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**1. Animal care**

Pregnant C57BL/6J mice (9 weeks old, 25-30 g, Charles River) were housed in a specific pathogen-free facility in cages of five until pregnancy day 16 (E16), at which time they were caged alone. The room was maintained at controlled temperature (21 ± 1°C) and humidity (55 ± 10%) with illumination at 12:12 light: dark cycles and *ad libitum* access to food and water. Randomly selected representative offspring from every litter were separated by sex on postnatal day 21, and kept in the same caging conditions as described above until the indicated time points (i.e., postnatal days 21, 70 or 155). Overall, 54 pregnant female mice, 165 fetuses and 187 pups were used for behavioral, electrophysiological, morphological, and synaptic brain studies.

**2. Infusion of IgG and assessment of transplacental transfer of antibodies**

Pooled IgG (800µg) from patients or controls was injected via tail vein to pregnant mice on days 14, 15 and 16 (E14, E15 and E16) of gestation (figure 1A). These experiments were planned according to the window of time in which the neonatal receptor (FcRn), which allows IgG transplacental transfer is expressed in placental tissue, and the immature fetal blood-brain barrier (BBB) does not restrict the crossing of IgG (e.g., around gestational day 16 the BBB becomes significantly more restrictive to maternal antibody penetration into the fetal brain).1

**3. Processing of brain and blood samples**

In subsets of mice, blood and brain from fetuses/offspring were collected on days 16, 17 and 18 of gestation, and on postnatal days 21, 70 and 155 (figure 1A). Blood samples from pregnant mice were also collected on the indicated gestational days. Blood samples were centrifuged to obtain serum. Brains were fixed with 4% paraformaldehyde for 1 hour, cryopreserved in 40% glucose for 48 hours, embedded in optimal cutting temperature compound and snapped frozen in isopentane chilled with liquid nitrogen. Representative brains from fetuses were kept fresh frozen for immunoprecipitation studies.

**4. Antibody determination in blood from pregnant mice and fetuses**

The presence of patients’ NMDAR antibodies in serum of pregnant mice and fetuses was confirmed using immunolabeling of live rat hippocampal neurons in culture (serum dilution, 1:5; for 1 hour at 4°C), and also with CBA with fixed HEK293T cells expressing GluN1/2B subunits of the NMDAR (serum dilution 1:10, incubation at 4°C, overnight), as reported.2 After washing, neurons were fixed with 4% paraformaldehyde and incubated with Alexa Fluor 488 goat anti-human IgG (A11013, diluted 1:500 from Invitrogen, Carlsbad, CA, USA) for 1 hour at 4°C. The same secondary antibody and duration of incubation was used for CBA. Coverslips were mounted and scanned under a Zeiss LSM 710 confocal microscope (Carl Zeiss GmbH, Jena, Germany). Antibody titration was obtained by serial antibody dilution using the indicated CBA.

**5. Determination of human IgG, NMDAR clusters, and cortical plate thickness in fetal brain tissue**

To determine whether human NMDAR antibodies injected to pregnant mice reached the brain of fetuses, 5 µm-thick fetal brain sections were immunostained for human IgG using Alexa Fluor 488 goat anti-human IgG, as above. Quantification of fluorescence intensity in the brain was done using the public domain Fiji ImageJ software (*http://fiji.sc/Fiji*). Background was subtracted and intensity normalized by area. Median intensity of IgG immunostaining in control animals was defined as 100%.

To determine the effects of patients’ antibodies on total cell-surface and synaptic NMDAR clusters and postsynaptic density protein 95 (PSD95), non-permeabilized 5 µm-thick sections were blocked with 1% bovine serum albumin (BSA) for 30 minutes at room temperature (RT), incubated with human CSF containing NMDAR antibodies (used as primary antibody) for 2 hours at RT, washed with PBS, permeabilized with Triton X-100 0.3% for 10 minutes at RT, and incubated with rabbit polyclonal antibody against PSD95 (diluted 1:250, Ab18258, Abcam, Cambridge, UK) overnight at 4°C. Next day, the slides were washed and incubated with the corresponding secondary antibodies (Alexa Fluor 488 goat anti-human IgG, A11013, and Alexa Fluor 594 goat anti-rabbit IgG, A11012; both 1:500, Invitrogen, Carlsbad, CA, USA) for 1 hour at RT, as reported.3 Slides were then mounted as described above and results scanned under a Zeiss LSM710 confocal microscope. Standardized z-stacks including 50 optical images were acquired from five different areas of the developing hippocampus. Images were then deconvolved using theoretical point spread functions of Huygens Professional 17.04 software (Scientific Volume Imaging, Hilversum, NL). For cluster density analysis a spot detection algorithm from Imaris 8.1 software (Oxford instruments, Belfast, UK) was used. Density of clusters was expressed as spots/µm3. Three-dimensional colocalization of clusters (e.g. NMDAR and PSD95) was done using a spot colocalization algorithm implemented in Imaris. Synaptic localization was defined as colocalization of NMDAR with PSD95. Synaptic NMDAR cluster density was expressed as colocalized spots/µm3, and was normalized to the median cluster density of brains of fetuses exposed to controls’ IgG (100%).

The thickness of the cortical plate was measured using DAPI-stained fetal sagittal brain sections, and quantified using Fiji ImageJ software.

**6. Immunoprecipitation of fetal brain tissue**

In order to confirm that the human antibody detected in fetal brains was specifically bound to NMDAR, homogenates of brain tissue were washed, incubated with protein A/G sepharose beads, precipitated, run in a gel, and blotted with a commercial GluN1 polyclonal rabbit antibody (G8913, 1:200, Sigma-Aldrich, St. Louis, MO, USA).

**7. Determination of human IgG, levels of NMDAR clusters, synaptic density, cortical layer thickness, and microglial activation in offspring**

The presence of human IgG in the brain of offspring (postnatal days 21 and 70), and density of NMDAR (postnatal days 21, 70, and 155) were determined as indicated above for fetal brains. In this case, NMDAR clusters were quantified from a total of 15 images acquired from CA1, CA3 and dentate gyrus of hippocampus (five different areas per region).

The density of glutamatergic synapses (postnatal days 21 and 70) was assessed with immunohistochemistry using pre- and postsynaptic markers: anti-Bassoon (1:250, SySy 141 003) and anti-Homer1 (1:250, SySy 160 004) for 2 hours at RT, both from (Synaptic Systems, Goettingen, Germany), followed by incubation with the corresponding secondary antibodies (Alexa Fluor 594 goat anti-rabbit IgG, A11012; and Alexa Fluor 488 goat anti-guinea pig IgG, A11073; both diluted 1:500, Invitrogen) for 1 hour at RT. Acquisition and quantification of synaptic markers density were performed as above.

Cortical layer thickness was measured in sections of brains obtained on postnatal days 21, 70 and 155, and immunostained with specific cortical layer markers including a monoclonal mouse anti-CUTL1 (1:100, ab54583, Abcam) for layers II-IV, and a polyclonal sheep anti-FoxP2 (1:40, AF5647, R&D systems, Minneapolis, MN, USA) for layer VI, overnight at 4°C. Secondary antibodies included Alexa Fluor 488 goat anti-mouse IgG and Alexa Fluor 594 donkey anti-sheep IgG (A11001 and A11016, both 1:500, Invitrogen) for 2 hours at RT. Images were acquired with a Zeiss LSM710 confocal microscope and the layers’ thickness was determined as described above for the fetal cortical plate. Cell density in CUTL1-labeled layers was measured on brain sections from postnatal day 21 using DAPI staining with spots algorithm in Imaris software.

Microglial activation was assessed in sections of brain (postnatal days 21, 70 and 155) with a monoclonal rat antibody against CD68 (pan-macrophage marker, 1:800, MCA1957GA, Bio-Rad, Hercules, CA, USA), and a polyclonal rabbit antibody against Iba-1 (activated microglia, 1:1000, 019-19741, Wako Chemicals, Neuss, Germany). Incubations were done overnight at 4°C, followed by incubation with secondary antibodies (Alexa Fluor 488 goat anti-rat IgG, A11006, and Alexa Fluor 594 goat anti-rabbit IgG, A11012, both diluted 1:1000, Invitrogen) for 2 hours at RT. Samples were mounted and scanned as above and the CD68- or Iba-1-stained surface density was quantified using Imaris software.

**8. DiOlistic staining and confocal imaging for dendritic complexity (Sholl analysis) and spine morphology analysis**

Cortical and hippocampal neurons from fixed brains of animals on postnatal days 21 and 70 were labeled using the Helios Gene Gun System (165-2431, Bio-Rad) as described.4 Briefly, a suspension containing 3 mg of DiI (Molecular Probes, Eugene, OR, USA) dissolved in 100 μl of methylene chloride (Sigma-Aldrich) and mixed with 50 mg of tungsten particles (1.7 mm diameter; Bio-Rad) was spread on a glass slide and air-dried. The mixture was resuspended in 8 ml distilled water and sonicated. Subsequently, the mixture was drawn into Tefzel tubing (Bio-Rad), and then removed to allow tube drying during 5 minutes under nitrogen gas flow. The tube was then cut into 13-mm pieces to be used as gun cartridges. One hundred eighty μm coronal sections of 1.5% paraformaldehyde-fixed brain samples were shot at 80 psi through a membrane filter of 3 μm pore size and 8 × 10 pores/cm2 (Millipore, Burlington, MA, USA) to deliver dye-coated particles in the cortex or the hippocampus. Sections were stored at RT in PBS for 3 hours protected from light and then incubated with DAPI, and mounted in Mowiol to be acquired.

The dendritic complexity was examined with Sholl analysis5 in cortical and CA1 hippocampal pyramidal neurons imaged using a Zeiss LSM710 confocal microscope. Briefly, images were segmented, and the Imaris-implemented filament tracer algorithm was applied to obtain the dendritic traces. The images were then thresholded to a binary mask and saved as Tiff files. The Sholl intersection profile was obtained by counting the number of dendritic branches at a step distance of 10 μm from the soma using ImageJ software.5

The spine morphology analysis was examined in DiI-labeled segments of apical secondary dendrites of cortical and CA1 hippocampal pyramidal neurons. Confocal z-stacks including the entire volume of the dendrite were taken with a digital zoom of 5 and a lateral resolution of 1024 × 1024 pixels. Images were deconvolved in order to improve contrast and resolution using Huygens Professional software. Quantification of mushroom-shaped dendritic spines was performed with the spine classification algorithm implemented in Imaris software.

**9. Hippocampal long-term potentiation (LTP) and paired-pulse facilitation**

Subsets of mice on postnatal days 18-23 and 70-80 were deeply anesthetized with isoflurane and decapitated. Brains were removed in ice-cold, high sucrose extracellular artificial cerebrospinal fluid (aCSF1, in mM: 206 sucrose, 1.3 KCl, 1 CaCl2, 10 MgSO4, 26 NaHCO3, 11 glucose, 1.25 NaH2PO4; purged with 95% CO2/5% O2, pH 7.4), and subdivided into hemispheres. Thick (380 μm) coronal slices of hippocampus were obtained with a vibratome (VT1000S; Leica Microsystems, Wetzlar, Germany) and transferred into an incubation beaker with extracellular aCSF appropriate for neurophysiological recordings (aCSF2, in mM: 119 NaCl, 2.5 KCl, 2.5 CaCl2, 1.25 NaH2PO4, 1.5 MgSO4, 25 NaHCO3, 11 glucose, purged with 95% CO2/5% O2, pH 7.4). Slices were kept at 32°C for 1 hour and subsequently at RT for at least 1 additional hour. For field potential measurements, single slices were then transferred into a measurement chamber perfused with aCSF2 at 2 ml/minute at 28-30°C (controls’ IgG: postnatal days 18-23, number of acute slices n = 6, prepared from brain hemisections of five mice; days 70-80 n = 7 from hemisections of five mice; patients’ IgG: postnatal days 18-23 n = 5 prepared from brain hemisections of five mice, days 70-80 n = 10 from hemisections of five mice). A bipolar stimulation electrode (Platinum-Iridium stereotrode, PI2ST30.1A5, Science Products GmbH, Hofheim, Germany) was placed in the Schaffer collateral pathway.6 Recording electrodes were made with a puller (P-1000, Sutter Instrument Company, Novato, CA, USA) from thick-walled borosilicate glass with a diameter of 1.5 mm (BF150-86-10, Sutter Instrument). The recording electrode filled with aCSF2 was placed in the dendritic branching of the CA1 region for local field potential measurement (field excitatory postsynaptic potential, fEPSP). A stimulus isolation unit A385 (World Precision Instruments, Sarasota, FL, USA) was used to elicit stimulation currents between 25-700 μA. Before baseline recordings for long-term potentiation (LTP), input-output curves were recorded for each slice at 0.03 Hz. The stimulation current was then adjusted in each recording to evoke fEPSPs at which the slope was at 50-60% of maximally evoked fEPSP slope value. After baseline recording for 30 minutes with 0.03 Hz, LTP was induced by theta-burst stimulation (TBS; 10 theta bursts of four pulses of 100 Hz with an interstimulus interval of 200 ms, repeated seven times with 0.03 Hz). After LTP induction, fEPSPs were recorded for 1 additional hour with 0.03 Hz. Recordings with unstable baseline measurements (variations higher than 20% in baseline fEPSPs) were discarded. Paired-pulse fEPSPs in the test pathway were measured before baseline recordings with an interstimulus interval of 50 ms. All recordings were amplified and stored using amplifier AxonClamp P2 (Molecular Devices, San José, CA, USA). Traces were analyzed using Axon pClamp software (Molecular Devices, version 10.6).

**10. Neurobehavioral assessment in postnatal and adult stages**

From birth to weaning (breastfeeding withdrawal on postnatal day 21) mice were assessed daily for achievement of developmental milestones using a modified Fox battery, similar to that previously reported.7 This includes body weight, ear detachment, eye opening, skin color change, fur growth, tactile rooting and auditory startle responses, open field test (locomotion), and innate reflexes (i.e., surface body righting and negative geotaxis). The schedule used for assessment of developmental milestones is shown in figure e-1A.

From weaning to adulthood (155 days) subsets of mice underwent a battery of behavioral tests consisting of locomotor activity (LocAct), novel object location (NOL), prepulse inhibition of acoustic startling reflex (PPI), nest building (NB), social interaction (SIT), accelerating rotarod (ARR), and tail suspension (TST) tests, at 1, 2 and 4 months of age (figure e-1B). Selection and timing of these tasks were based on findings in our previously reported animal model of passive transfer of NMDAR antibodies in adult mice.3 All experiments were performed during the light phase and by researchers blinded to the animals’ experimental conditions. Locomotor activity assessment and tail suspension tests were performed as previously reported.6 Details on NOL, PPI, nest building, social interaction, and rotarod tasks are provided in the following sections.

**11. Novel object location (NOL) test**

Animals were habituated to an empty, squared arena with visual cues, and underwent two daily trials of 15 minutes each, for four days. The day of the test, animals were placed into the arena in presence of two equal objects positioned at two opposite corners and they were allowed to explore the objects for 9 minutes (familiarization phase). After a retention time of three hours, animals were reintroduced to the arena, where one of the objects had been moved to a different corner. The animal was allowed to explore the objects for 9 minutes (test phase) and the time of exploration of each object was recorded. A discrimination index (NOL Index) was calculated using the following formula: Time of exploration of the moved object minus time of exploration of the not moved object, divided by total time of exploration of both objects. A higher discrimination index indicates a better memory of the position of both objects. Object exploration is defined as any exploratory behavior triggered by the presence of the object (sniffing, biting, touching) with the orientation of the nose toward the object within a distance of < 2 cm.8

**12. Prepulse inhibition of the acoustic startle response (PPI) test**

The PPI is a classic paradigm to measure alterations in sensorimotor gating, which have been shown to occur in models of psychotic-like behavior.9 For this study, mice were restrained using a plexiglass cylinder placed within a startle box (Panlab, Barcelona) following a modification of an existing protocol.10 After 5 minutes of habituation, a series of 10 trials of pulses (8 KHz. 115 dB, 40 miliseconds [ms]) was administered and the startle response (SR) was measured for 1000 ms (intertrial interval 29 seconds) in order to establish the basal response. The animal was subsequently exposed to a total of 40 trials randomly administered and equally divided into 4 different stimuli: pulse alone (8 KHz, 115 dB, 40 ms), prepulse alone (10 KHz, 80 dB, 20 ms), prepulse-pulse, and no stimulus (absence of pulse). Both habituation and test were always performed in presence of background white noise (60 dB) and light. The amount of inhibition of the SR due to the administration of the prepulse prior to the pulse was calculated as:

**13. Nest building (NB) test**

Nest building test was performed introducing 9 grams of nestlet material (Ancare, Bellmore, NY, USA) overnight in the cage of previously individualized mice. The next day the nest is scored as previously described,11 and unused nestlet material is weighted.

**14. Social interaction test (SIT)**

Social memory was evaluated by the five-trial social interaction test, based on an habituation/dishabituation paradigm previously reported.12 Briefly, after the experimental mouse has been kept alone for one week, a mouse of same sex and similar age (intruder) is introduced in the cage of the experimental mouse for 1 minute, and then removed. The same intruder exposure is performed for 1 minute in 4 different trials separated by 10 minutes’ intertrial intervals. In the fifth trial, the intruder is changed for a different mouse for 1 minute. Trials are recorded and the total amount of time the experimental mouse interacts with the other mouse in each 1-minute trial is measured. Development of social memory is indicated by a reduction of exploration time during the interactions with the same animal (trials 1-4) and increase of exploration time during the interaction with a new animal in trial 5.13

**15. Accelerating Rotarod (ARR) test**

Balance and motor coordination were assessed in an accelerating-mode Rotarod (Panlab, Harvard Apparatus) as reported14 with some modifications. Briefly, mice were previously habituated to the apparatus at a constant speed of 4 rpm for two trials with 1.5 hours of intertrial period in one day. The next day, animals were placed on the Rotarod at accelerating conditions of four to 40 rpm in 300 seconds and two trials per day with 1.5 hours of intertrial period for three consecutive days. Latency to fall was measured. Longer times on the rotarod indicate better balance and motor coordination.15

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Day 21** | **Day 70\*** | **Day 155** |
| **NMDAR clusters, dendritic and synaptic changes, and microglial activation** | Cortical layers II-IV width | **↓** | N | - |
| Dendritic arborization | **↑** | N | - |
| Mushroom-shaped spine density  Homer1/Bassoon colocalization cluster density | **↓** | N | - |
| Total NMDAR cluster density | **↓** | **↓** | N |
| Synaptic NMDAR cluster density | **↓** | N | N |
| Microglial activation | **↑** | **↑** | N |
| **Hippocampal electrophysiology** | Synaptic plasticity (LTP) | **↓** | N | - |
| **Neurodevelopment and behavior** | Innate reflexes  (Surface righting and negative geotaxis) | Delayed | N | N |
| Eye opening | Delayed | N | N |
| Spatial memory | Abn | N | N |
| Nest building | Abn | N | N |
| Social memory | Abn | N | N |
| Balance and motor coordination | Abn | Abn | N |
| Behavioral despair (Depressive-like behavior) | - | Abn | N |

**16. Table e-1: Summary of tests obtained on postnatal days 21, 70, and 155**

**17. Supplemental figure e-1: Developmental milestones assessment and batteries of behavioral tests used in the offspring**

Panel **A:** Diagram of the modified Fox battery showing the tests and days of assessment (grey boxes) from birth (day 0) to day 21.

Panel **B**: Schedule of behavioral tests used in offspring. After the habituation (Hab) period, mice underwent locomotor activity assessment (LocAct), novel object location (NOL), prepulse inhibition of acoustic startle response (PPI), nest building (NB), social interaction (SIT), and accelerating rotarod (ARR) tests at one, two and four months of age. Tail suspension test (TST, brown) was performed at two and four months of age, as it is a final point task.

**18. Supplemental figure e-2: Intrauterine exposure to patients’ IgG transiently impairs hippocampal LTP in the young offspring**

Panel **A:** Example traces of individual recordings showing baseline recordings before LTP induction (grey, light blue traces) and after LTP (black, dark blue traces). Slope and peak amplitude of fEPSPs are increased after theta burst stimulation (TBS) in hippocampus of 21 day postnatal mice that were exposed *in utero* to controls’ IgG. In contrast, manifestation of LTP is strongly impaired in mice exposed *in utero* to patients’ IgG.

Panel **B:** Time course of fEPSP recordings demonstrating robust changes in fEPSP slope in hippocampus of 21 day postnatal mice that were exposed *in utero* to controls’ IgG (n = 6 recordings from 5 animals, black dots) and mice exposed *in utero* to patients’ IgG (n = 5 recordings from 5 animals, blue dots), which is stable throughout the recording period after TBS (arrow). In animals exposed *in utero* to patients’ IgG the induction of synaptic LTP is markedly impaired. Average fEPSP values are presented as mean ± SEM.

Panel **C**: Quantitative analysis of the fEPSP slope in hippocampus of 21 day postnatal mice that were exposed *in utero* to patients’ IgG compared to those exposed to controls’ IgG. Mean fEPSP slope before TBS was defined as 100% and post-TBS fEPSP slope data was normalized to it for each group. The number of animals is the same as in panel B. The box plots show the median, 25th, and 75th percentiles; whiskers indicate minimum and maximum values. Significance of treatment effect was assessed by independent sample *t*-test. \*\*\* *P* < 0.001.

Panels **D**, **E**, and **F** show similar studies as above on slices of hippocampus of mice at postnatal day 70. Note that LTP formation in mice exposed *in utero* to patients’ IgG is restored on postnatal day 70. In **E** and **F,** n = 7 recordings from 5 mice exposed *in utero* to controls’ IgG (black dots); n = 10 recordings from 5 mice exposed *in utero* to patients’ IgG (blue dots)

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