**Ref: JoVE58184R1  
Title:** The Unpredictable Chronic Mild Stress Mice Model of Depression   
**Journal:** JoVE

We would like to thank the editor for the enlightening comments which helped us to improve this manuscript significantly.

**Editorial Comments**

1. The editor has formatted the manuscript to match the journal's style. Please retain the same.

Answer: We have formatted the manuscript accordingly.

2. Please address all the specific comments marked in the manuscript.

Answer: Corrected.

3. Please change the title to reflect the protocol presented in the manuscript.

Answer: Title has been changed to reflect the protocol. The new title is: *"The Unpredictable Chronic Mild Stress Protocol for Inducing Anhedonia in Mice"*.

4. Please ensure that after formatting, the highlight is no more than 2.75 pages including heading and spacings as this is the upper limit for filming.

Answer: Highlights have been modified according to the limits.

5. The manuscript protocol talks about stress induction regime, however, no results are presented for this section. Please include a result to show how different stressors induce stress in mice. Also, please provide some marker studies to prove that indeed stress is induced in animals undergoing stressor treatment.

Answer: Results have been added to present both the efficacy of UCMS in inducing reduction in mice sucrose preference and in altering the density of a prominent biological marker of depression, namely hippocampal BDNF levels.

6. Screening for Antidepressant only present results for escitalopram and NHT. However there is a mention of other antidepressants as well in the protocol.Either move this to the discussion and specifically focus on the part you are doing or present the results for everything.

Answer: Doses of other antidepressants were moved to the discussion.

7. Sucrose consumption is not the standard test for depression. Please also show some marker stainings or western blots to corroborate the same.

Answer: Results of hippocampal BDNF levels (assessed via ELISA) were added to the results section to corroborate to anhedonic-like effect demonstrated in the sucrose preference test. However, anhedonia is a core factor in human depression, even conceptualized as an endophenotype of the disorder1, 2. Hence, the sucrose preference test is regarded an essential translational tool for modeling human depression in rodents3–6.

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2. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). *Diagnostic Stat Man Ment Disord 4th Ed TR*. 280, doi: 10.1176/appi.books.9780890425596.744053 (2013).

3. Treadway, M.T., Zald, D.H. Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neurosci Biobehav Rev*. **35** (3), 537–555, doi: 10.1016/j.neubiorev.2010.06.006 (2011).

4. Willner, P. Chronic mild stress (CMS) revisited: Consistency and behavioural- neurobiological concordance in the effects of CMS. *Neuropsychobiology*. **52** (2), 90–110, doi: 10.1159/000087097 (2005).

5. Willner, P., Towell, A., Sampson, D., Sophokleous, S., Muscat, R. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology (Berl)*. **93** (3), 358–364, doi: 10.1007/BF00187257 (1987).

6. Pothion, S., Bizot, J.C., Trovero, F., Belzung, C. Strain differences in sucrose preference and in the consequences of unpredictable chronic mild stress. *Behav Brain Res*. **155** (1), 135–146, doi: 10.1016/j.bbr.2004.04.008 (2004).