Chronic variable stress induces sex-specific depressive-like behavioral and brain changes in mice.

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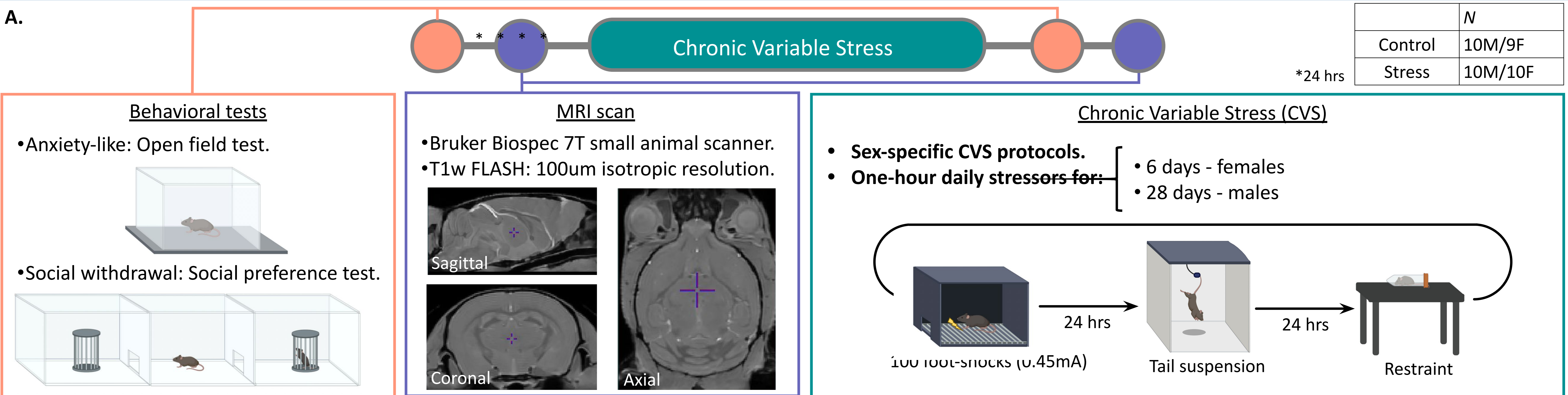
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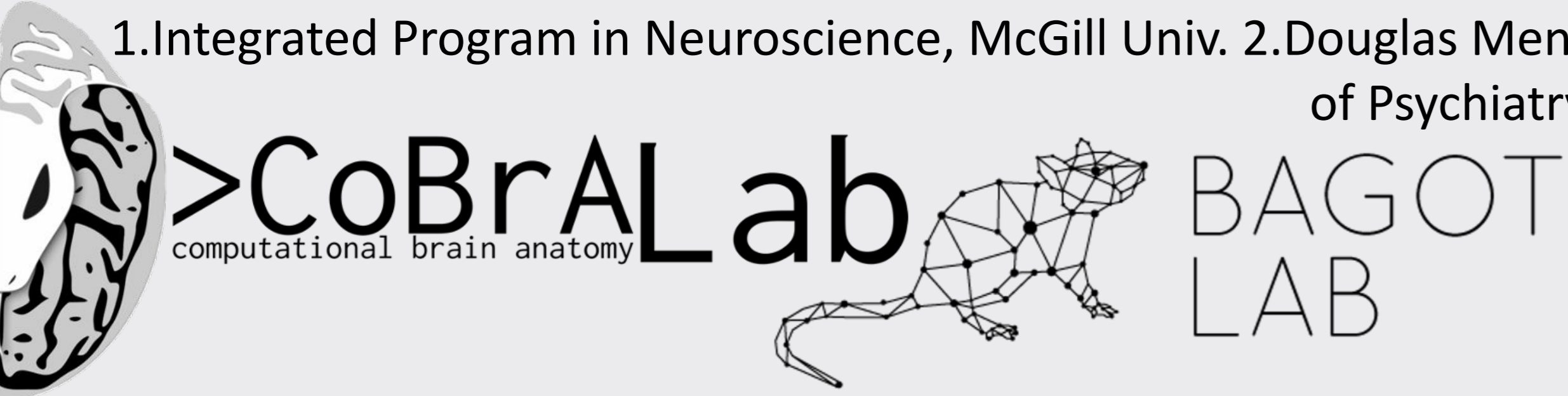
Background

- **Depressive disorders** are among the top leading causes of disability worldwide with 3.8% of the global population affected [1].
- There is a 1.7-fold greater incidence in women [2].
- **Stress** is a major risk factor for depression [3].
- Using chronic stress paradigms, animal models for depression, like chronic variable stress, reveal important **sex differences in stress susceptibility** [4].

Objective

We examined neuroanatomical remodeling associated with depressive- and anxiety-like behavior in chronically stressed male and female 8-week-old C57BL/6 mice.

Methods

	N
Control	10M/9F
Stress	10M/10F

*24 hrs

Behavioral tests
- Anxiety-like: Open field test.
- Social withdrawal: Social preference test.

MRI scan
- Bruker Biospec 7T small animal scanner.
- T1w FLASH: 100um isotropic resolution.

Sagittal / Coronal / Axial

Chronic Variable Stress (CVS)
- **Sex-specific CVS protocols.**
- **One-hour daily stressors for:**
  - 6 days - females
  - 28 days - males

100 foot-shocks (0.45mA) — 24 hrs — Tail suspension — 24 hrs — Restraint

B. Partial Least Squares

Brain volume (Jacobian Determinants) · Behavior · Correlation · Singular Value Decomposition · N Latent Variables · Behavior pattern · Brain pattern − / +
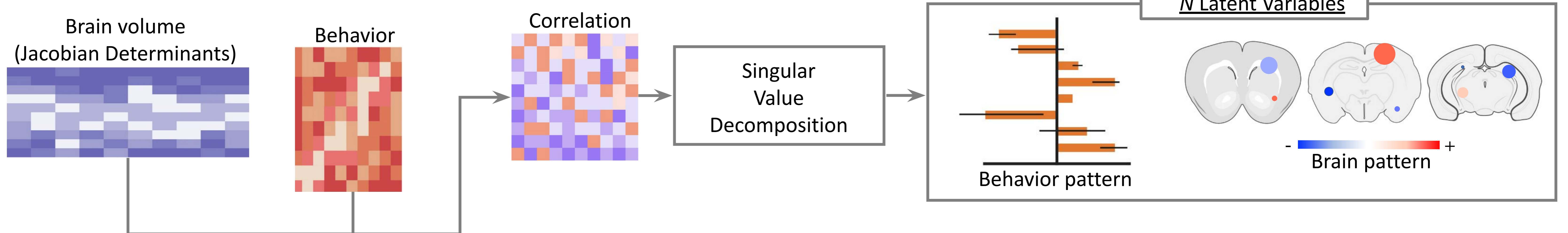
Figure 1. **A)** Longitudinal behavioral tests (pink) and MRI scans (purple) were acquired at baseline and 24-hours after the last stressor. T1w images were analyzed using longitudinal deformation based-morphometry. Linear mixed effects models were used to examine longitudinal behavioral and brain changes (fixed effects: group by timepoint interaction; random effects: subject; output: Jacobian determinants or behavior of interest; corrected with False Discovery Rate). **B)** Neuroanatomical changes were related to depressive- and anxiety-like behavior using partial least squares. Statistical significance and bootstrap ratio were evaluated using permutation testing (n=1000) and bootstrap resampling (n=1000). Bootstrap ratios were thresholded at values corresponding to 95% confidence interval.
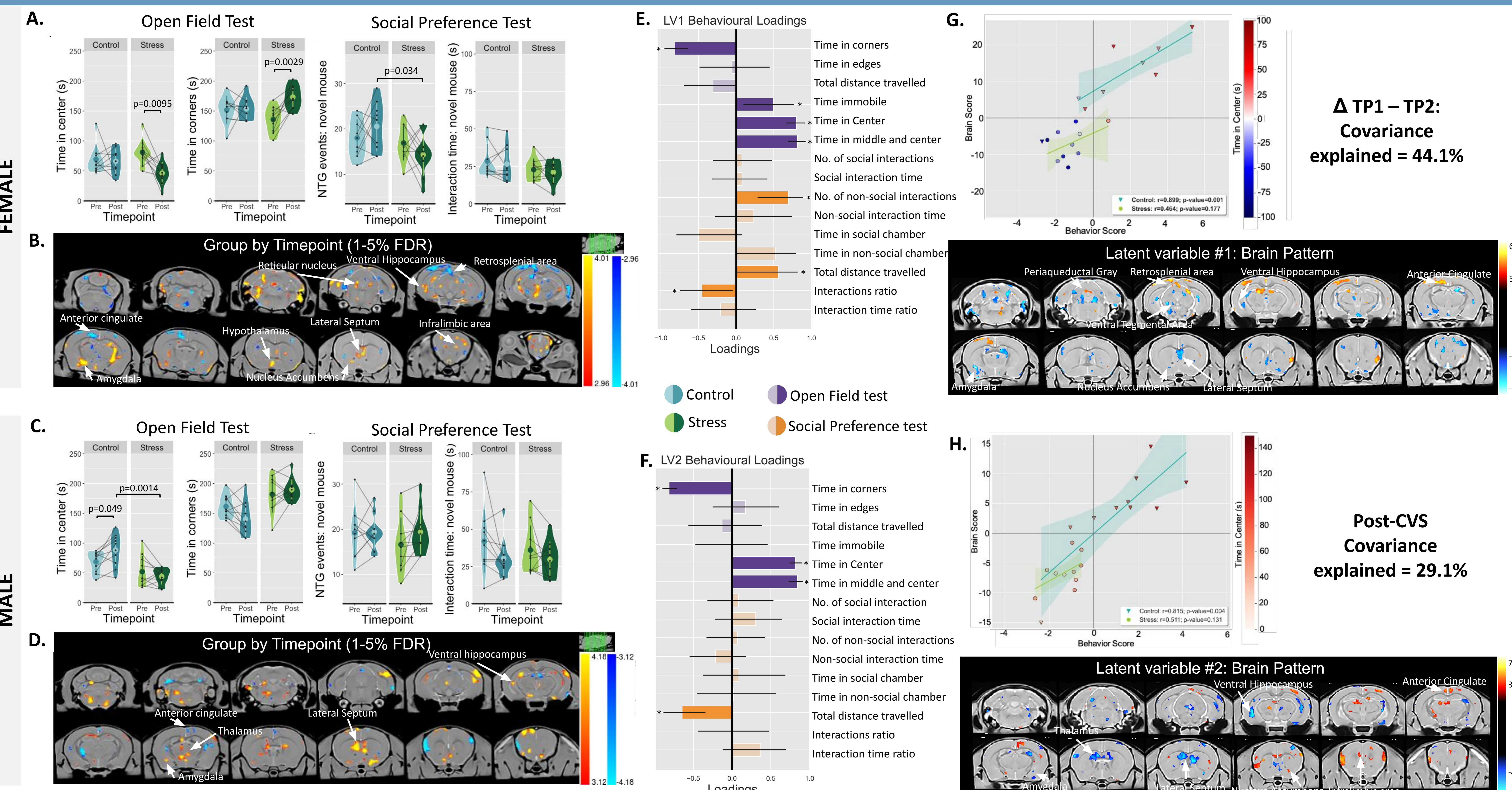

Results

FEMALE

A. Open Field Test / Social Preference Test

B. Group by Timepoint (1-5% FDR)

MALE

C. Open Field Test / Social Preference Test

D. Group by Timepoint (1-5% FDR)

E. LV1 Behavioural Loadings

F. LV2 Behavioural Loadings

Control · Stress · Open Field test · Social Preference test

G. Δ TP1 − TP2: Covariance explained = 44.1%

Latent variable #1: Brain Pattern

H. Post-CVS Covariance explained = 29.1%

Latent variable #2: Brain Pattern

Figure 2. **A and C)** Behavioral measures of anxiety-like behavior and social withdrawal. Light and dark colors denote pre- and post-CVS measures, respectively. **B and D)** Positive and negative t-statistics for volumetric brain changes. Warm colors: volumetric increases in stressed mice. Cool colors: decreased volume in stress mice. **E-H)** Significant latent variables (LVs) from partial least squares. **E and F)** Weights of each behavioral variable onto its respective LV. **G and H)** Top: Subject-specific brain and behavior scores, color coded trend line by group. Bottom: Weights of neuroanatomical changes onto its respective LV. Warm and cool colors denote positive or negative covariation with behaviors, respectively.

Conclusion

CVS induced both **sex-specific** and **shared** depressive-like changes in behavioral tests and sMRI. By using a data-driven approach we were able to identify sex-specific **phenotypes** that represented neuroanatomical changes specifically associated with **depressive-** and **anxiety-like behavior**.

References

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4. Hodes GE, et al. J Neurosci. 2015.