

Examining depressive-like phenotypes induced by chronic variable stress, using partial least squares

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Introduction

- Stressful life events often precede the onset of a major depressive episode¹.
- Depressive-like phenotypes induced by chronic variable stress (CVS), an animal model of depression, suggest that alterations between interconnected brain structures underlie depressive-like behavior.
- Goal:** We used structural magnetic resonance imaging (sMRI) along with behavioral assays to investigate latent associations between depressive-like brain and behavioral phenotypes induced by CVS in mice.

Methods

Figure 1

- Male mice were left undisturbed or exposed to a sex-specific CVS protocol².
- CVS consisted of one daily stressor:
 - 20min forced swim
 - 1hr tail suspension
 - 1hr restraint.
- We acquired T1-weighted sMRI (FLASH sequence, res: 100µm³) and behavioral assays (social preference and open field test)

Figure 2

Linear mixed effects models were used in all statistical analyses with subject ID as random effects, followed by Tukey HSD test post-hoc.

Figure 3

- Partial Least Squares correlation (PLSC) was used to identify linear combinations of changes in neuroanatomy (Z-scored NIfTI images of volumetric change measured by deformation-based morphometry), and z-scored measures of depressive- and anxiety-like behavior.
- Statistical significance and bootstrap ratio were evaluated using permutation testing (n=1000) and bootstrap resampling (n=1000), respectively. Bootstrap ratios were thresholded at values corresponding to a 95% confidence interval.

Conclusion

Using a hypothesis free data driven multivariate technique we identified that male mice exposed to CVS display changes in neuroanatomy associated with depressive- and anxiety-like behavior. The LV identified comprised neuroanatomical changes in brain regions that have been previously implicated in depressive-like phenotypes^{3,4}.

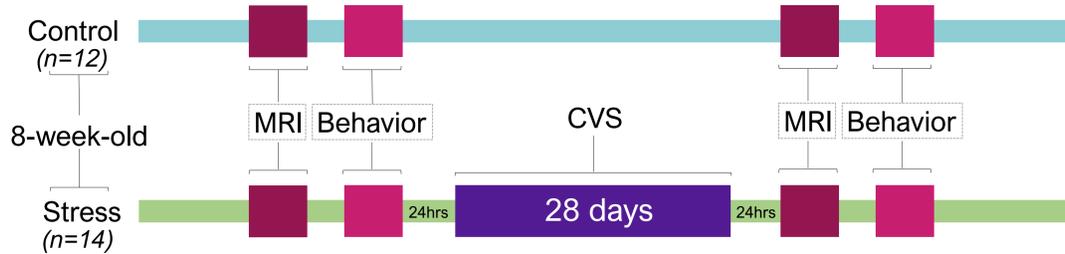
*The experiment was also performed in females (6 days of CVS²), however we did not observe a depressive-like phenotype thus results were not included.

References

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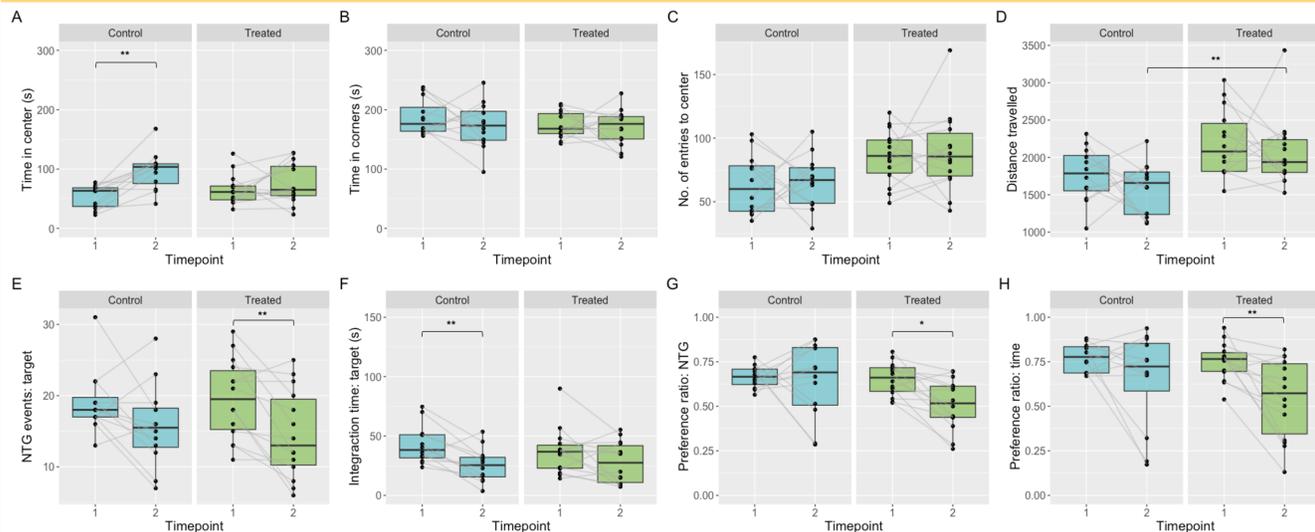
METHODS

Figure 1. Experimental timeline.



RESULTS

Figure 2. Behavioral tests.



Boxplots comparing behavioral metrics before and after CVS, top: open field test (A-D) and bottom: social preference tests (E-H). *p<0.05, **p<0.01. Blue: control. Green: stress.

- A-C) No significant differences in time spent in the center or corners of the open field area, nor in the number of entries to the center.
- D) Stressed mice showed increased distance travelled in the arena relative to controls (t=-2.914, p=0.02).
- E) Compared to baseline, stressed mice showed a significant decrease in NTG events (t=3.68, p=0.01).
- F) Control mice showed a significant decrease in the time spent interacting with a novel conspecific (t=3.23, p=0.01).
- G) Stressed mice showed a significant decrease in the preference ratio of NTG events (t=2.714, p=0.05) and H) interaction time (t=3.23, p=0.01).

RESULTS

Figure 3. PLSC.

First latent variable (LV) of PLSC analysis (54% of covariance explained, p<0.05).

- A) Covariance explained (left Y axis) and permutation p-values (right Y axis) for all 14 LVs in the analysis.
- B) Behavior weight for each behavioral measure included in the analysis. Size of the bar was estimated through singular value decomposition, confidence intervals were calculated by bootstrapping. Lines that cross the zero line should not be considered. Characterized by:
- Decreased NTG events, and in the preference ratio of social interactions and time spent interacting with a novel conspecific mouse.
 - Increased interaction time and NTG events with an empty cup. and time spent in the periphery of the open field arena
- C) Posterior to anterior view of brain bootstrapping ratios of deformation patterns overlaid on population average, warm colors (yellow-orange) indicate larger volume whereas cool colors (blue) indicate smaller volumes.
- D) Individual mouse brain and behaviour score, color coded by group with a trend line per group. Analyses were repeated without the outlier circled in black, we observed no changes.

