

Supplementary materials

1. Supplemental methods

1.1 Unpredictable Chronic Mild Stress (UCMS)

UCMS are performed according to previous publication with reasonable modifications^[1]. UCMS consists of a randomized schedule of 1-2 mild stressors per day and sustained for 5 weeks. Each stressor was used no more than three times during the whole period. The stressors used in this protocol are listed in Table S1. The application of stress starts at a different time every day to minimize its predictability (from 8:00 a.m. to 8:00 p.m.).

Table S1. Description of Stressors

Stressor	Duration
Forced swim	5 min
Restraint	1 h
Water deprivation	24 h
Isolation	24 h
Food deprivation	24 h
Wet bedding	24 h
No bedding	24 h
Tilt cages	24 h
Tail clipping	1 min (×3 times)
Crowded space	24h
Continuous illumination	24h

1.2 Behavioral tests

1.2.1 Forced Swim Test (FST)^[2]

- The glass cylinder is filled with water (23-25°C) to a height of 15 cm.
- On the first day, all mice are trained to swim for 15 minutes without monitoring.
- The next day, place mice in the water for 6 minutes. Locomotor activity is monitored using a video tracking system (EthoVision pro, Noldus Inc., Leesburg, VA). Immobility is defined as the absence of all movement except motions required to keep the animals head above the water, which is extracted calculated from the last four minutes of video.
- Dry mouse in a new cage with paper towels and heat lamps.

1.2.2 Sucrose Preference Test (SPT)^[3]

- Mice are presented to two drinking bottles: one containing 1% sucrose (w/v) and another water for 3 days in their home cage. The positions of two bottles are switched daily to reduce any confound produced by a side bias.
- Mice were fasted for 24 h, then separated single into a new cage and presented to two drinking bottles for two hours: one containing 1% sucrose and the other water, using the same kind of bottle and volume before.
- The intake of water and sucrose solution is measured by weighing changes in the bottles.

$$\text{Sucrose preference} = \frac{W(\text{sucrose solution})}{[W(\text{sucrose solution}) + W(\text{water})]} \times 100\%$$

1.2.3 Tail Suspension Test (TST)^[4]

- Bring the animals into the testing room for an acclimation period of one hour.
- Tape the tip of each tail using black electrical tape to a piece to the aluminum suspension bar and suspend the animal above the floor (20 cm).

- c) Record the movement of mice once all tapes are applied. After 6 min-testing, return the animals to their homecage and carefully remove the tape from each tail by gently pulling it off.
- d) Score the duration of immobility (defined as the absence of all movement except for those required for respiration) in the last 4 min of recording.

1.2.4 Open Field Test (OFT)^[5]

- a) The open filed consisted of a square arena (50 cm×50 cm) enclosed by continuous, 40.5 cm-high, light-gray opaque walls made of plexiglass. The apparatus is placed in a room illuminated by adjustable lamps giving a dim light within the arena (65 lux).
- b) Bring the animals into the testing room for an acclimation period of one hour.
- c) Mice are placed into the middle of one side of the arena facing the wall. The animals are allowed to move freely for 8 min, while their activity is monitored using a video tracking system (EthoVision pro, Noldus Inc., Leesburg, VA), and time spent (proportion) in the center zone was measured.
- d) After testing, mice are carefully removed from the open filed and returned to their home cage. The test equipment is cleaned with 70% ethanol and dried between subjects to avoid olfactory cuing.

1.2.5 Elevated Plus Maze (EPM)^[6]

- a) The apparatus is placed in an isolated room away from any extraneous interference of noises, scents, or movement, with adjustable lamps giving a dim light within the arena (65 lux).
- b) Bring the animals into the testing room for an acclimation period of one hour.
- c) The animal is placed in the center square of the maze facing one of the open arms (preferably the one opposite to the experimenter).
- d) After 5 min of free exploration, the mouse is moved out of the maze and back into its home cage. Behavior videotaped for 5 minutes, score entries into dark arms, entries into light arms, time in light arms is analyzed.
- e) The test equipment is cleaned with 70% ethanol and dried between subjects to avoid olfactory cuing.

2. Supplemental results

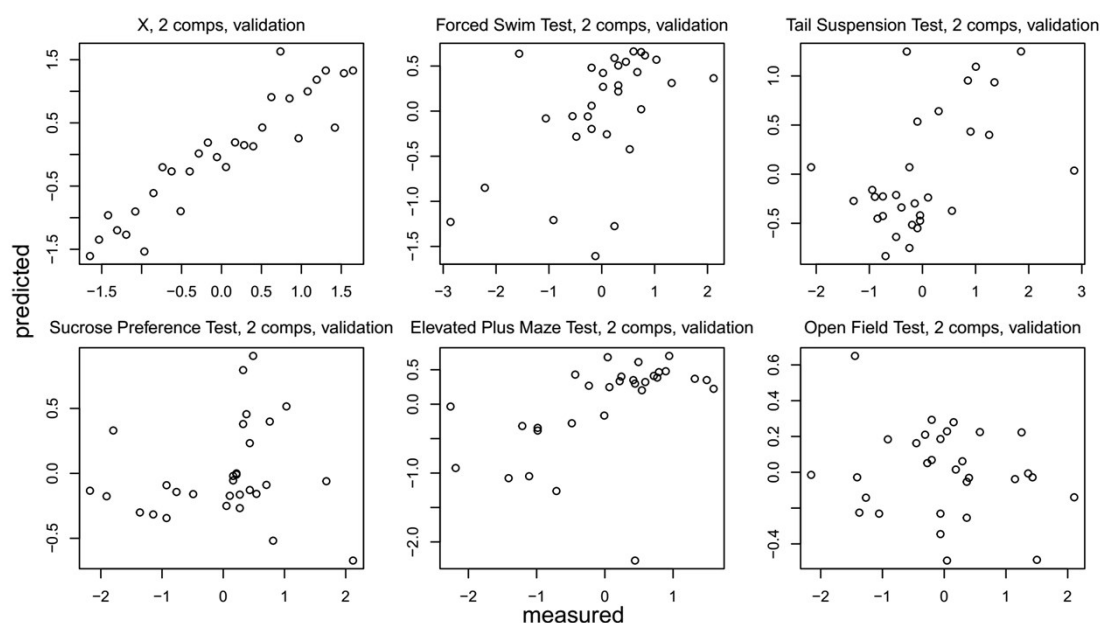


Figure S1 Cross-validated predictions for the neurobiological data.

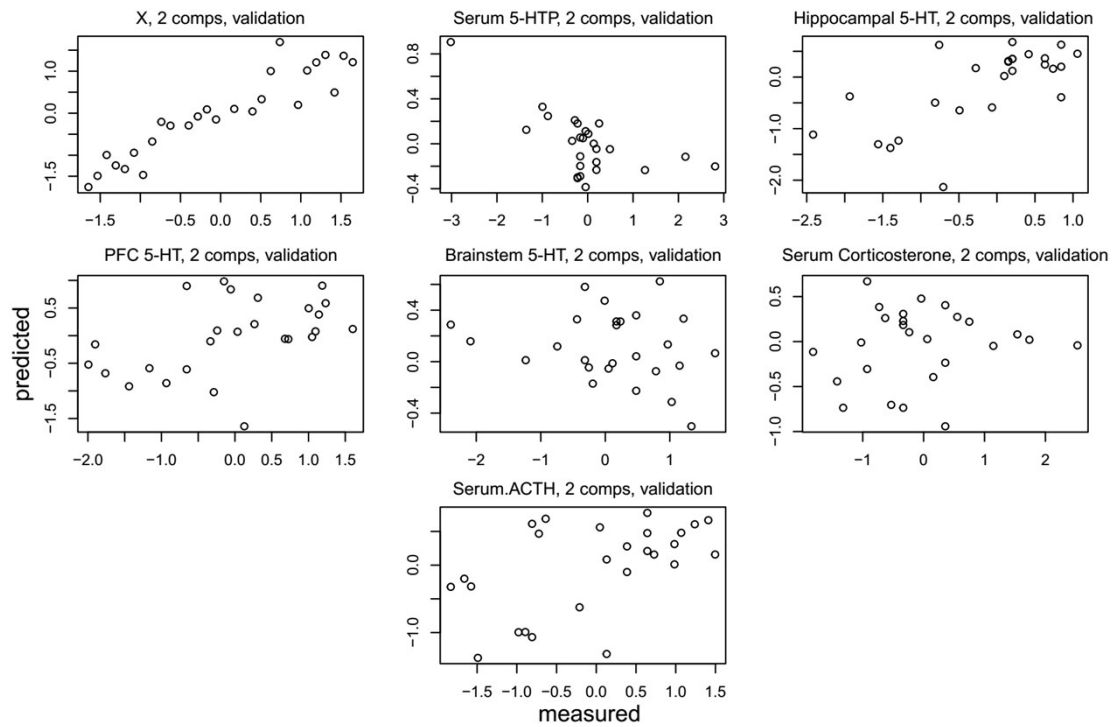


Figure S2 Cross-validated predictions for the neurobiological data.

3. Reference

- [1] Slattery D A, Cryan J F. Modelling Depression in Animals: At the Interface of Reward and Stress Pathways[J]. *Psychopharmacology*, 2017, 234(9-10): 1451-1465.
- [2] Slattery D A, Cryan J F. Using the Rat Forced Swim Test to Assess Antidepressant-Like Activity in Rodents[J]. *Nature Protocols*, 2012, 7(6): 1009-1014.
- [3] Liu M-Y, Yin C-Y, Zhu L-J, et al. Sucrose Preference Test for Measurement of Stress-Induced Anhedonia in Mice[J]. *Nature Protocols*, 2018, 13(7): 1686-1698.
- [4] Cryan J F, Mombereau C, Vassout A. The Tail Suspension Test as a Model for Assessing Antidepressant Activity: Review of Pharmacological and Genetic Studies in Mice[J]. *Neuroscience and Biobehavioral Reviews*, 2005, 29(4-5): 571-625.
- [5] Golden S A, Covington Iii H E, Berton O, et al. A Standardized Protocol for Repeated Social Defeat Stress in Mice[J]. *Nature Protocols*, 2011, 6(8): 1183.
- [6] Walf A A, Frye C A. The Use of the Elevated Plus Maze as an Assay of Anxiety-Related Behavior in Rodents[J]. *Nature Protocols*, 2007, 2(2): 322-328.