15.3 cm x 6.4 cm x 6.1 cm, L x W x H) containing a metal stairway for easy access that was not visible unless mice approached the hole directly. Other holes were equipped identical cylindrical entrances, but without escape box. Visual extra-maze cues (50 x 50 cm) composed of black and white patterns were mounted on the walls ~70 cm away from the maze. Three fans surrounding the maze (60 cm away from the maze spaced ~120° apart) and produced a variable airflow across the entire maze by slow 90° horizontal movement, serving as an aversive environment. Several fluorescent tube lights mounted at the ceiling provided bright illumination (1000 lx). A speaker mounted to the ceiling provided background sound.

Protocol: Mice received training sessions twice a day, typically in the morning and afternoon for 5 or 6 days. Mice were introduced in an opaque cylinder (Ø 10 cm diameter, 25 cm H) placed in the center of the maze, after which the experimenter left the room and closed the door. The cylinder was pulled upwards 30 s later, and mice could explore the maze to locate the escape hole. If the latency to enter the escape hole exceeded 300 s, mice were gently guided toward the escape hole. During the first 2 habituation sessions (H1 and H2), the escape box contained cage bedding from the mouse's own home cage, and once in the escape box mice were left in there for 60 s before returning it to the home cage. After each mouse, the platform and escape box were thoroughly cleaned with 70 % ethanol. The platform was rotated by 90° after each trial to avoid the use of any remaining odors cue. The first probe trial (P1) was performed after two habituation trials and seven training trails (H1, H2 and T1-T7). During the 120-s probe trial 1 the

escape hole was identical to all 23 other holes. In order to check reversal learning a target hole was re-located to the diametrically opposite position after training session and animals were trained for 2 to 3 more days. The second probe trial (P2) lasted 300 s and was performed after third reversal trial (R1-R3). The third probe trial (P3) lasted 5 minutes and was performed after three additional reversal trials (R4-R6). Long-term memory was determined by testing animals in the maze one week after the training session.

Data analysis: The path travelled by a mouse was video tracked by an overhead camera and analyzed using Viewer 2 software with Barnes maze plugin (Viewer 2, Biobserve GmbH, Bonn, Germany). The distance and latency to reach the target location were recorded, as well as hole visits defined by crossing of the head reference point into a hole zone drawn 1 cm around each hole. Multiple consecutive hole visits were counted as single hole visit, and the number of single hole visits to holes other that the target hole were counted as errors. To detect a spatial search strategy, the Barnes maze was divided into octants, and all 24 holes were assigned to one of 5 zone categories based on the distance away from the target hole (i.e. target, 1^{st}, 2^{nd}, 3^{d} and 4th zone). The proportion of hole visits to a specific zone was calculated as follows: (total number of visits to a hole in a given zone) / [(total number of hole visits)*(number of zones in the category)]. This proportion was calculated for all zones, both during training as well as probe trials, and analyzed to detect a spatial search strategy.

Modified Barnes maze

The modified Barnes maze was performed as previously described (*86*), using a large round platform (Ø 122 cm) with 44 holes pseudorandomly arranged in such a way that no serial exploration is possible. Mice were trained to target the target hole using visual extra maze cues

placed on the wall (as for the classical Barnes maze). All holes contained white double-floored cup underneath (Ø 5 cm).

The platform can be divided in 4 quadrants, each containing 2, 3 and 6 holes in the inner, middle and outer ring respectively. The target hole was always placed in the middle ring. To prevent odor cues, the target location was varied between each animals and the platform was clean with 70% ethanol solution and rotated between trials. All the cups were removed and washed under running water once a day. A dark cylinder (Ø 12 cm, 6.8 cm H) served as transport container from the home cage to the Platform, to minimize the handling stress.

A video camera placed above the center of the platform, monitored the performance of mice during trials. Images were recorded and analyzed by a computer located in an adjacent room by using Viewer software (Viewer 2, Biobserve GmbH, Bonn, Germany). The experimenter was not present in the experimental room during trials but observed the experiments on the computer screen. The distance and latency to reach the target location were recorded and tracked by the software.

5-choice serial reaction time test

At 8 to 9 weeks of age, mice were food-restricted to gradually decrease their body weight to 90–95% of their initial body weight before daily training in operant cages commenced (5 days each week). Water was available ad libitum throughout the experiment. Mice were trained to perform the 5-choice serial reaction time task (5-CSRTT) on an individually paced schedule, as described previously (*85, 87*). During the first week, mice underwent 1 habituation and 4 magazine training sessions. In the next week, mice were trained to perform an instrumental response (nose poke) into the stimulus holes to earn a food reward, and only commenced to 5-CSRTT training when

they earned at least 50 rewards within one session. During 5-CSRTT training a trial started with a response of the subject into the illuminated magazine, which switched off the magazine light and after an ITI of 5 s a stimulus in 1 of the 5 stimulus holes was presented for a limited duration (stimulus duration). A response in the correct stimulus hole within the limited hold time of 4 s after termination of the stimulus switched on the magazine light and delivered a food pellet. Both an incorrect response into a non-illuminated stimulus hole and an omission of a correct response resulted in a time-out period, during which all stimulus lights and the house light were turned off. When the time-out period ended, both the house light and the magazine light were switched on, and the subject could start the next trial. An impulsive response into a non-illuminated stimulus hole during the delay period also resulted in a time-out period, but a subsequent response into the illuminated magazine restarted the same trial. The percentage of omission errors was defined as [100 x (omissions) / (omissions + number of correct and incorrect responses)]. Response accuracy was defined as [100 x (number of correct responses) / (number of correct and incorrect responses)]. Impulsivity in terms of the percentage impulsive responses was defined as [100 x (number of impulsive responses) / (number of omissions + correct + incorrect responses)]. In the first 5-CSRTT session, the stimulus duration was set at 16 s, which was decreased in subsequent sessions to 8, 4, 2, 1.5 and 1 s as soon as the subject reached criterion performance (omissions < 30%, response accuracy > 60%, started trials > 50) or after 10 sessions. Intra-individual variability in correct response latencies (response variability in short) was defined by the standard deviation of the correct response latencies. The total number of sessions required to reach the stimulus duration of 1 s was used as measure of required training sessions. Dependent measures were calculated from the 6th until the 10th session at stimulus duration of 1 s, and the average of these sessions was used as standard 5-CSRTT performance. In the week following the

10th session, the ITI was programmed to vary (5, 7.5 and 12.5 s), with each interval occurring an equal number of times within session. Strains that completed fewer than 50 trials on average in combination with long magazine latencies (>4 s), together indicative of reduced motivation, were excluded. Individual mice were excluded from analyses if they initiated fewer than 30 trials on average, had long magazine latencies, or made no correct or incorrect responses during two or more standard sessions.

Three-Chamber Test

The test took place in a test arena made of clear Perspex (20 cm × 40.5 cm × 22 cm, L x W x H) that was equally divided into three chambers, as described previously (*88*). The chambers were connected through two small openings (5 × 10 cm) in both dividing walls. In the outer chambers, a wire cup (pencil holder) was placed up-side-down, with a weight on top, to prevent mice from climbing onto the cup. Prior to each test, the apparatus was thoroughly cleaned with 70% alcohol. During the first phase of the test, the subject mouse was placed in the inner chamber for 10 min, with both openings to the outer chambers blocked. During the next 10 min, doors to the outer chambers were open and the outer chamber could be explored. To prepare for the third phase of the test, the mouse was confined in the middle chamber, while the outer chambers were equipped with a wire cup placed up-side-down, with a weight on top to prevent mice from climbing it. Under one of the two wire cups a stimulus mouse was placed (docile strain, similar weight and age as the subject mouse), that had been habituated to this procedure during previous days. During all three phases, the behavior of a subject mouse was monitored with one overhead camera and video tracking software that was following the head of the mouse (Viewer 2, Biobserve GmbH, Bonn, Germany). The time spent in, and frequency of entering the three

compartments (mouse, middle and object compartment), as well as zones immediately around the wire cups (mouse zone and object zone) were determined.

Morris Water Maze

Spatial memory was tested in a Morris water maze setup. Before testing, mice were handled for at least 5 days, until they did not try to jump of or walk from the experimenter's hand. A circular pool (Ø 125 cm) was filled with water (30 cm below the rim) which was painted white with non-toxic paint and kept at a temperature of 25°C. An escape platform (Ø 9 cm) was placed at 30 cm from the edge of the pool submerged 1 cm below the water surface. Visual cues were located around the pool at a distance of ~1.5 m. During testing lights were dimmed and covered with white sheets and mice were video-tracked using ViewerII (Viewer 2, Biobserve GmbH, Bonn, Germany). Mice were trained for 5 consecutive days, 2 sessions of 2 trials per day with a 1-3 min inter-session interval. In each trial, mice were first placed on the platform for 30 s, and then placed in the water at a random start position and allowed a maximum of 60 s to find the platform. Mice that were unable to find the platform within 60 s were placed back on the platform by hand. Within each 2-trial session, after 30 s on the platform mice were tested again. On day 5 or 6 a probe trial was performed with the platform removed. Mice were placed in the pool opposite from the platform location and allowed to swim for 60 s. During training trials, the latency, distance and speed to reach the platform were measured; in the probe trial, the time spent and distance traveled in each quadrant of the pool were measured, as well as the number of platform-zone crossings.

Statistical statement

With this statement we want to point to the several potential uncertainties based on the statistical analysis that we performed in the present paper.

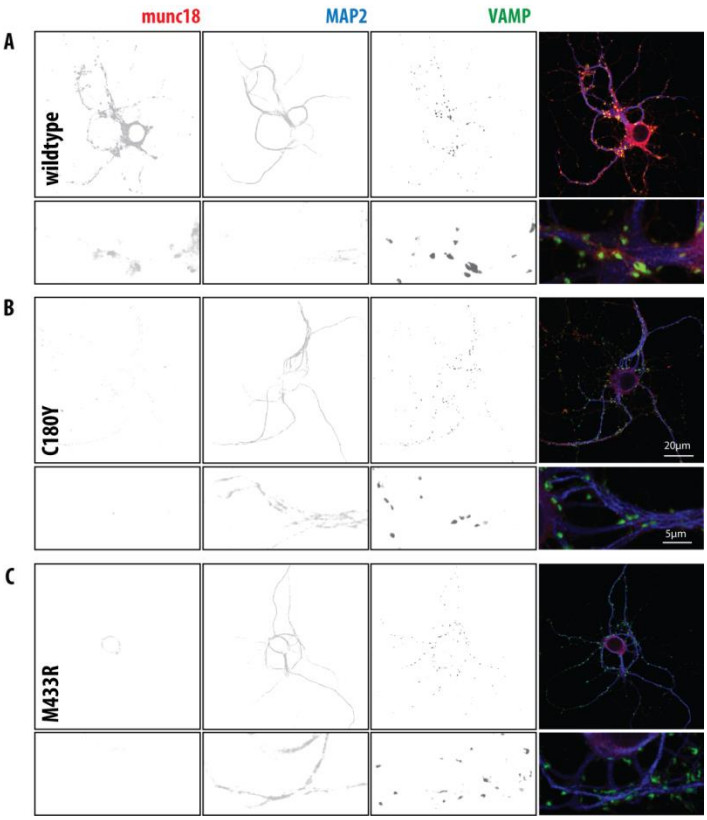
First, we want to consider analysis of data from expression of human disease variants in null mutant mouse neurons (Figure 1). We are aware that unequal sample size in this experiment could affect the homogeneity of variance assumption for ANOVA results. There is no strong recommendation how to deal with this issue; however, there are suggestions of performing nonparametric tests, such as Kruskal-Wallis test (KWT) instead. We performed KWT and we did not find differences in the conclusions compared to ANOVA results; except for the mEPSC frequency, where KWT did not detect any differences for the human disease variants groups compared to WT group. Finally, we decided to present results from ANOVA.

In addition to previous commentaries, we would like to add that the strength of the conclusion for group G544D is limited by small sample size (n = 2-5).

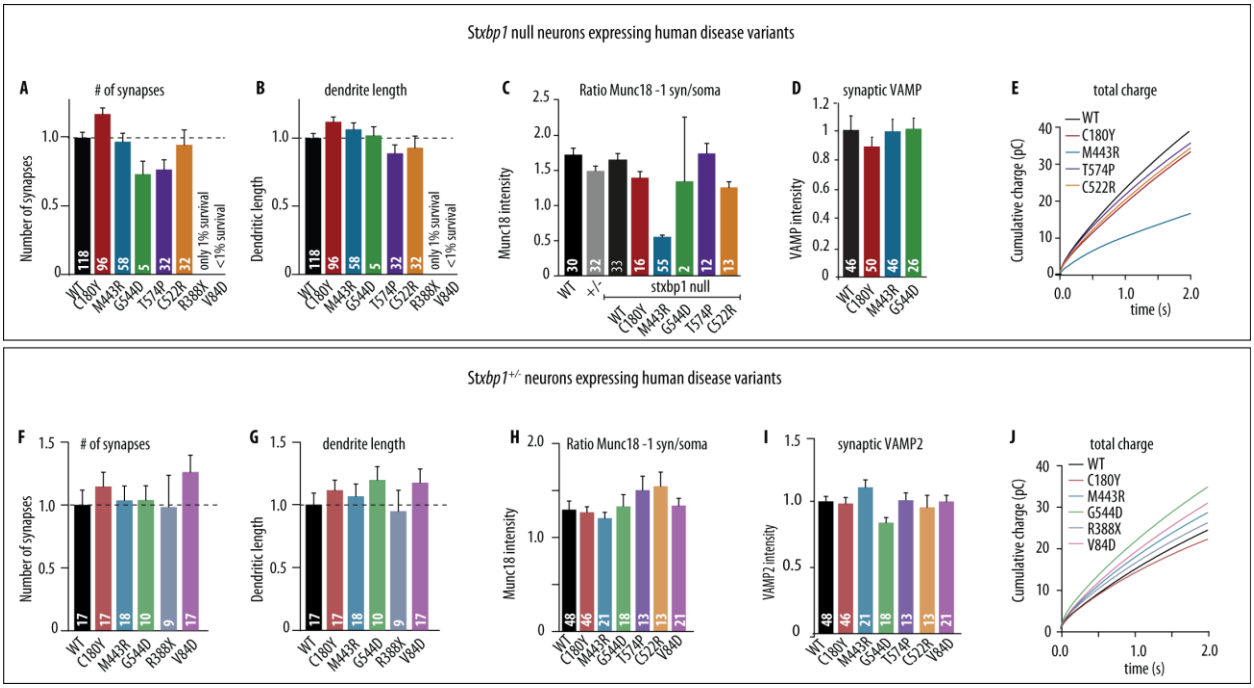
Second, we want to consider the analysis of data from the CognitionWall DL/RL task (Figure 10). It has been previously published that the fraction of mice that reached 80% performance criterion is the parameter studied to assess learning in this task (*33*). Differences in the performance has been assessed using the log-rank test for differences between two or more Kaplan-Meier curves. In the present study, we used similar method to assess genotype differences for conditional and congenic BL6 mice (Log rank test on Kaplan Meier curves). However, we performed additionally the two-way ANOVA to assess the effect of the genetic background on the number of entries made to reach 80% performance criterion. This analysis revealed that there were no significant differences between congenic BL6 and conditional null mice ($F(1,40) = 0.170$, p = n.s), while there was a significant effect of genotype ($F(1,40) = 5.668$, $p = 0.022$) and trend for a significant genotype and genetic background interaction ($F(1,40) =$

3.144, p =0.084). Moreover, in accordance with conclusions from log rank test on Kaplan Meier curves, post hoc test revealed significant genotype effect for congenic BL6, but not for conditional mice. In our opinion the results from the two-way ANOVA were hampered by small but similar trend of differences between *Stxbp1*$^{cre/+}$ mice and their controls, and congenic BL6 mice.

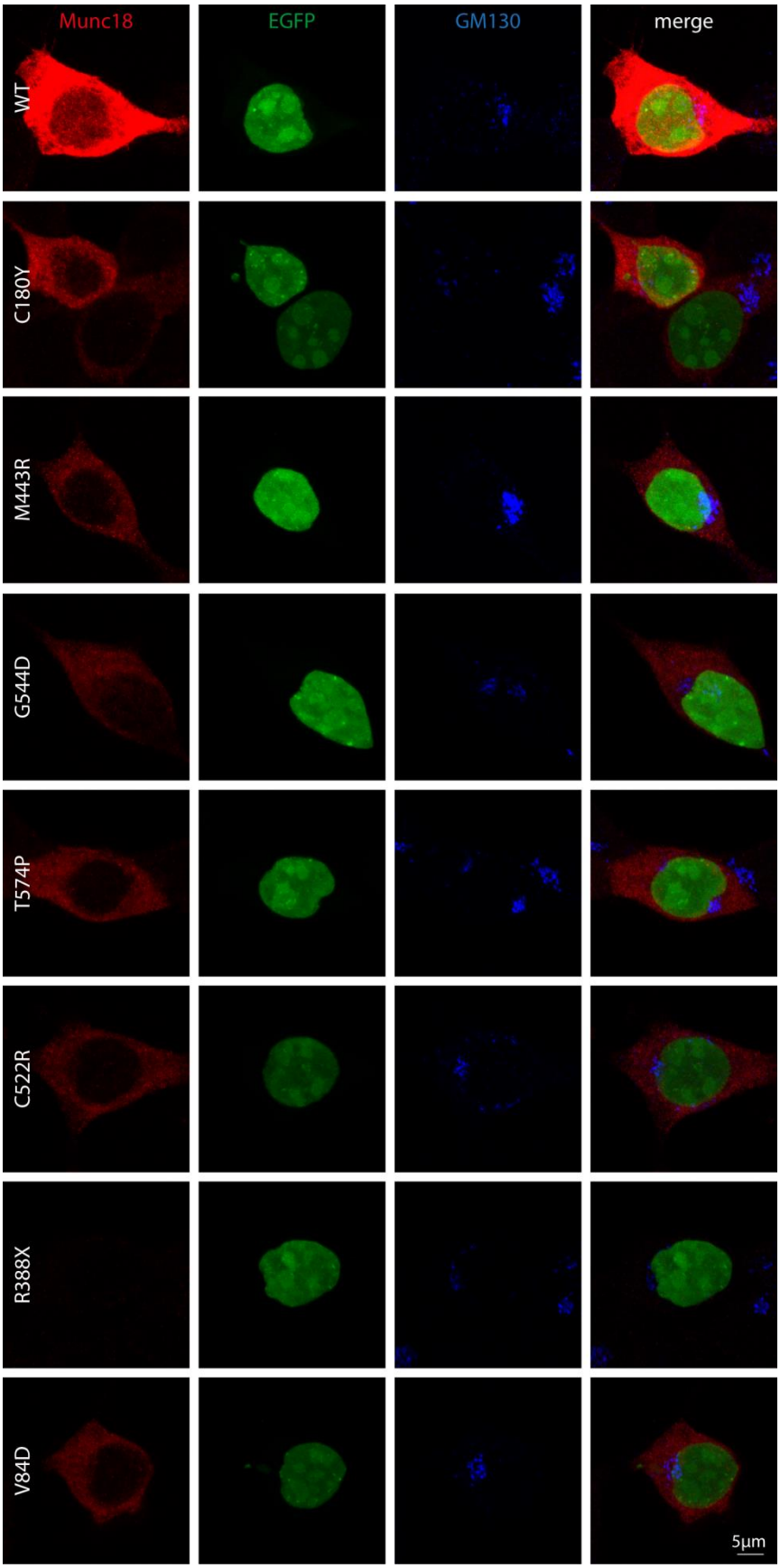
Supplementary Figures



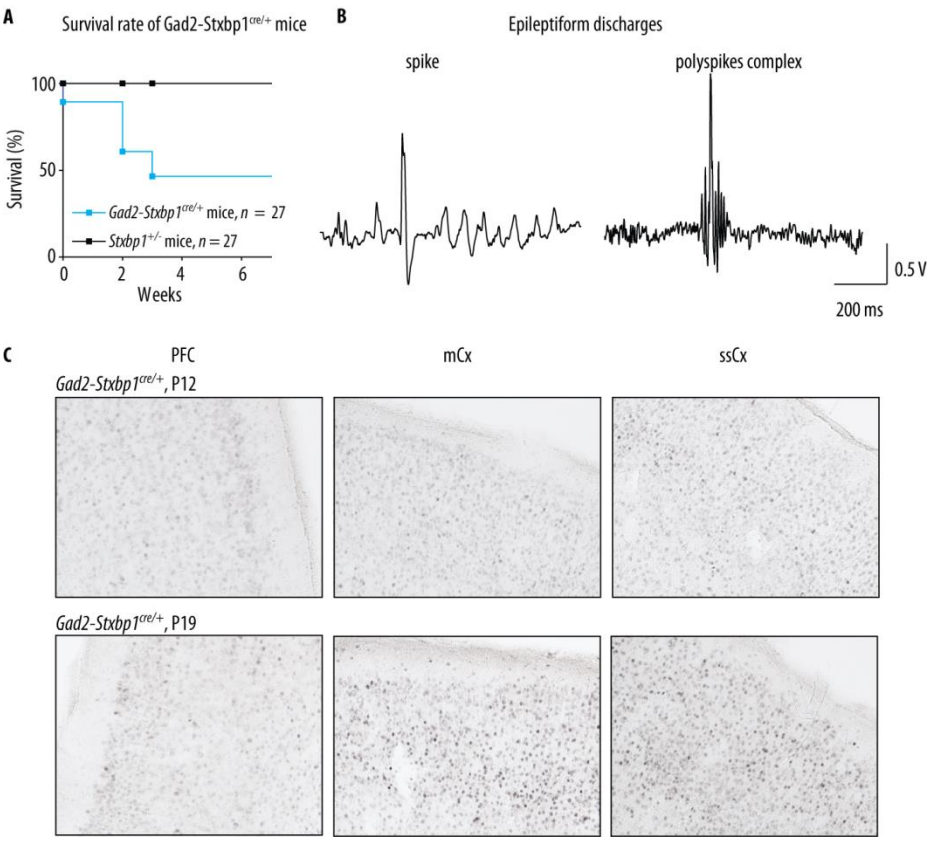
Supplementary Fig. 1: Staining of dissociated cortical *Stxbp1* null neurons for Munc18-1, dendritic marker MAP2 and synaptic marker synaptobrevin (VAMP). Examples represent *Stxbp1* null neurons expressing (A) wild type Munc18-1,(B) C180Y or (C) M433R human disease variants. Panels represent single channels for Munc18, MAP2 and VAMP staining and merged picture of these three markers: munc18-1 (red), MAP2 (blue) and VAMP (green).



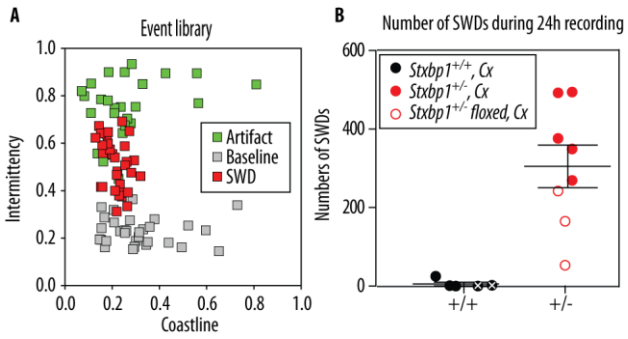
Supplementary Fig. 2. Morphological and electrophysiological characteristics of *Stxbp1* null and *Stxbp1*$^{+/-}$ neurons expressing one of the human disease variants. (A-E) Immunostaining and cumulative charge of dissociated hippocampal *Stxbp1* null neurons expressing human disease variants. (F-J) Immunostaining and cumulative charge of dissociated hippocampal *Stxbp1*$^{+/-}$ neurons expressing human disease variants (A/F) Number of synapses detected using synapsin marker, normalized to the wild type level. (B/G) Dendritic length normalized to the WT level. (C/H) Ratio Munc18-1 syn/soma: relative intensity of Munc18-1 level in synapses compared to soma. (D/I) Relative VAMP intensity in synapses. (E/J) Total charge represented as the cumulative plot of EPSC charge during a 40 Hz train (100 APs).


Munc18
EGFP
GM130
merge
WT
C180Y
M443R
G544D
T574P
C522R
R388X
V84D
5µm

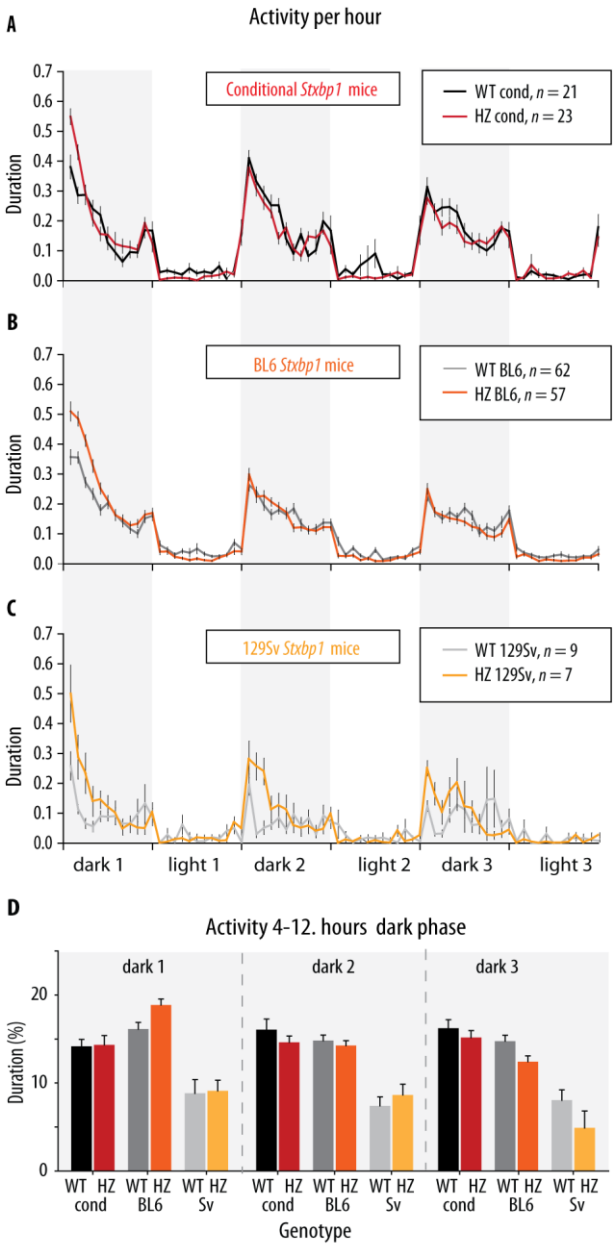
Supplementary Fig. 3. Immunostaining of HEK cells infected with lenti virus containing WT or 7 disease human variants of Munc18-1: C180Y, M443R, C544D, T574P, R388X and V84D. Pictures show lower level of Munc18-1 (red) in cells expressing disease variants while expressing approximately same level of EGFP (green). Staining with Golgi marker (GM130, blue) shows there was no retention of Munc18-1 protein in the Golgi complex.



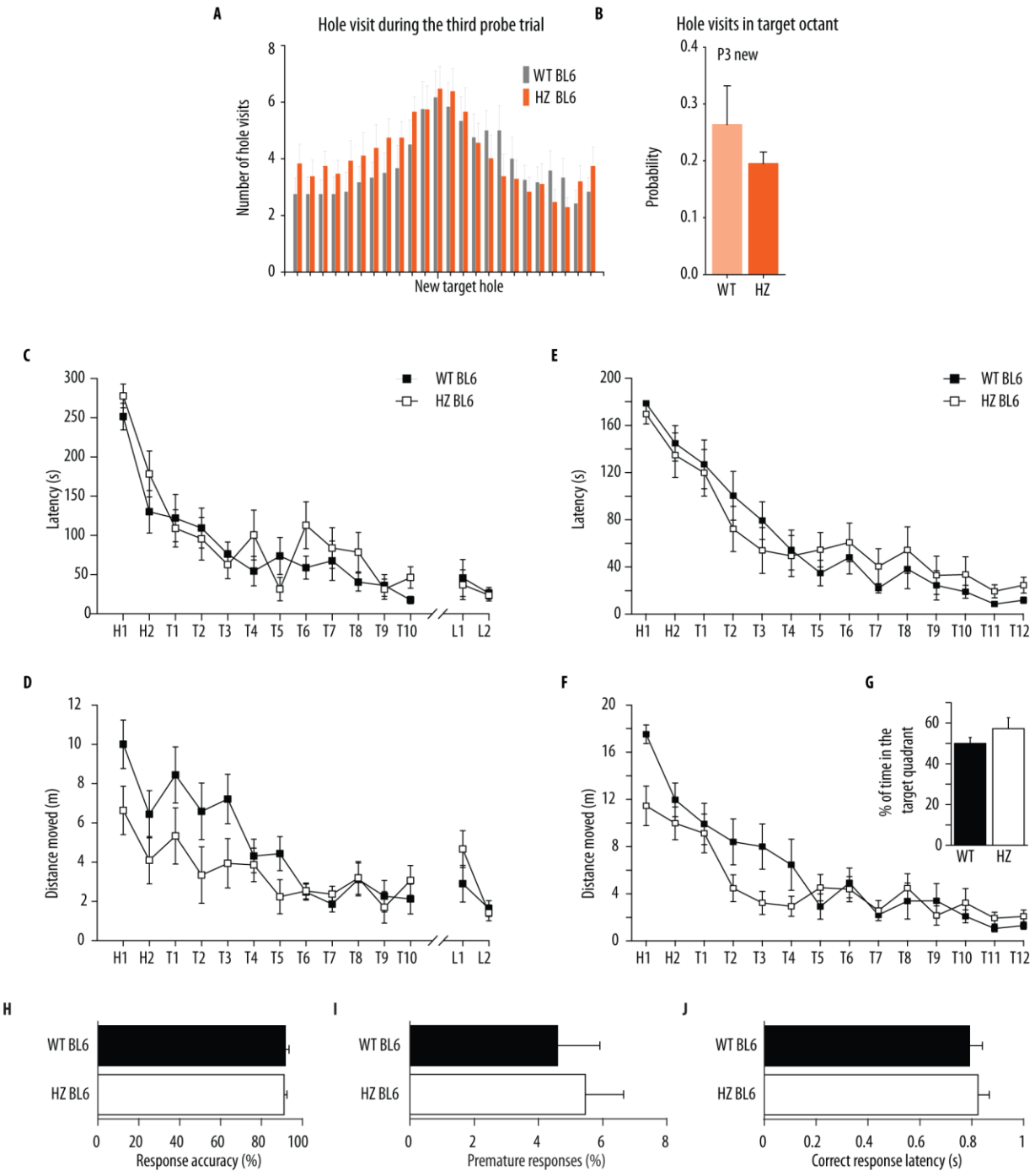
Supplementary Fig. 4. Survival, epileptiform activity and c-Fos expression in Gad2-*Stxbp1*$^{cre/+}$mice. (A) Kaplan-Meier survival plot for *Gad2-Stxbp1*$^{cre/+}$ mice shows decreased survival rate in the first postnatal weeks for Gad2-*Stxbp1*$^{cre/+}$ mice. (B) ECoG recording from Gad2-*Stxbp1*$^{cre/+}$ mice (around 12 weeks of age) shows epileptiform activity represented with spike during the sleep and polyspikes complex during awake state. (C) Increased c-Fos activity was detected in the prefrontal cortex (PFC), motor cortex (mCx) and somatosensory cortex (ssCx) of Gad2-*Stxbp1*$^{cre/+}$ mice at postnatal days 12 and 19.



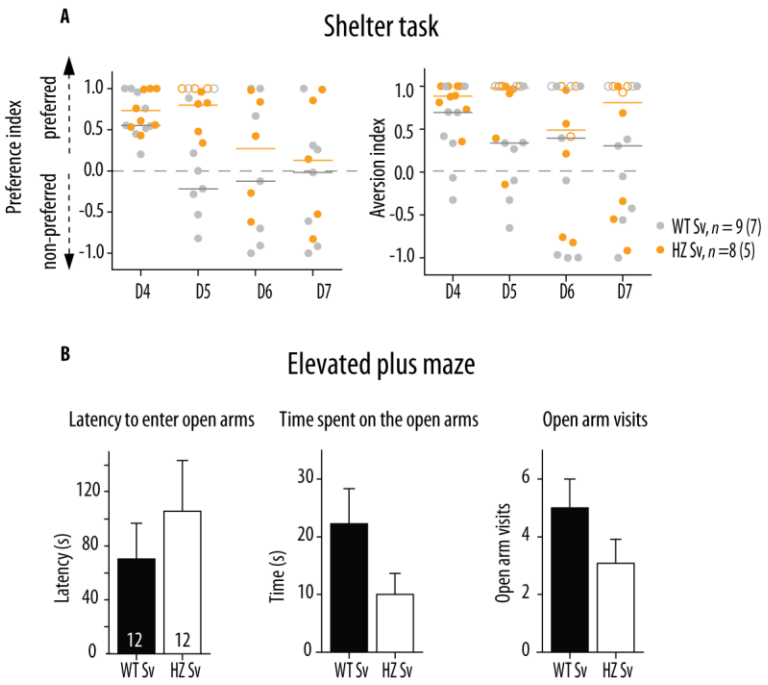
Supplementary Fig. 5. Automatic spike wave discharges (SWDs) detection during 24h of ECoG recording. (A) Library representation as a function of two categories (Intermittency and Coastline). Three different types of events were detected: named artifact, baseline and spike wave discharges (SWD). (B) Number of SWDs detected during 24 h recording in 5 control mice (mice with white crossed line were not littermates to the mutant mice), 5 congenic BL6 *Stxbp1*$^{+/-}$ and 3 *Stxbp1*$^{cre/+}$ mice.



Supplementary Fig. 6. Activity duration in the PhenoTyper for *Stxbp1* mice. (A-C) Proportion of activity duration in 1-h bins across first 3 days in the PhenoTyper for conditional *Stxbp1 mice* (A), congenic BL6 *Stxbp1* mice (B) and reverse 129Sv *Stxbp1* mice (C) and their respective controls. (D) Proportion of activity duration from 4 to 12 h of the dark phases was similar between genotypes. The number of animals assigned in the graphs.


A
Hole visit during the third probe trial
WT BL6
HZ BL6
Number of hole visits
New target hole
B
Hole visits in target octant
P3 new
Probability
WT
HZ
C
Latency (s)
H1 H2 T1 T2 T3 T4 T5 T6 T7 T8 T9 T10 L1 L2
D
Distance moved (m)
E
Latency (s)
H1 H2 T1 T2 T3 T4 T5 T6 T7 T8 T9 T10 T11 T12
F
Distance moved (m)
G
% of time in the target quadrant
H
Response accuracy (%)
I
Premature responses (%)
J
Correct response latency (s)

Supplementary Fig. 7. Performances of congenic BL6 *Stxbp1*$^{+/-}$ mice in the Barnes maze and 5-choice serial reaction time test. (A) Distribution of hole visits during the third probe trial (P3) for congenic BL6 *Stxbp1*$^{+/-}$ mice (HZ BL6) and their controls (WT BL6). (B) Probability of hole visits in the new target octant during the third probe trial was similar for HZ BL6 and their controls.(C-D) Latency and distance to find the escape box of the Barnes maze with 24 peripheral holes. (E-F) Latency and distance to find the escape box of the modified Barnes maze with 44 holes in 3 circles shown across trials in HZ BL6 and WT BL6 mice. (G) Time spent in the target quadrant during the probe trial of the modified Barnes maze. (H-J) Percentage of correct responses, percentage of premature (impulsive) responses and latency for correct responses in the 5-choice serial reaction time task. There was no significant difference between genotypes in any measure depicted here. H1-2: habituation trials; T1-12: training trials with escape hole, L1-2: Long-term memory tests.



Supplementary Fig. 8. Behavior of reverse 129Sv *Stxbp1*$^{+/-}$ mice in the Shelter task and elevated plus maze test. (A) A high percentage (~40%) of *Stxbp1*$^{+/-}$ mice had to be excluded from analysis because they failed to reach the criterion of not visiting the non-preferred entrance during dark phase 5: preference index = 1 (*27*). The remaining mice showed highly variable behavior during D5, D6 and D7. (B) Both reverse 129Sv *Stxbp1*$^{+/-}$ and wild type mice showed profound anxiety-like behavior on the EPM in comparison to conditional and congenic B6 mice (see Fig 12). Despite this floor effect, reverse 129Sv *Stxbp1*$^{+/-}$ mice showed a tendency of increased anxiety-like behavior in the EPM represented by increased latency to visit open arms, less time spent on the open arms and less number of visits to the open arms compared with controls.

Supplementary Tables

Supplementary Table 1. Tests and experimental batches used in the present study. Number of outliers per test is indicated between brackets.

Experiment	**C57BL6**		**Conditional mice**		**129Sv**		**Comments/duration/sequence**
	WT	**HZ**	**WT**	**HZ**	**WT**	**HZ**	
Body weight	13[1]	13[1]	12[1]	12[1]	12[1]	12[1]	age: 7-8 weeks
Automated home cage	62[1+3-5]	57[1+3-5]	21[1+2]	23[1+2]	9[1]	7[1]	7 days protocol no human interference
CognitionWall test	12[6]	12[6]	10(2)[2]	12[2]	-	-	4 nights automated test for initial discrimination learning and reversal learning
Shelter task	62[1+3-5]	57[1+3-5]	11	12	9	8	day 5 and day6 aversive learning, day 7 assessment
Novelty induced hypophagia	13[1]	12(1)[1]	10(2)[1]	11(1)[1]	12[1]	12[1]	3 days habituation prior test, 10min max
Grip strength	13[1]	13[1]	11(1)[1]	11(1)[1]	12[1]	12[1]	5 session front paws
Elevated plus maze	13[1]	13[1]	10(2)[1]	12[1]	12[1]	12[1]	5 min
Open field	12(1)[1]	12(1)[1]	12[1]	12[1]	12[1]	12[1]	10 min
Dark-light box	12(1)[1]	12(1)[1]	12[1]	12[1]	12[1]	12[1]	10 min
Rotarod	13[1]	13[1]	12[1]	12[1]	-	-	10 trials over 2 days
Barnes maze	13[1] + 12[6]	13[1] + 11[6]	12[1]	12[1]	-	-	2 trials per day for training (+probe1: 2 min) + 2 trials per day reversal(+probe2: 5 min)
Passive avoidance	12[3]	12[3]	-	-	-	-	Training, retention & extinction tests
Modified Barnes Maze	12[4]	11[4]	-	-	-	-	performed at reversed day-night cycle
5-Choice SRTT	12[5]	12[5]	-	-	-	-	food restricted to 90-95% of initial weight
Morris Water maze	-	-	-	-	11[1]	12[1]	4 trials per day for 5 day + probe trial (6th day)
Three chamber test	12[6]	12[6]	11[2]	12[2]	-	-	4 phase: habituation to center chamber, habituation to 3 chamber, test for sociability and social novelty
Video monitoring	6[7]	6[7]	6[2]	6[2]	12[1]	6[1]	recording of the individually caged mice, several hours
ECoG + EEG	4+2[8]	4+2[8]	3[4]				2WT and 2 HZ C57BL/6J mice were used for intrahippocampal recordings
ECoG LEV		5[9]					Treatment with levetiracetam (LEV) 50mg/kg, *i.p.*, once daily for 5 days

[1, 2, 3, 4, 5, 6,7,8,9,] assigned batches of mice

Supplementary Table 2. Spontaneous home cage behavior of congenic BL6 *Stxbp1* mice. 115 parameters derived from X-Y coordinates recorded for 3 consecutive days without human interference. Alpha level was corrected by FDR to $p \leq 0.032$.

			Wild-type mice			Heterozygous mice			Statistics		
			Mean	SEM	N	Mean	SEM	N	DF	T-test	P-value
Spontaneous behavior (activity)	Activity duration	dark	6682.27	260.45	64	6112.78	293.01	59	118.03	1.45	0.149
	Mean activity duration	dark	24.76	0.54	63	23.06	0.47	57	117.93	2.3	**0.0234**
	Activity number	dark	286.73	11.17	64	281.41	12.86	59	104.74	0.59	0.5568
	Feeding zone duration	dark	8272.85	381.26	64	10622.25	521.01	59	111.29	-3.53	**0.0006**
	OnShelter zone duration	dark	1980.05	148.63	64	1098.71	152.77	59	118.59	3.15	**0.002**
	OnShelter zone number	dark	93.07	7.22	64	55.31	10.85	59	117.82	4.2	**0.0001**
	Spout zone duration	dark	1579.79	84.53	64	2342.05	342.08	59	105.55	-3.07	**0.0027**
	Activity duration	light	1359.18	107.09	64	805.43	102.23	59	96.81	3.59	**0.0005**
	Mean activity duration	light	22.6	1.98	62	15.61	0.88	54	96.1	4.8	**<0.0001**
	Activity number	light	65.62	4.2	64	50.23	4.76	59	101.5	2.69	**0.0083**
	Feeding zone duration	light	2352.73	143.82	64	2592.55	279.17	59	87.22	-0.76	0.4471
	OnShelter zone duration	light	245.03	31.25	64	129.57	36.18	59	103.96	4.54	**<0.0001**
	OnShelter zone number	light	14.35	1.67	64	6.58	1.17	59	117.6	5.17	**<0.0001**
	Spout zone duration	light	321.99	27.99	64	852.37	672.92	59	90.28	3.2	**0.0019**
Spontaneous behavior (dark-light ratio)	Activity duration	dark-light index	0.83	0.01	63	0.89	0.01	57	117.58	-3.72	**0.0003**
	Mean activity duration	dark-light index	0.54	0.01	62	0.62	0.01	54	105.01	-4.24	**<0.0001**
	Activity number	dark-light index	0.81	0.01	63	0.85	0.01	57	116.35	-2.78	**0.0064**
	Mean short arrest duration	dark-light index	0.5	0	63	0.49	0	56	99.75	2.09	0.0387
	Long arrest duration	darklight index	0.78	0.01	64	0.81	0.02	58	114.2	-1.81	0.0723
	Mean long arrest duration	dark-light index	0.45	0.01	62	0.43	0.01	54	99.81	1.31	0.1946
	Long arrest number	dark-light index	0.81	0.01	63	0.85	0.01	57	113.07	-2.47	**0.0152**
	Feeding zone duration	dark-light index	0.78	0.01	64	0.81	0.01	59	108.77	-1.72	0.0882

	Mean short shelter visit duration	dark-light index	0.49	0.01	43	0.48	0.02	21	41.93	0.81	0.4238
	Long shelter visit duration	dark-light index	0.35	0.01	62	0.33	0.01	57	112.44	1.61	0.111
	Long shelter visit number	dark-light index	0.54	0.01	62	0.55	0.02	56	104.38	-0.15	0.8813
	Mean long movement distance	dark-light index	0.51	0	62	0.51	0	54	99.93	-0.43	0.666
	Mean short movement distance	dark-light index	0.51	0	63	0.5	0	55	83.1	1.67	0.0987
	OnShelter zone duration	dark-light index	0.89	0.01	62	0.91	0.02	59	97.3	-0.68	0.4959
	Spout zone duration	dark-light index	0.83	0.01	64	0.9	0.01	59	115.57	-3.81	**0.0002**
Spontaneous behavior (habituation)	Activity duration	habituation ratio dark	1.79	0.03	64	1.56	0.03	59	121	5.04	**<0.0001**
	Mean activity duration	habituation ratio dark	1.85	0.02	63	1.71	0.02	57	116.78	4.31	**<0.0001**
	Activity number	habituation ratio dark	1.93	0.03	64	1.8	0.03	59	119.21	2.97	0.0036
	Mean short arrest duration	habituation ratio dark	2.09	0.01	63	2.18	0.02	57	103.08	-4.52	**<0.0001**
	Long arrest duration	habituation ratio dark	2.13	0.04	64	2.21	0.05	59	108.02	-1.07	0.2868
	Mean long arrest duration	habituation ratio dark	2.12	0.03	63	2.31	0.05	57	101.11	-3.54	**0.0006**
	Long arrest number	habituation ratio dark	2	0.04	64	1.92	0.04	59	118.93	1.47	0.1434
	Feeding zone duration	habituation ratio dark	2.1	0.04	64	2.26	0.06	59	98.85	-2.16	**0.0335**
	Mean short shelter visit duration	habituation ratio dark	2.04	0.03	63	2.13	0.05	57	103.54	-1.51	0.1346
	Long shelter visit duration	habituation ratio dark	2.04	0.04	61	2.31	0.08	55	98.3	-3.09	**0.0026**
	Mean long movement distance	habituation ratio dark	2.01	0.01	63	2	0.01	57	100.19	0.51	0.6113

	Mean short movement distance	habituation ratio dark	1.98	0.01	63	1.95	0.01	57	101.8	3.41	**0.0009**
	OnShelter zone duration	habituation ratio dark	2.08	0.08	63	1.63	0.08	59	117.96	4.7	**<0.0001**
	Spout zone duration	habituation ratio dark	1.95	0.04	64	2.59	0.7	59	69.4	0.03	0.9735
	Activity duration	habituation ratio light	1.86	0.09	64	1.83	0.08	56	116.1	0.24	0.8143
	Mean activity duration	habituation ratio light	2.08	0.11	62	1.84	0.05	54	108.23	2.6	**0.0107**
	Activity number	habituation ratio light	1.8	0.04	64	1.97	0.07	57	101.01	-1.78	0.0783
	Mean short arrest duration	habituation ratio light	1.98	0.01	63	2.06	0.02	56	94.13	-3.32	**0.0013**
	Long arrest duration	habituation ratio light	2.28	0.29	64	2.61	0.17	58	115.95	-2.51	**0.0136**
	Mean long arrest duration	habituation ratio light	2.27	0.07	62	2.39	0.08	51	102.38	-1.21	0.2291
	Long arrest number	habituation ratio light	1.83	0.06	64	2.19	0.15	53	84.2	-2.44	**0.0168**
	Feeding zone duration	habituation ratio light	2	0.07	64	2.83	0.2	58	85.75	-4.44	**<0.0001**
	Mean short shelter visit duration	habituation ratio light	1.93	0.05	36	2.08	0.05	15	38.71	-2.33	**0.0252**
	Long shelter visit duration	habituation ratio light	2.01	0.02	63	1.98	0.02	58	118.18	0.79	0.4321
	Mean long movement distance	habituation ratio light	1.99	0.01	62	1.98	0.02	54	97.47	0.38	0.7069
	Mean short movement distance	habituation ratio light	2	0.01	63	1.99	0.01	55	88.59	0.55	0.583
	OnShelter zone duration	habituation ratio light	1.87	0.09	55	1.63	0.08	36	68.39	2.27	**0.0266**
	Spout zone duration	habituation ratio light	2.02	0.09	59	1.87	0.14	41	74.06	1.6	0.1144

Spontaneous behavior (kinematics)	Long movement fraction of total movement		0.45	0.01	64	0.46	0.01	59	120.08	-1.15	0.2538
	Long movement max. velocity		19.44	0.23	64	17.83	0.26	59	113.6	4.74	**<0.0001**
	Long arrest threshold		6.62	0.15	64	6.76	0.16	59	118.29	-0.61	0.5417
	Short arrest duration	dark	3934.75	147.95	64	3647.01	157.19	59	119.76	1.33	0.1851
	Mean short arrest duration	dark	2.13	0.02	63	2.17	0.03	57	111.19	-1.19	0.235
	Short arrest number	dark	3555.48	134.97	64	3230.56	172.2	59	103.65	0.98	0.3308
	Long arrest duration	dark	11254.96	703.4	64	13350.86	761.57	59	66.04	-0.21	0.8306
	Mean long arrest duration	dark	27.75	1.19	63	32.37	1.25	57	117.14	-2.95	**0.0039**
	Long arrest number	dark	413.68	15.67	64	415.34	17.86	59	104.36	0.44	0.6629
	Long movement distance	dark	19697.13	941.26	64	18455.6	1315.19	59	103.2	0.87	0.3858
	Mean long movement distance	dark	13.46	0.25	63	13.35	0.26	57	116.92	0.3	0.761
	Long movement number	dark	1584.49	67.39	64	1469.42	83.66	59	104.34	0.91	0.3674
	Short movement distance	dark	2541.6	135.31	64	2101.5	157.55	59	106.1	1.35	0.1789
	Mean short movement distance	dark	2.08	0.02	63	1.98	0.02	57	110.03	3.56	**0.0005**
	Short movement number	dark	2301.41	92.75	64	2092.25	113.45	59	104.04	0.97	0.3356
	Short arrest duration	light	797.16	54.54	64	512.32	56	59	98.3	3.26	**0.0015**
	Mean short arrest duration	light	2.12	0.03	63	2.21	0.03	56	108.35	-2.11	0.0373
	Short arrest number	light	738.17	55.47	64	446.87	55.28	59	99.74	3.54	**<0.0001**
	Long arrest duration	light	4098.14	879.26	64	4110.73	976.48	59	118.48	-0.01	0.9924
	Mean long arrest duration	light	39.06	5.15	62	47.71	3.65	54	111.22	-2.65	**0.0092**
	Long arrest number	light	94.83	5.89	64	79.1	9.63	59	97.14	2.57	**0.0117**
	Long movement distance	light	3710.35	322.91	64	2261.56	313.93	59	98.17	3.22	**0.0018**
	Mean long movement distance	light	13.18	0.27	62	13.03	0.29	54	112.13	0.37	0.7158

	Long movement number	light	305.26	24.17	64	194.65	25.9	59	99.48	3.59	**0.0005**
	Short movement distance	light	551.97	50.01	64	319.12	44.03	59	102.47	3.62	**0.0005**
	Mean short movement distance	light	2.06	0.02	63	1.98	0.02	55	115.02	2.38	**0.0188**
	Short movement number	light	502.2	36.05	64	317.67	38.57	59	99.86	3.4	**0.001**
	Long movement threshold		2.4	0.05	64	2.31	0.04	59	116.83	1.33	0.1868
Spontaneous behavior (sheltering)	Short shelter visit duration	dark	647	42.83	64	552.21	36.87	59	119.62	1.68	0.0961
	Mean short shelter visit duration	dark	9.76	0.48	63	9.28	0.51	57	113.6	0.87	0.3866
	Short shelter visit number	dark	79.68	5.13	64	81.32	7.21	59	106.25	0.72	0.4756
	Long shelter visit duration	dark	20132.72	770.39	64	19123.18	883.51	59	117.3	0.86	0.3909
	Long shelter visit number	dark	7.93	0.38	64	6.74	0.35	59	117.19	1.9	0.0594
	Mean long shelter visit duration		4968.57	149.11	63	6168.19	429.4	58	97.12	-3.09	**0.0026**
	Short shelter visit threshold		4.66	0.09	64	4.41	0.1	59	118.29	1.99	0.049
	Long shelter visit fraction of total visits		1.1	0.01	64	1.08	0.01	59	120.55	2.56	**0.0118**
	Long shelter visit threshold		9.96	0.08	64	9.93	0.1	59	115.55	0.22	0.8249
	Short shelter visit duration	light	171.69	14.67	64	95.14	13.96	59	103.5	3.88	**0.0002**
	Mean short shelter visit duration	light	9.73	0.54	43	9.69	0.65	21	46.13	-0.17	0.8633
	Short shelter visit number	light	22.31	2.16	64	11.67	1.77	59	116.19	4.34	**<0.0001**
	Long shelter visit duration	light	36214.98	885.65	64	37117.32	989.27	59	118.28	-0.68	0.4981
	Long shelter visit number	light	6.59	0.26	64	5.57	0.25	59	112.85	2.27	**0.0254**
Spontaneous behavior (pattern)	Activity change in anticipation of dark		0.02	0.01	64	0.02	0.01	59	110.3	0.11	0.9123
	Activity change in anticipation of light		0.03	0.01	64	0.03	0.01	59	119.89	0.41	0.6809
	Activity change in response to to dark		0.18	0.01	64	0.2	0.01	59	112.7	-1.02	0.3092

	Activity change in response to to light	-0.07	0.01	64	-0.07	0.01	59	120.31	0.26	0.7936
	Feeding zone change in anticipation dark	0.01	0.03	61	0.04	0.04	51	102.77	-0.5	0.617
	Feeding zone change in response to dark	-0.01	0.03	63	0.04	0.03	58	118.89	-1.53	0.1279
	Feeding zone change in anticipation light	-0.2	0.03	62	-0.2	0.04	52	102.25	0.1	0.9177
	Feeding zone change in response to light	-0.03	0.04	51	0.06	0.05	36	72.65	-1.34	0.1831
	OnShelter zone change in anticipation dark	0.01	0.01	61	0	0.01	51	108.72	0.86	0.3897
	OnShelter zone change in response to dark	0	0.01	63	-0.01	0.01	58	116.11	0.83	0.4108
	OnShelter zone change in anticipation light	0.08	0.01	62	0.04	0.01	52	110.96	3.31	**0.0013**
	OnShelter zone change in response to light	-0.04	0.01	51	-0.03	0.01	36	70.68	-0.5	0.6164
	Spout zone change in anticipation dark	0.01	0.01	61	0	0.01	51	100.12	0.06	0.949
	Spout zone change in response to dark	-0.01	0.01	63	-0.01	0.01	58	89.07	-0.21	0.835
	Spout zone change in anticipation light	0.04	0.01	62	0.05	0.02	52	69	-0.7	0.4877
	Spout zone change in response to light	0	0.02	51	-0.03	0.01	36	84.82	1.43	0.1562

Supplementary Table 3. Spontaneous home-cage behavior of conditional *Stxbp1*$^{cre/+}$ mice. 115 parameters derived from X-Y coordinates recorded for 3 consecutive days without human interference. Alpha level was corrected by FDR to $p \leq 0.036$

Conditional Stxbp1$^{cre/+}$			WT mice			HZ mice			Statistics		
			Mean	SEM	N	Mean	SEM	N	DF	T-test	P-value
Spontaneous behavior (activity)	Activity duration	dark	8189.84	467.76	11	8131.61	431.61	12	20.66	0.09	0.928
	Mean activity duration	dark	23.26	0.81	11	22.6	0.85	12	21	0.57	0.5741
	Activity number	dark	346.49	14.88	11	353.71	13.29	12	20.36	-0.37	0.7159
	Feeding zone duration	dark	9015.71	705.94	11	10658.15	581.77	12	18.3	-1.81	0.086
	OnShelter zone duration	dark	2417.38	184.78	11	592.21	156.87	12	13.13	5.71	**0.0001**
	OnShelter zone number	dark	145.39	14.68	11	26.99	6.47	12	15.38	7.23	**>0.0001**
	Spout zone duration	dark	1806.37	96.62	11	2120.32	155.75	12	19.75	-1.82	0.0837
	Activity duration	light	1064.49	149.36	11	546.78	217.43	12	14.28	1.85	0.0847
	Mean activity duration	light	19.33	1.08	11	14.22	2.36	12	13.77	1.89	0.0805
	Activity number	light	55.18	6.78	11	38.97	9.72	12	16.49	1.39	0.1843
	Feeding zone duration	light	1898.13	202.07	11	1886.63	221.46	12	20.96	0.04	0.9698
	OnShelter zone duration	light	192.29	35.47	11	12.52	14.13	12	12.21	3.62	**0.0034**
	OnShelter zone number	light	12.76	3.11	11	1.34	0.81	12	19.07	4.91	**0.0001**
	Spout zone duration	light	250.12	50.8	11	96.94	49.01	12	15.29	2.11	0.0514
Spontaneous behavior (Dark-Light ratio)	Activity duration	dark-light index	0.88	0.01	11	0.9	0.04	12	13.42	-0.57	0.5814
	Mean activity duration	dark-light index	0.55	0.02	11	0.61	0.04	12	14.48	-1.62	0.1267
	Activity number	dark-light index	0.86	0.01	11	0.88	0.02	12	17.12	-0.92	0.3702

	Mean short arrest duration	dark-light index	0.5	0	11	0.48	0.01	12	14.54	2.12	0.0518
	Long arrest duration	dark-light index	0.84	0.02	11	0.86	0.02	12	20.86	-0.72	0.4801
	Mean long arrest duration	dark-light index	0.47	0.02	11	0.38	0.04	11	14.3	1.82	0.0898
	Long arrest number	dark-light index	0.86	0.01	11	0.89	0.03	12	16.14	-1.29	0.2137
	Feeding zone duration	dark-light index	0.82	0.02	11	0.85	0.02	12	19.73	-0.84	0.4086
	Mean short shelter visit duration	dark-light index	0.51	0.01	10	0.46	0.01	5	8.58	2.88	**0.0191**
	Long shelter visit duration	dark-light index	0.3	0.01	11	0.27	0.01	12	20.92	1.3	0.2083
	Long shelter visit number	dark-light index	0.49	0.03	11	0.44	0.03	12	20.36	0.99	0.336
	Mean long movement distance	dark-light index	0.51	0.01	11	0.51	0.01	12	19.72	-0.33	0.7454
	Mean short movement distance	dark-light index	0.51	0	11	0.5	0	12	20.23	1.89	0.0728
	OnShelter zone duration	dark-light index	0.92	0.01	11	0.91	0.04	12	13.32	0.36	0.7271
	Spout zone duration	dark-light index	0.86	0.02	11	0.91	0.03	12	19.25	-1.37	0.1876
Spontaneous behavior (habituation)	Activity duration	habituation ratio dark	0.92	0.06	11	0.8	0.07	12	20.89	1.42	0.1702
	Mean activity duration	habituation ratio dark	0.88	0.04	11	0.78	0.06	12	17.61	1.33	0.2005
	Activity number	habituation ratio dark	1.05	0.04	11	1.02	0.03	12	20.36	0.47	0.6399
	Mean short arrest duration	habituation ratio dark	1.01	0.02	11	1.11	0.03	12	16.99	-2.91	**0.0097**
	Long arrest duration	habituation ratio dark	1.06	0.05	11	1.14	0.06	12	20.97	-1.02	0.32
	Mean long arrest duration	habituation ratio dark	1.06	0.05	11	1.12	0.05	12	20.99	-0.79	0.4364
	Long arrest number	habituation ratio dark	1	0.04	11	1.03	0.05	12	18.74	-0.37	0.7182

	Feeding zone duration	habituation ratio dark	1	0.05	11	1.06	0.05	12	20.14	-0.77	0.4495
	Mean short shelter visit duration	habituation ratio dark	1.01	0.04	11	1.11	0.07	12	19.22	-1.36	0.1899
	Long shelter visit duration	habituation ratio dark	0.93	0.05	11	1.01	0.06	12	20.78	-1.06	0.2996
	Mean long movement distance	habituation ratio dark	1.01	0.02	11	1	0.03	12	19.82	0.3	0.7654
	Mean short movement distance	habituation ratio dark	1	0.01	11	0.96	0.01	12	20.72	2.02	0.0566
	OnShelter zone duration	habituation ratio dark	1.19	0.1	11	0.81	0.19	12	15.25	1.73	0.1037
	Spout zone duration	habituation ratio dark	0.9	0.05	11	0.9	0.05	12	21	-0.02	0.9869
	Activity duration	habituation ratio light	0.76	0.07	11	1.64	0.38	12	11.69	-2.88	**0.0142**
	Mean activity duration	habituation ratio light	0.86	0.07	11	1.26	0.2	12	13.54	-2.14	0.0512
	Activity number	habituation ratio light	0.88	0.07	11	1.27	0.15	12	15.86	-2.5	**0.0236**
	Mean short arrest duration	habituation ratio light	0.98	0.02	11	1.15	0.06	12	15.53	-2.82	**0.0125**
	Long arrest duration	habituation ratio light	1	0.1	11	1.42	0.25	12	14.83	-1.71	0.1086
	Mean long arrest duration	habituation ratio light	1.04	0.1	11	0.99	0.17	12	13.44	0.28	0.7813
	Long arrest number	habituation ratio light	0.99	0.1	11	1.33	0.22	9	14.21	-1.55	0.142
	Feeding zone duration	habituation ratio light	0.93	0.09	11	1.33	0.28	10	12.98	-1.52	0.1525
	Mean short shelter visit duration	habituation ratio light	0.87	0.07	10	1.12	0.01	12	9.35	-3.46	**0.0068**
	Long shelter visit duration	habituation ratio light	1.01	0.01	11	0.97	0.01	3	20.68	2.57	**0.0179**
	Mean long movement distance	habituation ratio light	1.03	0.03	11	0.98	0.03	12	18.65	1.32	0.2023
	Mean short movement distance	habituation ratio light	1	0.02	11	1.01	0.02	12	20.43	-0.3	0.7678

	OnShelter zone duration	habituation ratio light	1.04	0.12	11	0.79	0.33	12	2.51	0.74	0.5239
	Spout zone duration	habituation ratio light	1.01	0.22	11	1.05	0.78	3	4.84	-0.06	0.9521
Spontaneous behavior (kinematics)	Long movement fraction of total movement		0.43	0.01	11	0.49	0.01	12	16.6	-3.48	**0.003**
	Long movement max. velocity		19.77	0.47	11	17.74	0.51	12	20.65	2.96	**0.0076**
	Long arrest threshold		5.41	0.13	11	6.08	0.2	12	19.58	-2.82	**0.0106**
	Short arrest duration	dark	4459.45	209.59	11	4404.26	166.62	12	19.54	0.21	0.8388
	Mean short arrest duration	dark	1.03	0.02	11	1.19	0.04	12	16.27	-4.09	**0.0008**
	Short arrest number	dark	4276.54	236.14	11	3677.02	222.25	12	20.97	1.9	0.0715
	Long arrest duration	dark	12162.84	658.92	11	14022.04	518.11	12	18.03	-2.22	0.0394
	Mean long arrest duration	dark	24.9	1.32	11	30.52	1.28	12	19.62	-3.07	**0.0061**
	Long arrest number	dark	488.68	28.16	11	459.62	11.07	12	13.54	1.01	0.3316
	Long movement distance	dark	26899.87	1889.68	11	24511.25	2121.93	12	20.53	0.87	0.3959
	Mean long movement distance	dark	14.25	0.61	11	13.1	0.58	12	20.99	1.39	0.18
	Long movement number	dark	1889.22	124.24	11	1872.09	126.82	12	20.99	0.1	0.9215
	Short movement distance	dark	3407.18	317.05	11	1983.54	138.48	12	19.07	4.84	**0.0001**
	Mean short movement distance	dark	1.24	0.06	11	0.94	0.02	12	15.07	5.32	**0.0001**
	Short movement number	dark	2749.42	166.66	11	2115.4	114.9	12	20.51	3.31	**0.0034**
	Short arrest duration	light	616.7	77.23	11	332.67	90.92	12	15.89	2.3	**0.0356**

	Mean short arrest duration	light	1.03	0.02	11	1.3	0.06	12	16.21	-4.55	**0.0003**
	Short arrest number	light	598.3	78.3	11	257.84	77.26	12	15.56	2.91	**0.0105**
	Long arrest duration	light	2327.66	212.34	11	2359.63	310	12	19.12	-0.09	0.9331
	Mean long arrest duration	light	28.48	1.96	11	51.87	11.62	12	12.09	-2.8	**0.016**
	Long arrest number	light	78.68	7.59	11	40.3	12.81	12	13.45	2.3	0.0377
	Long movement distance	light	3191.49	503.13	11	1349.49	393.83	12	17.33	2.92	**0.0094**
	Mean long movement distance	light	13.75	0.58	11	12.46	0.43	12	19.73	1.85	0.0791
	Long movement number	light	232.32	31.94	11	108.79	33.32	12	15.8	2.56	**0.0211**
	Short movement distance	light	496.87	85.19	11	168	50.28	12	17.91	3.55	**0.0023**
	Mean short movement distance	light	1.2	0.06	11	0.94	0.02	12	13.77	4.19	**0.0009**
	Short movement number	light	417.36	53.47	11	178.08	53.21	12	15.43	2.96	**0.0095**
	Long movement threshold		1.7	0.11	11	1.25	0.05	12	16.95	4.01	**0.0009**
Spontaneous behavior (sheltering)	Short shelter visit duration	dark	871.85	125.67	11	1000.64	131.9	12	21	-0.71	0.4874
	Mean short shelter visit duration	dark	7.31	0.58	11	7.62	0.99	12	18.2	-0.29	0.7768
	Short shelter visit number	dark	110.99	9.33	11	121.77	22.8	12	15.56	-0.49	0.6325
	Long shelter visit duration	dark	16158.49	891.16	11	14249.64	724.8	12	19.75	1.66	0.1124
	Long shelter visit number	dark	5.41	0.55	11	4.21	0.48	12	20.98	1.73	0.0988
	Mean long shelter visit duration		5164.85	244.83	11	6068.01	409.2	12	19.44	-2.01	0.0581

	Short shelter visit threshold		4.53	0.13	11	4.43	0.17	12	19.82	0.47	0.644
	Long shelter visit fraction of total visits		0.07	0	11	0.05	0.01	12	20.52	2.64	**0.0156**
	Long shelter visit threshold		10.33	0.14	11	10.39	0.14	12	20.99	-0.29	0.7717
	Short shelter visit duration	light	121.35	27.04	11	48.91	38.36	12	13.64	1.48	0.1605
	Mean short shelter visit duration	light	7.02	0.57	10	9.64	1.11	12	7.96	-2.33	0.0484
	Short shelter visit number	light	17.83	3.56	11	7.48	3.71	5	15.69	1.98	0.065
	Long shelter visit duration	light	38274.44	446.35	11	37983.87	947.84	12	15.58	0.28	0.7852
	Long shelter visit number	light	5.75	0.55	11	5.25	0.39	12	19.21	0.78	0.4423
Spontaneous behavior (pattern)	Activity change in anticipation of dark		-0.01	0.01	11	0.01	0.01	12	20.68	-0.92	0.3706
	Activity change in anticipation of light		0.11	0.01	11	0.13	0.03	12	14.17	-0.86	0.4057
	Activity change in response to to dark		0.26	0.02	11	0.3	0.02	12	19.99	-1.33	0.1993
	Activity change in response to to light		-0.08	0.01	11	-0.09	0.02	12	20	0.69	0.4968
	Feeding zone change in anticipation dark		0.12	0.11	11	0.02	0.06	12	16.22	0.78	0.4487
	Feeding zone change in response to dark		-0.07	0.05	11	0.01	0.04	12	20.04	-1.28	0.2149

	Feeding zone change in anticipation light	-0.1	0.04	11	-0.19	0.06	12	19.46	1.23	0.2352
	Feeding zone change in response to light	0.07	0.1	6	-0.2	0.12	5	8.34	1.78	0.111
	OnShelter zone change in anticipation dark	0	0.02	11	0	0.01	12	17.72	-0.11	0.9116
	OnShelter zone change in response to dark	-0.01	0.01	11	0	0.01	12	17.97	-0.78	0.4468
	OnShelter zone change in anticipation light	0.09	0.02	11	0.02	0.01	12	19.18	3.44	**0.0027**
	OnShelter zone change in response to light	-0.07	0.03	6	-0.04	0.04	5	8.21	-0.62	0.5532
	Spout zone change in anticipation dark	-0.02	0.02	11	0.05	0.03	12	19.88	-1.61	0.1224
	Spout zone change in response to dark	0	0.01	11	0.02	0.01	12	19.07	-1.78	0.0909
	Spout zone change in anticipation light	0.01	0.01	11	0.08	0.01	12	20.72	-4.65	**0.0001**
	Spout zone change in response to light	0.01	0.02	6	-0.01	0.04	5	5.98	0.25	0.8078

Supplementary Table 4. Spontaneous home cage behavior of reverse 129Sv *Stxbp1* mice. 97 parameters derived from X-Y coordinates recorded for 3 consecutive days without human interference. *statistics done on log10 data MWU: Mann Whitney U-test

			Wild-type mice			Heterozygous mice			Statistics		
			Mean	SEM	N	Mean	SEM	N	DF	T test	P-value
Spontaneous behavior (activity)	Activity duration	dark	3870.76	905.73	9	4758.67	829.00	7	MWU		0.142
	Mean activity duration*	dark	26.85	8.20	9	20.30	1.32	7	14	0.41	0.689
	Activity number	**dark**	158.91	18.09	9	227.80	25.33	7	14	-2.28	**0.039**
	Feeding zone duration*	**dark**	5656.66	1091.73	9	11595.74	1650.71	7	14	-3.03	**0.009**
	Spout zone duration*	dark	2271.01	904.60	9	5233.82	1390.63	7	14	-1.99	0.066
	Activity duration*	**light**	631.37	162.06	9	257.96	70.88	7	14	2.57	**0.022**
	Mean activity duration	light	22.20	1.38	9	18.99	2.27	7	14	1.61	0.136
	Activity number*	light	27.51	8.06	9	16.63	3.71	7	14	1.22	0.244
	Feeding zone duration	light	1064.50	213.59	9	1383.91	413.01	7	14	-0.73	0.475
	Spout zone duration	light	370.39	157.77	9	673.81	268.85	7	14	-1.03	0.323
Spontaneous behavior (dark-light ratio)	**Activity duration**	**dark-light index**	0.84	0.04	9	0.95	0.01	7	MWU		**0.012**
	Mean activity duration	dark-light index	0.50	0.04	9	0.55	0.03	7	14	0.96	0.355
	Activity number	**dark-light index**	0.85	0.03	9	0.93	0.01	7	MWU		**0.042**
	Mean short arrest duration	**dark-light index**	0.54	0.01	9	0.49	0.02	7	14	-3.15	**0.007**
	Long arrest duration	darklight index	0.86	0.03	9	0.89	0.03	7	14	0.58	0.569
	Mean long arrest duration	dark-light index	0.48	0.01	9	0.41	0.03	7	MWU		0.055
	Long arrest number	dark-light index	0.86	0.03	9	0.93	0.02	7	MWU		0.091
	Feeding zone duration	dark-light index	0.82	0.04	9	0.90	0.02	7	MWU		0.252
	Long shelter visit duration	**dark-light index**	0.42	0.01	9	0.37	0.01	7	14	-3.33	**0.005**
	Long shelter visit number	**dark-light index**	0.79	0.02	9	0.66	0.03	7	14	-4.10	**0.001**
	Mean long movement distance	dark-light index	0.49	0.02	9	0.55	0.03	7	14	1.77	0.098
	Mean short movement	dark-light index	0.50	0.01	9	0.50	0.01	7	14	0.31	0.764

	distance										
	Spout zone duration	dark-light index	0.86	0.04	9	0.91	0.03	7	14	1.06	0.307
Spontaneous behavior (habituation)	Activity duration*	habituation ratio dark	0.89	0.18	9	0.77	0.14	7	14	-0.32	0.751
	Mean activity duration*	habituation ratio dark	1.16	0.32	9	0.77	0.16	7	14	-1.17	0.26
	Activity number	habituation ratio dark	0.84	0.08	9	1.04	0.08	7	14	1.66	0.12
	Mean short arrest duration	habituation ratio dark	1.03	0.05	9	1.05	0.05	7	MWU		0.351
	Long arrest duration	habituation ratio dark	1.19	0.14	9	1.31	0.10	7	14	0.65	0.526
	Mean long arrest duration	habituation ratio dark	1.39	0.27	9	1.24	0.06	7	MWU		0.918
	Long arrest number	habituation ratio dark	0.92	0.07	9	1.07	0.08	7	14	1.48	0.162
	Feeding zone duration	habituation ratio dark	0.96	0.11	9	1.18	0.07	7	14	1.55	0.144
	Mean short shelter visit duration	habituation ratio dark	1.05	0.08	9	0.99	0.13	7	14	-0.45	0.657
	Long shelter visit duration	habituation ratio dark	0.99	0.02	9	1.02	0.07	7	14	0.45	0.663
	Mean short movement distance	habituation ratio dark	0.99	0.01	9	1.05	0.04	7	MWU		0.174
	Spout zone duration	habituation ratio dark	0.68	0.17	9	1.19	0.27	7	14	1.68	0.116
	Activity duration*	habituation ratio light	0.72	0.12	9	0.47	0.14	7	14	-1.85	0.086
	Mean activity duration	habituation ratio light	1.10	0.10	9	0.94	0.10	7	14	-1.12	0.281
	Activity number	habituation ratio light	0.63	0.09	9	0.48	0.10	7	14	-1.03	0.321
	Mean short arrest duration	habituation ratio light	0.94	0.04	9	1.03	0.08	7	14	0.99	0.337
	Long arrest duration	habituation ratio light	0.90	0.17	9	0.77	0.24	7	MWU		0.47
	Mean long arrest duration	habituation ratio light	1.30	0.25	9	1.51	0.16	7	14	0.67	0.516
	Long arrest number*	habituation ratio light	0.71	0.11	9	0.49	0.12	7	14	-1.54	0.146
	Feeding zone duration	habituation ratio light	1.00	0.13	9	0.67	0.17	7	14	-1.61	0.13
	Long shelter visit duration	habituation ratio light	1.06	0.05	9	1.05	0.03	7	MWU		0.606
	Mean long movement distance	habituation ratio light	1.02	0.06	9	0.96	0.08	7	14	-0.73	0.479
	Mean short movement distance	habituation ratio light	1.00	0.03	9	0.99	0.04	7	14	-0.17	0.867
	Spout zone duration	habituation ratio light	0.93	0.18	9	0.62	0.22	7	14	-1.10	0.29

Spontaneous behavior (kinematics)	**Long movement fraction of total movement**		0.46	0.01	9	0.50	0.00	7	14	-2.52	**0.025**
	Long movement max. velocity		20.17	1.33	9	22.83	1.60	7	14	-1.29	0.218
	Long arrest threshold		5.79	0.47	9	7.03	0.77	7	14	-1.45	0.17
	Short arrest duration	dark	1638.35	216.42	9	2445.69	352.84	7	14	-2.04	0.06
	Mean short arrest duration	dark	1.12	0.07	9	1.16	0.12	7	14	-0.28	0.782
	Short arrest number*	dark	1548.93	256.05	9	2362.74	617.18	7	14	-1.46	0.166
	Long arrest duration	**dark**	7228.09	766.15	9	10660.15	973.58	7	14	-2.81	**0.014**
	Mean long arrest duration	dark	44.34	13.00	9	46.11	9.77	7	MWU		0.408
	Long arrest number	dark	202.22	23.91	9	266.86	33.50	7	14	-1.62	0.129
	Long movement distance	**dark**	8060.39	1636.25	9	14908.90	2325.42	7	14	-2.48	**0.026**
	Mean long movement distance	dark	10.95	0.58	9	14.29	1.86	7	14	-1.90	0.078
	Long movement number*	dark	719.22	126.64	9	1121.91	233.41	7	14	-1.77	0.098
	Short movement distance	dark	904.62	140.96	9	1414.77	459.93	7	MWU		0.252
	Mean short movement distance	dark	1.00	0.03	9	1.01	0.04	7	14	-0.18	0.857
	Short movement number	dark	1.00	0.03	9	1.01	0.04	7	14	-0.18	0.857
	Short arrest duration	light	322.56	89.49	9	150.62	52.40	7	MWU		0.114
	Mean short arrest duration	light	0.94	0.06	9	1.24	0.15	7	14	-2.03	0.062
	Short arrest number*	**light**	357.69	102.60	9	115.97	33.03	7	14	3.36	**0.005**
	Long arrest duration	light	1089.07	258.45	9	1398.02	335.11	7	14	-0.74	0.47
	Mean long arrest duration	**light**	34.89	2.76	9	47.74	3.04	7	14	-3.12	**0.008**
	Long arrest number*	light	33.71	10.12	9	22.23	8.03	7	14	1.13	0.276
	Long movement distance*	**light**	2013.63	719.82	9	631.74	217.81	7	14	2.64	**0.019**
	Mean long movement distance	light	11.43	0.62	9	11.62	1.14	7	14	-0.16	0.878
	Short movement distance*	**light**	203.35	53.42	9	80.72	23.24	7	14	2.87	**0.012**

	Mean short movement distance*	light	1.02	0.04	9	1.03	0.08	7	14	0.09	0.933
	Short movement number	**light**	201.47	56.85	9	81.00	24.16	7	MWU		**0.023**
	Long movement threshold		1.29	0.08	9	1.31	0.12	7	MWU		0.918
Spontaneous behavior (sheltering)	Short shelter visit duration	dark	281.32	69.15	9	573.39	180.63	7	MWU		0.299
	Mean short shelter visit duration	dark	10.95	2.88	9	8.79	0.97	7	14	0.64	0.536
	Short shelter visit number*	dark	36.62	13.28	9	64.06	15.03	7	14	-2.02	0.063
	Long shelter visit duration	**dark**	29540.43	1104.51	9	24671.49	732.11	7	14	3.44	**0.004**
	Long shelter visit number	dark	11.24	1.30	9	7.54	1.07	7	14	2.11	0.053
	Mean long shelter visit duration		4821.89	335.21	9	6297.34	550.56	7	14	-2.40	**0.031**
	Short shelter visit threshold		4.33	0.67	9	4.71	0.23	7	14	-0.49	0.635
	Long shelter visit fraction of total visits*		0.20	0.03	9	0.11	0.02	7	14	1.91	0.077
	Long shelter visit threshold		8.99	0.31	9	10.06	0.22	7	14	-2.67	**0.018**
	Short shelter visit duration	light	101.17	42.47	9	32.00	20.76	7	MWU		0.114
	Short shelter visit number	light	12.91	3.65	9	2.57	1.39	7	MWU		0.091
	Long shelter visit duration	light	41102.11	481.25	9	41353.16	432.59	7	14	-0.38	0.712
	Long shelter visit number*	light	2.93	0.38	9	3.83	0.54	7	14	-1.48	0.16
Spontaneous behavior (activity pattern)	Activity change in anticipation of dark		0.0010	0.0067	9	-0.0006	0.0042	7	14	0.19	0.856
	Activity change in anticipation of light		-0.0506	0.0720	9	-0.0026	0.0119	7	MWU		0.408
	Activity change in response to to dark		0.06	0.01	9	0.20	0.02	7	14	-5.86	< **0.0001**
	Activity change in response to to light		-0.09	0.07	9	-0.03	0.01	7	MWU		0.681
	Feeding zone change in anticipation		0.18	0.12	9	0.23	0.13	7	MWU		0.918

	dark									
	Feeding zone change in response to dark	0.04	0.09	9	-0.12	0.16	7	14	0.93	0.368
	Feeding zone change in anticipation light	-0.01	0.12	9	0.06	0.19	7	14	-0.31	0.758
	Spout zone change in anticipation dark	0.06	0.04	9	0.24	0.13	7	MWU		0.918
	Spout zone change in response to dark	-0.03	0.05	9	-0.01	0.14	7	14	-0.14	0.888
	Spout zone change in anticipation light	0.05	0.02	9	0.15	0.11	7	14	-0.91	0.378

Supplementary Table 5. 5-CSRTT task performance in congenic BL6 *Stxbp1* mice.

Measure (unit)	*Stxbp1*$^{+/+}$ n=12	*Stxbp1*$^{+/-}$ n=12	P value (ANOVA)
Attention and inhibitory control			
Response accuracy (%)	91.6±1.8	91±1.4	0.82
Response variability (s)	0.42±-0.04	0.48±0.05	0.33
Impulsive responses (n)	4.6±1.3	5.5±1.2	0.63
Omission errors (%)	54±2.5	52.9±0.9	0.68
Motivation			
Correct response latency (s)	0.79±0.05	0.82±0.04	0.63
Reward latency (s)	2.6±0.6	1.6±0.1	0.12

Supplementary Table 6. Anxiety-related behavior of the reverse 129Sv *Stxbp1* mice. Number of mice of the reverse 129Sv *Stxbp1* line indicating very high level of anxiety (and thus excluded from the analysis).

Number of animals that did not visit anxiety-related compartment or did not eat a cracker		
Measure and test	WT (N/Ntot)	HZ (N/Ntot)
Failure to enter open arms in the elevated plus maze test	**1**/12	**3**/12
Failure to enter the center area in the open field test	**9**/12	**8**/12
Failure to enter the bright compartment in the dark-light box test	**7**/12	**4**/12
Failure to consume the reward in the novelty-induced hypophagia test	**8**/12	**9**/12

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