Methods

Mice. Female and male C57BL/6 (~20 g) mice were purchased at 7 weeks old from Charles River Laboratories (Montréal, Canada) and allowed 7 days of acclimation at the housing facility of CERVO Brain Research Center. Sexually experienced retired male CD-1 breeders (~40 g) of at least 4 months of age (Charles River Laboratories) were used as aggressors (AGG). *ROSA26iDTR* male mice and *PDGFRβ-P2A-CreERT2* female mice were purchased from Jackson Laboratory (Strain #007900 and #030201, respectively) and bred at the CERVO Brain Research Center. Offspring *PDGFRβ-CreERT2-iDTR* were used between 6-9 weeks of age. All mice were singly housed following CSDS and maintained on a 12h/12h light/dark cycle throughout. Room temperature was maintained between 19 and 23 °C and humidity was kept around 40−45%. Mice were provided with *ad libitum* access to water and food. All mouse procedures were performed in accordance with the Canadian Council on Animal Care (1993) as well as Université Laval animal care committee (Certificate #2022-1061, VRR-22-1061).

Chronic social defeat stress (CSDS). The male 10-day CSDS paradigm was performed as detailed in Golden et al.[1] and our recent studies[2-4], and female 10-day CSDS was performed as previously described[4,5]. Briefly for females, urine of a particular male CD-1 was applied to the base of the tail (20 µL), vaginal orifice (20 µL) and upper back (20 µL) of the female mouse then it was immediately subjected to physical interactions with an unfamiliar CD-1 previously screened for aggressive behavior (AGG) for 10 mins. After antagonistic interactions, experimental mice were removed and housed on the opposite side of the social defeat cage divider, allowing sensory contact, for the subsequent 24h period. Throughout the sessions, mice were monitored for aggressive interactions and mounting behaviours. A session was immediately stopped if persistent mounting or fighting causing physical wounding occurred. Unstressed control mice were housed two per cage on either side of a perforated divider and rotated daily in a similar manner without being exposed to the CD-1 AGG mice. Experimental and control mice were singly housed after the last bout of physical interaction and the social interaction (SI) test was conducted 24h later. Physical wounding was scored at the time of tissue collection, 24h after the SI test, and consisted of counting the number of tail bites on the experimental animals as well as the surface area (cm^2) of lower back lacerations, if applicable.

Social interaction test (SI). SI test was performed as previously described[1-4], under red light conditions. Briefly, experimental, or unstressed mice were placed in a Plexiglass open field arena (50 cm^2, Nationwide Plastics) containing a small wire cage placed at one end. Movements were monitored and recorded automatically for 2.5 min with a tracking system (AnyMaze™ 6.1, Stoelting Co) to determine baseline exploratory behaviour and locomotion in the absence of a social target (AGG). After this first trial, the animal was removed, and the arena cleaned. Next, exploratory behaviour in the presence of a novel male CD-1 AGG target inside the small wire animal cage was measured for 2.5 min and time spent in the interaction and corner zones and overall locomotion were compared. SI ratio was calculated by dividing the time spent in the interaction zone when the AGG was present vs absent. All mice with a SI ratio below 1.0 were classified as stress-susceptible (SS) and all mice with a SI ratio above 1.0 were classified as resilient (RES).

Elevated plus maze (EPM). EPM was performed as previously described[2,4], under white light conditions. Mice were placed in the center of a black Plexiglas cross-shaped elevated plus maze (arms of 12 cm width × 50 cm length) for 5 min. The maze consists of a center area, two open

arms without walls and two closed arms with 40 cm high walls set on a pedestal 1 m above floor level. Locomotion was monitored and tracked using an automated system (AnyMaze™ 6.1 Stoelting Co). Cumulative time spent in open arms or open arm extremities (furthest half), center, and closed arms as well as total locomotion was compared between groups.

Splash test (ST). The splash test was used to compare motivated grooming behaviour and performed under red-light conditions as previously described[2,4]. A 10% sucrose solution was sprayed 3-times on the lower back of the mice and time spent grooming over 5 min was videotaped and then recorded with a stopwatch by a blinded observer.

Sucrose preference (SP) test. Anhedonic responses were evaluated with the SP test, as previously described[2,4]. Mice were habituated for 2-days prior to SP by replacing water bottles with two 50 mL conical tubes with sipper tops filled with water. Next, water from one of the tubes was replaced with a 1% sucrose solution and mice were allowed to drink *ad libitum* for a 48h period. Tubes were switched after 24h to prevent placement preference. Both water and sucrose tubes were weighed before, after 24h and at the end (48h) of the SP test. Sucrose preference was calculated by dividing the total amount of sucrose consumed by the total amount of fluid consumed over the 2-d of sucrose availability.

Forced swim test (FST). FST was used to evaluate helplessness, as previously described[2,4]. Mice were placed into a 4L glass beaker filled with 3L of room temperature water (25°C), under bright light conditions and videotaped for 6 mins. Immobility, defined as no or minor movement necessary to keep the nose above water, was measured by a blinded observer.

Transcriptional profiling of mouse tissue. Prefrontal cortex (PFC) or nucleus accumbens (NAc) samples were collected and processed as described previously[2,4]. Briefly, bilateral 2.0 mm brain punches were collected from 1.0 mm coronal slices after rapid decapitation and flash frozen at -80°C until use. RNA was isolated with TRIzol (Invitrogen) homogenization and chloroform layer separation using the Pure Link RNA mini kit (Life Technologies). RNA concentration was determined with NanoDrop (ThermoFisher) and reversed transcribed to cDNA using the Maxima-H-minus cDNA synthesis kit (Fisher Scientific). Each qPCR reaction (well) contained 3ng of sample cDNA, 5µL of Power up SYBR green (Fisher Scientific), 1µL of PrimeTime qPCR primer (Integrated DNA Technologies) and 1µL ddH2O. Plates were heated at 95°C for 2mins, followed by 40 cycles of 95°C for 15s, 60°C for 33s and 72°C for 33s. The ΔΔCt method was used for analysis, using mouse *Gapdh* as a housekeeping gene. Primer pairs (Integrated DNA Technologies) are listed in the **Suppl.Table 12**.

Microvessel isolation for RNA-sequencing. Microvessel isolation was performed as previously described[6], with minor modifications. Briefly, 4 bilateral 2-mm punches (30-50 mg tissue) from 1.0 mm coronal brain slices of PFC or NAc were collected after rapid decapitation in MCDB 131 media (Gibco, 10372-019). Samples were homogenized with a 7mL Dounce homogenizer in MCDB 131 containing 0.5% bovine serum albumin (BSA) and centrifuged at 2000g for 10 minutes at 4°C. Pellets were then resuspended in a 18.75% (wt/vol) 70-kDa Dextran solution (Sigma, 31390-25G) and ultracentrifuged at 12000 rpm for 21 mins at 4°C (SW60 rotor, Beckman Coulter). Myelin layer and debris were removed by aspiration, before transferring pellets containing microvessel fragments to a 20-µm cell strainer and washing with hypotonic solution (20 mM Tris-HCl, 10 mM NaCl, 3 mM $MgCl_2$ in nuclease-free water). Finally, microvessels were collected by inverting filter onto a new tube and eluting with 1.4 mL hypotonic solution. Suspension was

centrifuged at 2000g for 10 minutes at 4°C, and pelleted cells resuspended in 200 µL of Trizol for downstream applications.

Immunohistochemistry and quantification of mouse pericyte morphology. 24h after the SI test, mice were anesthetized with a mixture of ketamine (100mg/kg of body weight) and xylazine (10mg/kg of body weight). Animals were perfused with ice-cold 0.1M phosphate-buffered saline (PBS), brain were extracted and post-fixed overnight in 2% PFA at 4°C, then sliced on a vibratome (Leica) at 40µm thickness. Free-floating sections were washed in 0.1M PBS and incubated for 2h at room temperature (RT) in blocking solution containing 4% normal donkey serum (NDS) and 0.4% Triton X-100 in 0.1M PBS, before overnight incubation at 4°C with primary antibodies diluted in blocking solution. The next day, after three washes in 0.1M PBS, sections were incubated with secondary antibodies and/or Lycopersicon Esculentum (Tomato) Lectin DyLight® for 2h. Sections were again washed, counterstained with DAPI, then mounted and coverslipped with ProLong Diamond Antifade Mountant (Invitrogen). Antibodies and concentration used are listed in **Suppl.Table 13.**

Twenty-micrometer-thick z-stack images of the region of interest were acquired on an LSM-700 microscope with Apotome (Carl Zeiss). Images were taken using a 40x lens. For pericyte coverage analyses, 12 planes from 3 non-consecutive sections were acquired from each animal and analysed in Imaris 9.6.1 software (Oxford Instruments, UK).

Immunohistochemistry and quantification of human pericyte morphology. 20-µm human PFC sections on slides were post-fixed for 10 min in ice-cold methanol before a quick wash in 0.1M PBS. Sections were incubated for 2h in blocking solution containing 4% NDS, 0.4% Triton X-100 in 0.1M PBS before being incubated overnight at 4°C in rabbit anti-PDGFRB (1:250, Abcam, ab32570) and sheep anti-CD31 (1:50, R&D, AF806). The next day, slides were washed three times in 0.1M PBS before incubation in anti-rabbit Alexa-Fluor 647 and anti-sheep Alexa-Fluor 594 for 2h at RT. Slides were washed, counterstained with DAPI, mounted and coverslipped with with ProLong Diamond Antifade Mountant (Invitrogen).

Five-micrometer-thick z-stack images of the region of PFC were acquired on an LSM-700 microscope with Apotome (Carl Zeiss). Images were taken using a 20× lens with a resolution of 2464x2056. Scaling was 0.173 µm x 0.173 µm x 1 µm in the x−y−z planes. Six planes from 2 sections were acquired from each individual and analysed with the Imaris 9.6.1 software (Oxford Instruments, UK).

Transmission electron microscopy (TEM). 24h after the SI test, mice were anesthetized with a mixture ketamine (100mg/kg of body weight) and xylazine (10mg/kg of body weight). Animals were perfused with ice-cold 0.1M PBS followed with a mixture of 4% PFA and 2% glutaraldehyde in 0.1M PB. Brains were isolated and sectioned at 50mm using a Leica VT1000S vibratome (Leica Biosystems). Post-fixation and resin embedding were performed as previously described by Deerinck et al. (2022). Briefly, 50mm-brain sections were washed in PBS and incubated in 3% potassium ferrocyanide and 4% aqueous osmium tetroxide in 0.1M PB (pH 7.4) for 1h at room temperature, followed by incubation in a thiocarbohydrazide (1% w/v) solution at room temperature for 20 mins. Sections were subsequently incubated for 30 mins in a 2% aqueous osmium tetroxide solutionand dehydrated by increasing ethanol concentrations followed by propylene oxide. Afterward, post-fixed sections were embedded in Durcupan ACM Epoxy resin (Sigma-Aldrich) between ACLAR sheets at 55°C for 72h. Ultrathin sections were generated at

80nm using a Leica EM UC6 ultramicrotome. Ten capillaries per animal were randomly photographed using a JEM-1400Flashtransmission electron microscope operating at 80kV and equipped with a 16MP digital camera (GATAN One View). For each capillary, a whole vascular profile (6000x) and a high-magnification mosaic (20,000x) were acquired for further analysis. Quantification of images was performed blindly in ImageJ.

Focused Ion Beam-Scanning Electron Microscopy (FIB-SEM). Sections containing region of interest were excised from ACLAR sheets and glued to Durcupan ACM Epoxy resin (Sigma-Aldrich) blocks. Tissue face was polished using a Leica Artos 3D ultramicrotome. Tissue containing resin block was cut, glued onto aluminum stub (Ted Pella) using CCC carbon adhesive paint (EMS), and coated with 30 nm of platinum using a Leica EM ACE600 sputter coater. The stub was loaded into a Zeiss Crossbeam 350 FIB-SEM. Region of interest containing blood vessel(s) was identified and ATLAS Engine 5 software (Fibics) was used to complete volume image acquisition. Briefly, exact region of interest was protected with platinum deposition and FIB trenching was performed to expose tissue face. Next, images were acquired at 5 nm resolution in x-and-y using the SE2 detector and SEM voltage at 1.4kV. Milling was performed at 20nm steps in z-direction using the FIB with the voltage at 30kV and current at 700pA. Image stacks were aligned, exported as TIFs, and uploaded into webKnossos software[7]. After unsupervised segmentation was performed and appropriate post-hoc corrections were completed, pericyte and endothelial morphologies and contacts were visualized.

Region-specific ablation of pericytes. This experiment was adapted from previously published work[8,9]. At 7 weeks of age, female and male *PDGFRβ-CreERT2-iDTR* mice were injected intraperitoneally with tamoxifen (40 mg/kg of body weight diluted in corn oil, Sigma Aldrich) for 5 days and allowed to recover for 72h before stereotaxic injections. All surgeries were performed under aseptic conditions using anesthetic as previously described[8]. Mice were anesthetised with isoflurane (3-4% in O_2 for induction and 1-1.5% in O_2 for maintenance at 1L/min flow rate) and positioned in a small stereotaxic instrument (Harvard Apparatus). The skull surface was exposed, and 0.1 ng in 0.5 µL of diphtheria toxin (Sigma Aldrich) or vehicle (VEH, saline) was bilaterally infused in the PFC (bregma coordinates: anteroposterior +1.80mm; mediolateral +/- 0.35mm; dorsoventral -2.35mm), at a flow rate of 0.1µl/min. Mice were allowed to recover for 7 days before assessment of social, anxiety and depressive-like behaviors. After the last behavioral test, brains were collected to confirm pericyte depletion by immunohistochemistry.

Bioluminescence for PHP.V1 serotype. To confirm that systemic injection of the PHP.V1 serotype could cross the BBB, 6-weeks old female CD1 mice were intravenously injected with an AAV2/PHP.V1-P2Pdgfb-Luc or an AAV2/PHP.V1-CAG-PDGFb-P2A-Luciferase (PHP.V1-Luc) AAV2/9-CAG-Luciferase (AAV2/9-Luc), a serotype with known limited penetration and CNS transduction[10,11]. CD1 mice were used for this experiment since black fur of C56BL/6J mice is not suitable for bioluminescence imaging[12]. At each timepoint, mice were intraperitoneally injected with D-Luciferine (Thermo Fisher, 150mg/kg of body weight) 25-30 minutes prior to imaging on the IVIS Spectrum 200 (Perkin Elmer, exposure time: 2 min). Mice were kept under isoflurane anesthesia during procedure (3-4% in O_2 for induction and 1-1.5% in O_2 for maintenance at 1L/min flow rate). Animals were imaged at the following time points: 1h prior to viral injection (baseline), D14, D21, D28, D35, D42.

Viral modulation of brain Pdgfb expression. At 6 weeks of age, C57BL/6J female mice were intravenously injected with $2x10^{10}$ VG of AAV2/PHP.V1- CAG-*PDGFb*-T2A-eGFP (PHP.V1-

Pdgfb) or AAV2/PHP.V1-CAG-eGFP (PHP.V1-GFP). A first cohort was subjected to a battery of depression- and anxiety-related behaviors in the absence of acute or chronic stressors. A second cohort was injected and exposed to 10-d CSDS before being subjected to the same battery of depression- and anxiety-related behaviors.

Electrophysiological recordings. Electrophysiological recordings were performed as previously described[13]. For the pericyte depletion cohort, female *PDGFRβ-CreERT2-iDTR* mice were injected intraperitoneally with tamoxifen for 5 days and allowed to recover for 72h before PFC stereotaxic injections of DTX or VEH. Mice were allowed to recover for 8 days before electrophysiological recordings of PFC pyramidal neurons (3 mice per group). For the PHP.V1 virus cohort, C57BL/6J female mice were intravenously injected at 6 weeks of age with $2x10^{10}$ VG of PHP.V1-*Pdgfb* or PHP.V1-GFP and allowed to recover for 21 days for virus expression (4 mice per group). The day of recordings, mice were anesthetized with isoflurane and transcardially perfused with 10 mL of an ice-cold and freshly prepared NMDG-artificial cerebrospinal fluid (aCSF) solution containing: 1.25 mM NaH_2PO_4, 2.5 mM KCl, 10 mM $MgCl_2$, 20 mM HEPES, 0.5 mM $CaCl_2$, 24 mM $NaHCO_3$, 8 mM D-glucose, 5 mM L-ascorbate, 3 mM Na-Pyruvate, 2 mM Thiourea 93 mM NMDG (osmolarity adjusted with sucrose to 300–310 mOsmol/l) and 2 mM kynurenic acid. Brains were then sliced at 250 µm in ice-cold perfusion solution. Then, slices were immersed in a 32°C oxygenated perfusion solution for 10 minutes, before being incubated in HEPES-aCSF solution (1.25 mM NaH2PO4, 2.5 mM KCl, 10 mM MgCl2, 20 mM HEPES, 0.5 mM CaCl2, 24 mM NaHCO3, 2.5 mM D-glucose, 5 mM L-ascorbate, 1 mM Na-Pyruvate, 2 mM Thiourea, 92 mM NaCl, 20 mM Sucrose for 1h at room temperature. Finally, slices were transferred to a recording chamber on the stage of an upright microscope (Zeiss) where it was perfused at a rate of 3–4 ml/min with artificial cerebrospinal solution (aCSF in mM: 120 NaCl, 5 HEPES, 2.5 KCl, 1.2 NaH_2PO_4, 2 $MgCl_2$, 2 $CaCl_2$, 2.5 glucose, 24 $NaHCO_3$, 7.5 sucrose). The perfusion chamber and the aCSF were kept at 32°C and all solutions were oxygenated at 95% O_2 and 5% CO_2. A water immersion x60 objective and a video camera (Zeiss, Germany) were used to visualize the glutamatergic pyramidal neurons in the mPFC. Whole-cell voltage-clamp recordings were performed with an Multiclamp 700B amplifier (Molecular Devices, San Jose, CA) using borosilicate patch electrodes (3-5 MΩ resistance). Pipettes were filled with an intracellular patch solution containing (in mmol/l): 115 Cesium methanesulfonate, 20 Cesium chloride, 10 HEPES, 2.5 MgCl2, 4 Na2-ATP, 0.4 Na-GTP, 10 Na-phosphocreatine, 0.6 EGTA, 5 QX314 and 0.2% Biocytin (pH 7.35). Signals were filtered at 5 kHz using a Digidata 1500B data acquisition interface (Molecular Devices, San Jose, CA) and acquired using pClamp 10.6 software (Molecular Devices, San Jose, CA). Pipette and cell capacitances were fully compensated. Passive membrane properties were measured. Spontaneous excitatory postsynaptic currents (sEPSCs) were recorded at -60 mV, and spontaneous inhibitory postsynaptic currents (sIPSCs) at 0 mV. A total of 63 neurons (27 neurons in 6 mice for pericyte ablation experiments, and 36 neurons from 8 mice in PHP.V1 experiments) was recorded. For the neurons where both sEPCSs and sIPSCs were recorded, a frequency ratio of sEPSCs/sIPSCs was calculated.

Human *postmortem* tissue collection. As previously described[4], human brains were collected and NAc or PFC tissue samples dissected by the Suicide section of the Douglas-Bell Canada Brain Bank (DBCBB; https://douglasbrainbank.ca) under the approval of the institution's Research Ethics Board. All brains are donated to the Suicide section of the DBCBB by familial consent through the Quebec Coroner's Office. In addition to consenting to tissue donation for research and access to relevant (including medical) files, families agree to participate in the psychological

autopsy that is conducted two months after the death of their next of kin. Blood toxicology was performed and individuals with evidence of drugs or psychotropic medications were excluded. Individuals with a known history of neurological disorders or head injury were also excluded. Demographic characteristics associated with each sample are listed in **Suppl.Table 3.** Clinical records and interviews were obtained for each case and reviewed by three or four mental health professionals to establish independent diagnoses followed by a consensus diagnosis in line with the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Groups were matched as closely as possible for gender, age, race, pH, postmortem interval. All experiments were performed with the approval of Université Laval and CERVO Brain Research Center Ethics Committee Neurosciences et santé mentale (Project #2019-1540).

Human blood collection and serum extraction. All human blood serum samples were provided by Signature Bank from the Centre de recherche de *l'Institut universitaire en santé mentale de Montréal* (CR-IUSMM) under approval of the institution's Ethics Committee. Samples from volunteers with MDD or BPD were collected at the emergency room of the *Institut Universitaire en santé Mentale de Montréal* of CIUSSS de l'Est-de-Montreal and samples from healthy volunteers at the CRIUSMM. All donors provided informed consent and signed a 7-page document detailing the goals of the Signature Bank, participants' involvement (questionnaires and tissue sampling), advantages vs risks, compensation, confidentiality measures, rights as participant and contact information. Subjects with a known history of drug abuse were excluded. Demographic characteristics associated with each sample are listed in **Suppl. Table 11.** Depressive behaviours were assessed by the Patient Health Questionnaire (PHQ-9), which scores each of the nine Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria[14]. All experiments were performed under the approval of Université Laval and CERVO Brain Research Center Ethics Committee Neurosciences et santé mentale (Project #2019-1540).

Quantification of human and mouse serum analytes. Human or mouse soluble PDGF-BB levels were assayed using the Bio-Plex Human Cytokine PDGF-BB Set (Bio-Rad #171B5024M) or the Bio-Plex Mouse Cytokine PDGF-BB Assay (#ZD0000003N), respectively and according to the manufacturer's protocol. Plates were read on a Bio-Plex 3D system (Bio-Rad) with 50 bead events per well, and data reduced against a four-parameter logistic curve using the Gen 5.0 software. Samples with a coefficient of variation above 20% between duplicates were removed from the analysis.

Cell culture experiments.

Cell lines. Mouse brain endothelial cells (bEnd.3i) were purchased from ATCC (# CRL-2299) and cultured according to manufacturer's instructions. Human brain endothelial cells (HBEC) and Human brain vascular pericytes (HBVP) were purchased from ScienCell (#1000 and #1200, respectively) and cultured according to manufacturer's instructions. bEND.3i and HBEC were cultured on 0.1% (w/v) gelatin-coated vessels in Dulbecco's Modified Eagle Medium F12 (DMEM: F12, Gibco #11330033) supplemented with 10% Fetal Bovine Serum (FBS, Corning #35-077-CV), 1X Endothelial cell growth supplement (ECGS, ScienCell #1052) and Gentamicin (25µg/mL, ThermoFisher # 15750060). HBVP were cultured on poly-D-lysine-coated vessels (PDL, 5µg/cm^2, Sigma-Aldrich #A-003-M) in Pericyte Medium (ScienCell #1201). For all experiments detailed below, cell seeding densities were determined according to manufacturer's

recommended densities, unless stated otherwise (bEND.3i/HBEC: 5 x 10^4 cells/cm^2, HBVP: 6 x 10^4 cells/cm^2). Cells were used between passages (P)3 and P5, inclusively.

Transcriptional profiling of virus-infected cells. bEND.3i were seeded on a 6-well plate. Once confluent, cells were infected with PHP.V1-GFP or PHP.V1-*Pdgfb* (1x10^6 VG per well) for 72h (n=6 per group). This timepoint was previously validated to efficiently transduce endothelial cells *in vitro*[10]. Then, cells were collected in 0.5 mL Trizol and processed as described above (see *Transcriptional profiling of mouse tissue*) for qPCR.

Transendothelial Electrical Resistance (TEER). bEND.3i were seeded on 12-mm transwell polycarbonate culture inserts (Millicell, Millipore #PITP01250) with 3 μm pore size (n=2 per group) Three days later, cells were infected with PHP.V1-GFP or PHP.V1-Pdgfb (1x10^6 VG per well) and TEER measurements were taken using the Millicell® ERS-2 Electrical Resistance System. Gelatin-coated insert with no cells was used as a blank. Electrodes were habituated in complete growth media at room temp for 10 mins before reading resistance across cell monolayers. TEER was calculated as resistance of sample minus resistance of blank, multiplied by membrane surface area (0.6 cm^2) and normalized to PHP.V1-GFP.

Scratch wound assay. bEND.3i were seeded in a 24-well plate. Once confluent, cells were infected with PHP.V1-GFP or PHP.V1-Pdgfb (1x10^6 VG per well) for 72h (n=4 per group). Then, a vertical wound was introduced down the center of each well. Cells were washed with PBS and provided with fresh medium. Brightfield wound images were immediately acquired (baseline, T0) then 1, 6 and 24h later. Images were blindly processed using the Wound Healing plugin in ImageJ. Briefly, relative wound healing was determined as % image area devoid of cells using T0 value as 0% (with 100% being a well where cell density inside the wound is the same as the cell density outside the initial wound).

***In vitro* exposition to human serum.** This experiment was adapted from previous studies[15,16]. To minimize intra-individual variability of serum contents and maximise reproducibility across experiments, age-matched groups of pooled serum (n=15 individuals per group) were created based upon PHQ-9 scores (CTRL: PHQ-9 total score < 4 without anhedonia or depressed mood, MDD: PHQ-9 total score > 15 with anhedonia and depressed mood).
For direct serum exposition studies, HVBP were incubated with 10% CTRL or MDD pooled serum in fresh media for 24h. Then, serum was replaced with fresh media for an additional 24h to produce pericyte secretome. Both cells and secretome were then collected for downstream experiments.
For indirect serum exposition studies, HBEC were first incubated with 10% CTRL or MDD pooled serum in fresh media for 24h. Then, serum was replaced with fresh media for an additional 24h to produce endothelial secretome. Subsequently, 100 μL of endothelial secretome was collected for downstream experiments and the rest was transferred to naïve HBVP for 24h. At this point, HBEC were collected. Finally, HBVP were provided with fresh media for an additional 24h to produce pericyte secretome, after which HBVP and secretome were collected for downstream experiments.

Flow cytometry for PDGFRβ internalization. This experiment was performed as previously described with minor modifications[17]. HBVP were grown in a 12-well plate and treated for 3h or 24h, then dissociated using StemPro Accutase for 5 mins at 37°C (Gibco, A11105). Samples were passed through a 70 μm cell strainer (Miltenyi #130-110-916) and centrifuged at 300g for 5 mins. Supernatant was removed and pellets were resuspended in cold buffer (1% FBS in PBS) as a wash.

For cell surface PDGFRβ labelling, samples were centrifuged at 300g for 5 mins and supernatant discarded before incubation with anti-human CD140b-PE (BD Biosciences, #558821) for 20 mins, on ice. Next, cells were washed in 1 mL cold buffer and centrifuged again at 300g for 5 mins. Supernatant was discarded and pellet was resuspended in 7-aminoactinomycin D (7-AAD, 5 µL in 100 µL cold buffer, BD Biosciences #51-68981E) for 15 mins. Volume was adjusted to 300 µL with cold buffer and fluorescence was measured on a BD LSR II. At least 10,000 events were gated based on forward and side scatter, excluding 7-AAD+ cells. Gating strategy is shown in **Suppl.Fig.8**. For total PDGFRβ labelling, cells in cold buffer were fixed by adding an equal volume of 8% PFA for 20 mins. Then, cells were washed and permeabilized with PBS+0.1% Triton X-100 and centrifuged at 300g for 5 mins. Supernatant was discarded and pellets were resuspended in anti-human CD140b-PE for 20 mins, at RT. Cells were washed once more in cold buffer, supernatant discarded and resuspended 7-AAD for 15 mins. Volume was adjusted to 300 µL with cold buffer and fluorescence was measured on a BD LSR II. At least 10,000 events were gated based on forward and side scatter, including 7-AAD+ cells. A small volume of fixed cell suspension was mounted on a slide and imaged. Data were analyzed with FACS Diva software (BD Biosciences, v.6.1.3).

Protein extraction, SDS-PAGE and Western blotting. HBVP were treated with human serum as described above for 3h, before collection in Lysis buffer (Cell Signaling #9803S) supplemented with protease inhibitor cocktail (Cell Signaling #5871). Samples were incubated for 30 mins on ice before centrifugation at 13 000 rpm for 10 mins, at 4°C. Protein concentrations were determined using the Pierce BCA Protein Assay Kit (Thermo 23225). Equal amounts of protein samples were separated by SDS-PAGE (4–15% polyacrylamide gels, Bio-Rad #4568084) and transferred to PVDF membranes (0.45 µm pore size, Milipore IPFL00005). Then, membranes were blocked with 5% BSA in Tris-Buffered saline supplemented with 0.1% Tween-20 (TBST) for 1h on agitation and incubated overnight with primary antibodies. The next day, membranes were washed 3x10-min with TBST and incubated for 2 h with secondary antibodies. Membranes were washed four more times with TBST and then antibody binding was detected using Clarity Max ECL Substrate-Luminol Solution (Bio-Rad #1705062) and Bio-Rad Molecular Imager ChemiDoc XRS detection system with Image Lab software. Quantification was performed with Image J (NIH). Antibodies and concentrations are listed in **Suppl. Table 13**.

Quantification of cell secretome. Secretome samples were kept at -80°C until use. Levels of human IL-6, IL-8, MCP-1 and CX3CL1 levels assayed using the Bio-Plex Human Chemokine Assay (Bio-Rad # 171AK99MR2) according to the manufacturer's protocol. Plate was read on a Bio-Plex 3D system (Bio-Rad) with 50 bead events per well, and data reduced against a four-parameter logistic curve using the Gen 5.0 software. Samples with a coefficient of variation above 20% between duplicates were removed from the analysis.

Illumina NovaSeq RNA-sequencing for mouse microvessels. RNA was extracted and RNA integrity (RIN) and concentration were assessed using a Bioanalyzer. Unstranded libraries were generated, and samples sequenced with the Illumina NovaSeq 6000 system. The quality of the raw reads was assessed with FASTQC v0.12.1. After examining the quality of the raw reads, no trimming was deemed necessary. The reads were aligned to the GRCm39 reference genome with STAR v2.7.11b with mean of 76 % of reads uniquely mapped. The raw counts were calculated with FeatureCounts v2.0.6 based on the GRCm39 reference genome (release 110). Differential

expression was performed using DESeq2 R package. DEGs heatmap was drawn based on z-score of normalized count. Bioinformatics analyses were performed at the Bioinformatics core facility from Montreal Clinical Research Institute (IRCM). Graphs including Venn diagrams and volcano plots were generated using publicly available R packages.

Illumina NovaSeq RNA-sequencing for human cells. RNA was extracted with TRIzol (Invitrogen) homogenization and chloroform layer separation using the Pure Link RNA mini kit (Life Technologies), then sent to Genome Quebec. RNA integrity (RIN) and concentration were assessed using a Bioanalyzer. Quality control was performed with the Bioanalyzer, libraries generated, and samples were sequenced with the Illumina NovaSeq 6000 system. Quality of the raw reads was assessed with FASTQC v0.11.9. After examining the quality of the raw reads, trimming was performed with TRIMMOMATIC v0.39. Reads were aligned to the human reference genome with STAR v2.7.9a with mean of 87 % of reads uniquely mapped. The raw counts were calculated with FeatureCounts v2.0.3 based on the human reference genome (release 109). Differential expression was performed using DESeq2 R package. DEGs heatmap was drawn based on z-score of normalized count. Functional enrichment analysis of DEGs (gene ontology and pathway enrichment) was performed with the gprofiler2 R package by the Bioinformatics core facility from Montreal Clinical Research Institute (IRCM). Graphs including heatmaps, Radar charts and Circos plot were generated using publicly available R packages.

Statistical analysis. The sample size for CSDS, virus-injected mouse cohorts as well as cell culture studies was calculated based on previous studies[1-4,17,18]. For studies involving human tissue (e.g post-mortem brain tissue, sera, etc.), sample size was not calculated due to scarcity of available material. In that case, all available samples were used. All mice were assigned to stress-susceptible (SS) or resilient (RES) groups based on their behavioural profile when compared to unstressed controls (CTRL). SI screening and behavioural tests were performed with automated tracking systems when possible. If not (for splash test, sucrose preference test and forced swim test), scoring was done by experimenters blinded to experimental conditions. Outliers for behavioural testing or qPCR normalized values were identified as being greater than 2 standard deviations SD from the group mean and excluded from statistical analysis. For behavioral cohorts, an animal found to be an outlier for at least 2 behavioural tests was removed completely from all further analyses. Normality was determined by D'Agostino–Pearson, Shapiro–Wilk and Kolmogorov–Smirnov normality tests using GraphPad Prism software (version 10.0). For normally distributed datasets, t-tests, one-way ANOVAs, two-way ANOVAs, and Pearson's correlations were performed with GraphPad Prism software. Tukey was used as a post hoc test when appropriate for one-way ANOVAs. Non-normally distributed datasets were analyzed with non-parametric Mann−Whitney or Kruskal−Wallis tests for two or three groups, respectively. Dunn's was used as post hoc test when appropriate for non-parametric ANOVAs. Ficher's LSD was used as post hoc for two-way ANOVAs when appropriate. Statistical significance was set at $p < 0.05$ with *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$. P-values between 0.05 and 0.1 were considered as trending (#) without reaching significance. For detailed statistics, please refer to the Excel spreadsheet provided in the ***Supplementary Information***. Heatmap representation of average and SEM in Figure 1 and others was done using Matlab-based software. Individual values were used to compute correlation matrices and p values were determined by Matlab-based software. All qPCR, immunohistochemistry and transcriptional quantification were performed in at least two different cohorts of mice. Principal component analyses (PCAs) were computed in R using the FactoMineR

package. Violin plots show the frequency distribution of the data. Full lines represent the median and dotted lines represent the first and third quartiles. Number of animals or subjects (n) is indicated on graphs. Source data are provided as a Source Data file.

Data availability statement. All data supporting the findings of the study are available within the paper and Supplementary Information files. Requests for additional information should be addressed to the corresponding author.

Methods References

1 Golden, S. A., Covington, H. E., 3rd, Berton, O. & Russo, S. J. A standardized protocol for repeated social defeat stress in mice. *Nat Protoc* **6**, 1183-1191 (2011). https://doi.org:10.1038/nprot.2011.361

2 Menard, C. *et al.* Social stress induces neurovascular pathology promoting depression. *Nat Neurosci* **20**, 1752-1760 (2017). https://doi.org:10.1038/s41593-017-0010-3

3 Dudek, K. A. *et al.* Molecular adaptations of the blood-brain barrier promote stress resilience vs. depression. *Proc Natl Acad Sci U S A* **117**, 3326-3336 (2020). https://doi.org:10.1073/pnas.1914655117

4 Dion-Albert, L. *et al.* Vascular and blood-brain barrier-related changes underlie stress responses and resilience in female mice and depression in human tissue. *Nat Commun* **13**, 164 (2022). https://doi.org:10.1038/s41467-021-27604-x

5 Harris, A. Z. *et al.* A Novel Method for Chronic Social Defeat Stress in Female Mice. *Neuropsychopharmacology* **43**, 1276-1283 (2018). https://doi.org:10.1038/npp.2017.259

6 Lee, Y. K., Uchida, H., Smith, H., Ito, A. & Sanchez, T. The isolation and molecular characterization of cerebral microvessels. *Nat Protoc* **14**, 3059-3081 (2019). https://doi.org:10.1038/s41596-019-0212-0

7 Boergens, K. M. *et al.* webKnossos: efficient online 3D data annotation for connectomics. *Nat Methods* **14**, 691-694 (2017). https://doi.org:10.1038/nmeth.4331

8 Nikolakopoulou, A. M. *et al.* Pericyte loss leads to circulatory failure and pleiotrophin depletion causing neuron loss. *Nat Neurosci* **22**, 1089-1098 (2019). https://doi.org:10.1038/s41593-019-0434-z

9 Willis, E. F. & Vukovic, J. Protocol for brain-wide or region-specific microglia depletion and repopulation in adult mice. *STAR Protoc* **1**, 100211 (2020). https://doi.org:10.1016/j.xpro.2020.100211

10 Ravindra Kumar, S. *et al.* Multiplexed Cre-dependent selection yields systemic AAVs for targeting distinct brain cell types. *Nat Methods* **17**, 541-550 (2020). https://doi.org:10.1038/s41592-020-0799-7

11 Song, R. *et al.* Selection of rAAV vectors that cross the human blood-brain barrier and target the central nervous system using a transwell model. *Mol Ther Methods Clin Dev* **27**, 73-88 (2022). https://doi.org:10.1016/j.omtm.2022.09.002

12 Ji, X., Adams, S. T., Jr. & Miller, S. C. Bioluminescence imaging in mice with synthetic luciferin analogues. *Methods Enzymol* **640**, 165-183 (2020). https://doi.org:10.1016/bs.mie.2020.04.033

13 Bittar, T. P. *et al.* Chronic Stress Induces Sex-Specific Functional and Morphological Alterations in Corticoaccumbal and Corticotegmental Pathways. *Biol Psychiatry* **90**, 194-205 (2021). https://doi.org:10.1016/j.biopsych.2021.02.014

14 Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* **16**, 606-613 (2001). https://doi.org:10.1046/j.1525-1497.2001.016009606.x

15 Cao, M. C. *et al.* Serum biomarkers of neuroinflammation and blood-brain barrier leakage in amyotrophic lateral sclerosis. *BMC Neurol* **22**, 216 (2022). https://doi.org:10.1186/s12883-022-02730-1

16 Stafford, P. *et al.* Astrocytes and pericytes attenuate severely injured patient plasma mediated expression of tight junction proteins in endothelial cells. *PLoS One* **17**, e0270817 (2022). https://doi.org:10.1371/journal.pone.0270817

17 Smyth, L. C. D. *et al.* Characterisation of PDGF-BB:PDGFRbeta signalling pathways in human brain pericytes: evidence of disruption in Alzheimer's disease. *Commun Biol* **5**, 235 (2022). https://doi.org:10.1038/s42003-022-03180-8

18 Hodes, G. E. *et al.* Sex Differences in Nucleus Accumbens Transcriptome Profiles Associated with Susceptibility versus Resilience to Subchronic Variable Stress. *J Neurosci* **35**, 16362-16376 (2015). https://doi.org:10.1523/JNEUROSCI.1392-15.2015