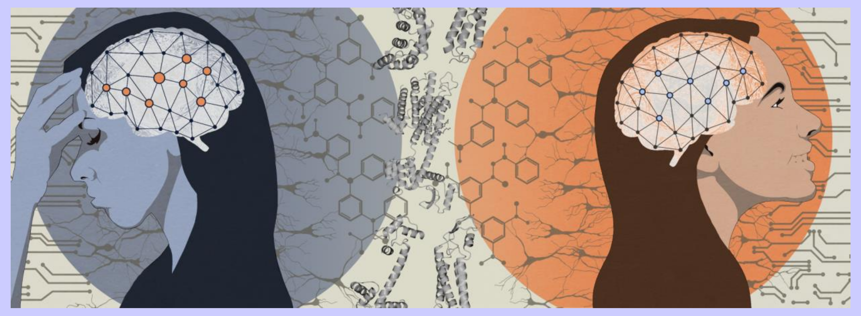
Stress, vulnerability, and the maternal experience: Electrical network and behavioral assessments of the maternal mouse brain



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Background

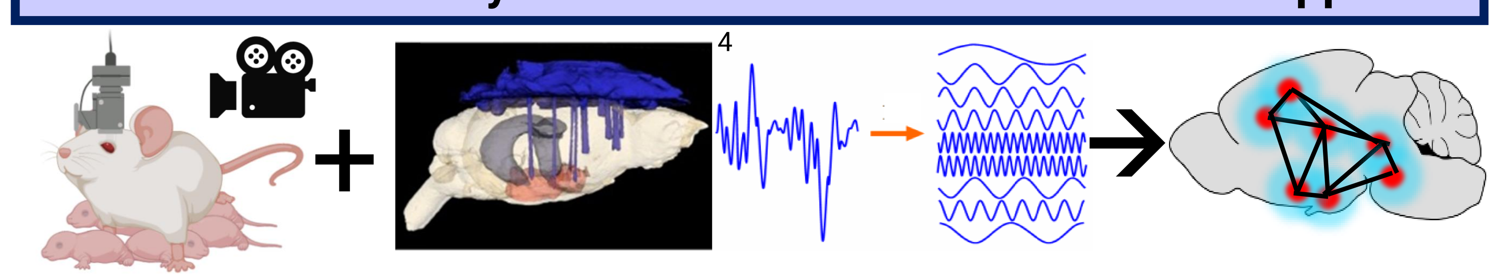
Early life stress, vulnerability, and the maternal brain

- **Adverse early life experiences** can impact the developing brain[1].
- These early neural impacts lead to **increased vulnerability** later in life.
- Alterations to **neural networks** following female ELS also affect brain components relevant to **maternal care** and behaviors[2].
- The **maternal brain** arises from a cascade of alterations.
- Maternal brain changes may not be entirely adaptive, resulting in **increased neuropsychiatric risk** over the perinatal period.
- **Stress-relevant brain regions** largely overlap with those important for **maternal engagement behaviors**[7,8].
- **Objective:** Assess brain-wide electrical dynamics of the maternal brain alongside network signatures of stress and maternal behavior.

Methods and Approach

- **Mouse Model:** Outbred CD1 strain, commonly used in maternal studies [3]
- **ELS:** Combination paradigm of maternal separation, early weaning, and limited nesting
- **Behavioral Assessments**: adolescent phenotype panel and adult maternal behavior
- **Neurophysiologic Recordings:** collected before, during, and fixed times after pregnancy
- **Maternal/Vulnerability multi-site depth electrodes include implantation of the following regions:** infralimbic and prelimbic cortices (IL and Prl), nucleus accumbens (NAc), basolateral, medial, and central amygdala (BLA, MeA, CeA), ventral hippocampus (Vhipp), and ventral tegmental area (VTA).

Brain-wide network dynamics: A validated and innovative approach

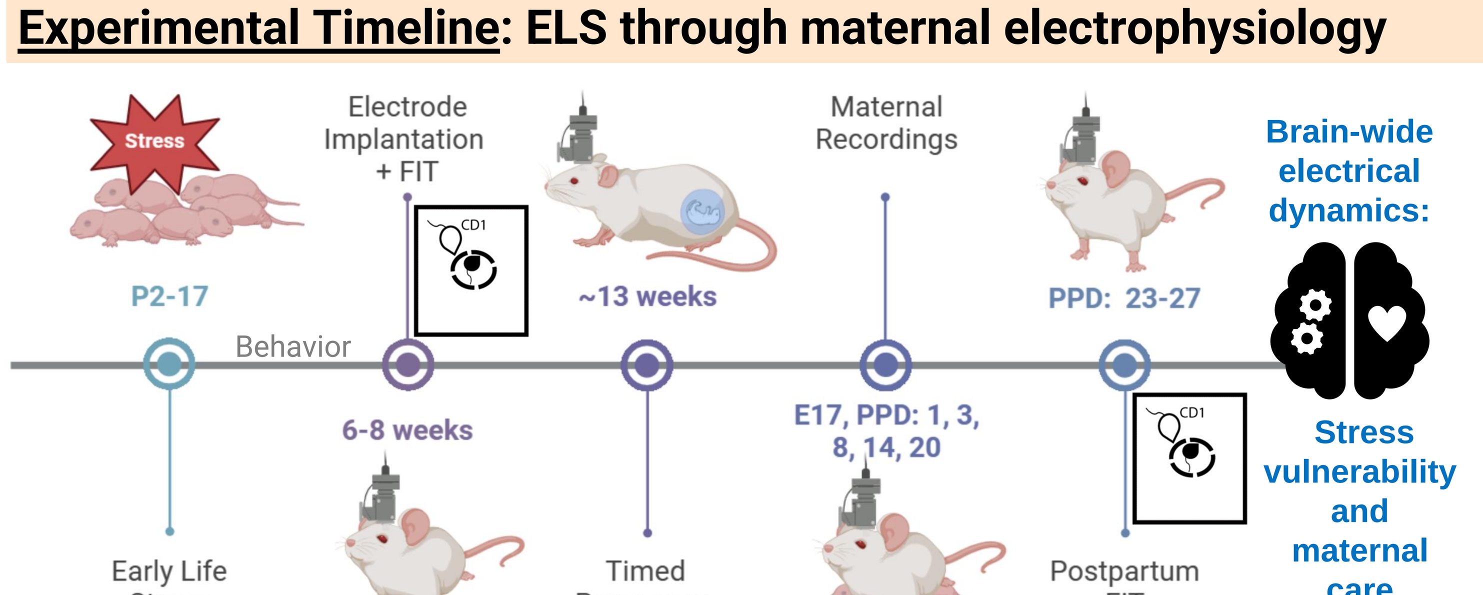


Electome Factors (EFs): electrical functional connectome networks/factors

- Spatiotemporal local field potential (LFP) patterns/signatures with brain state relevance
- Machine learning is used to build models: Discriminative cross spectral factor analysis (dCSFA) previously identified six *EFs* as latent stress-relevant networks[5].

***EF*1**	Stress vulnerability predictive	***EF*4**	General stress-relevant
***EF*2**	Depressive, DBS responsive	***EF*5**	General stress-relevant
***EF*3**	Depressive, ketamine responsive	***EF*6**	General stress-relevant

Experimental Timeline: ELS through maternal electrophysiology

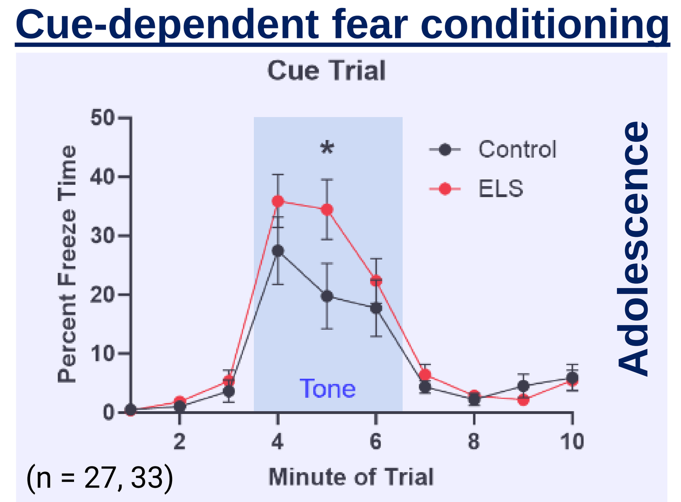


P: Postnatal Day | FIT: Forced Interaction Test | E: Embryonic Day | PPD: Postpartum Day

Response and reactivity: A circuit assessment

Females with prior ELS exposure display altered behavioral response and prefrontal reactivity to negative affect stimuli.

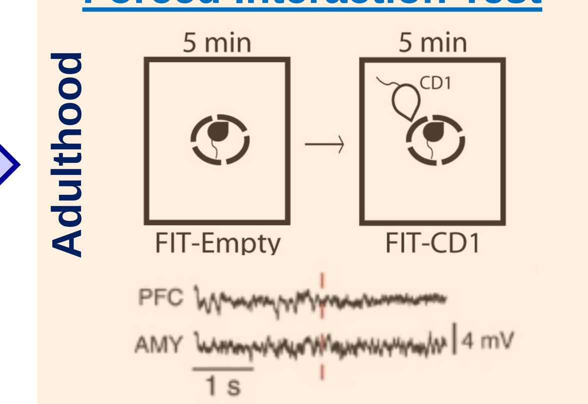
Cue-dependent fear conditioning

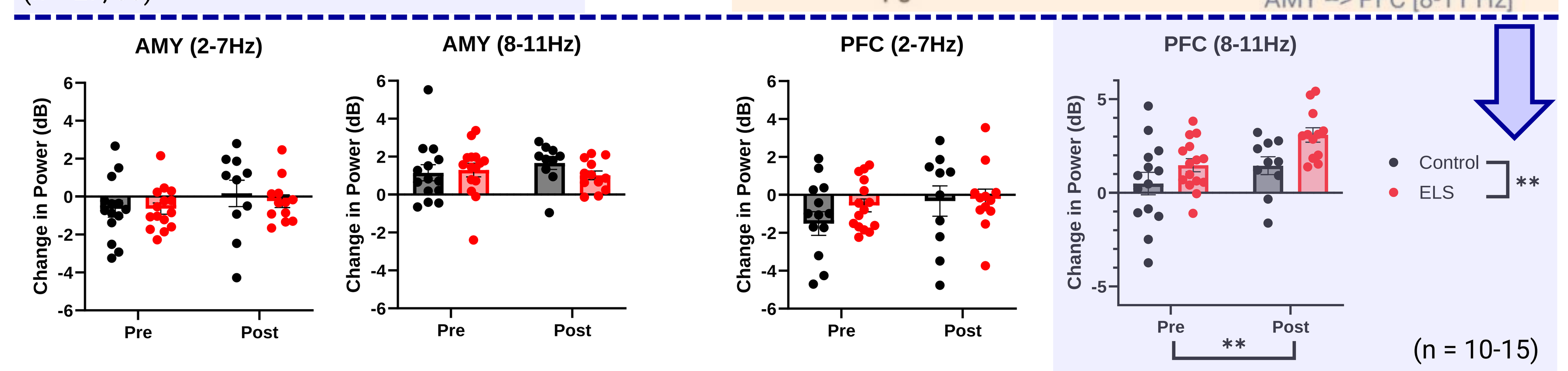


The PFC-AMY circuit and trait vulnerability[6]

Forced Interaction Test

Timepoints:
Pre = pre-gestation
Post = postpartum

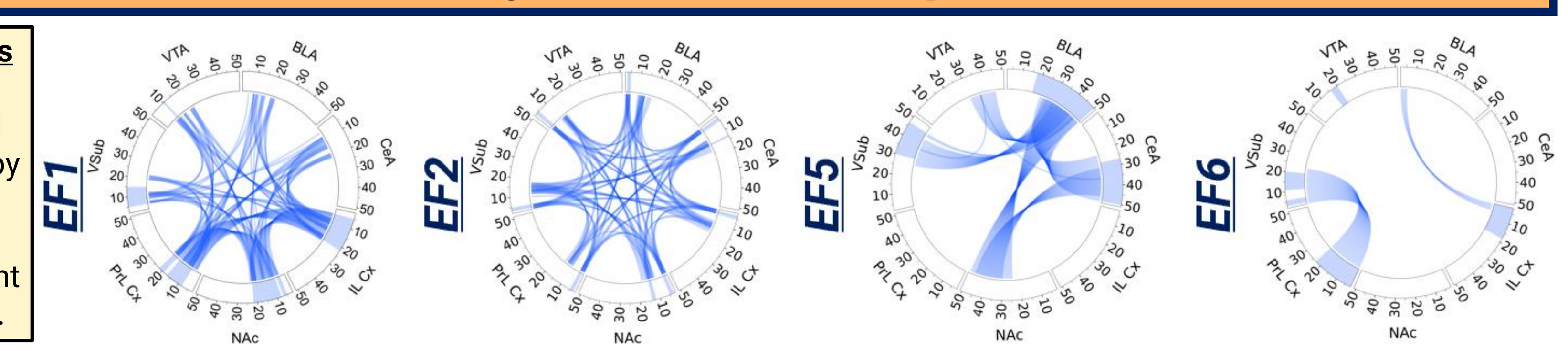




ELS increases freezing with conditioned cue in a tone-shock paired paradigm in adolescence (p=0.001 at 5-min, passing FDR). In adulthood, PFC activation, or reactivity, in response to an aggressor shows a significant effect based on parity (p=0.0091) and stress condition (p=0.0078) at 8-11 Hz.

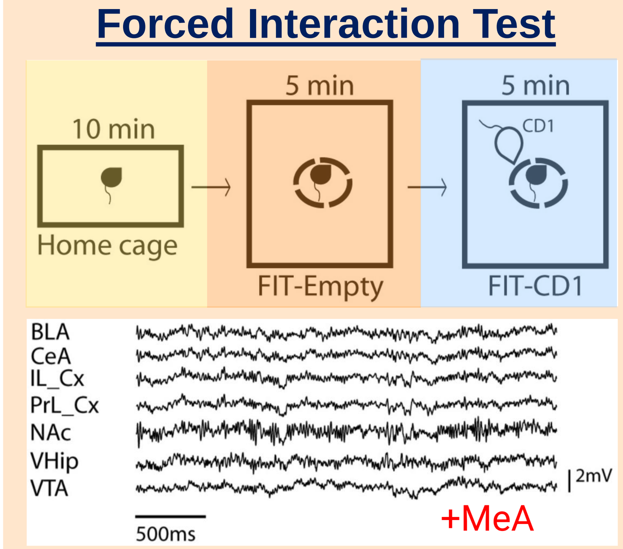
Brain-wide networks: Negative affect response and motherhood

Circos plots displaying power and synchrony by region in relation to four different stress *EFs*.



There is an ELS-specific increase in *EF*2, but not *EF*1 network activity during a negative affect task for postpartum females.

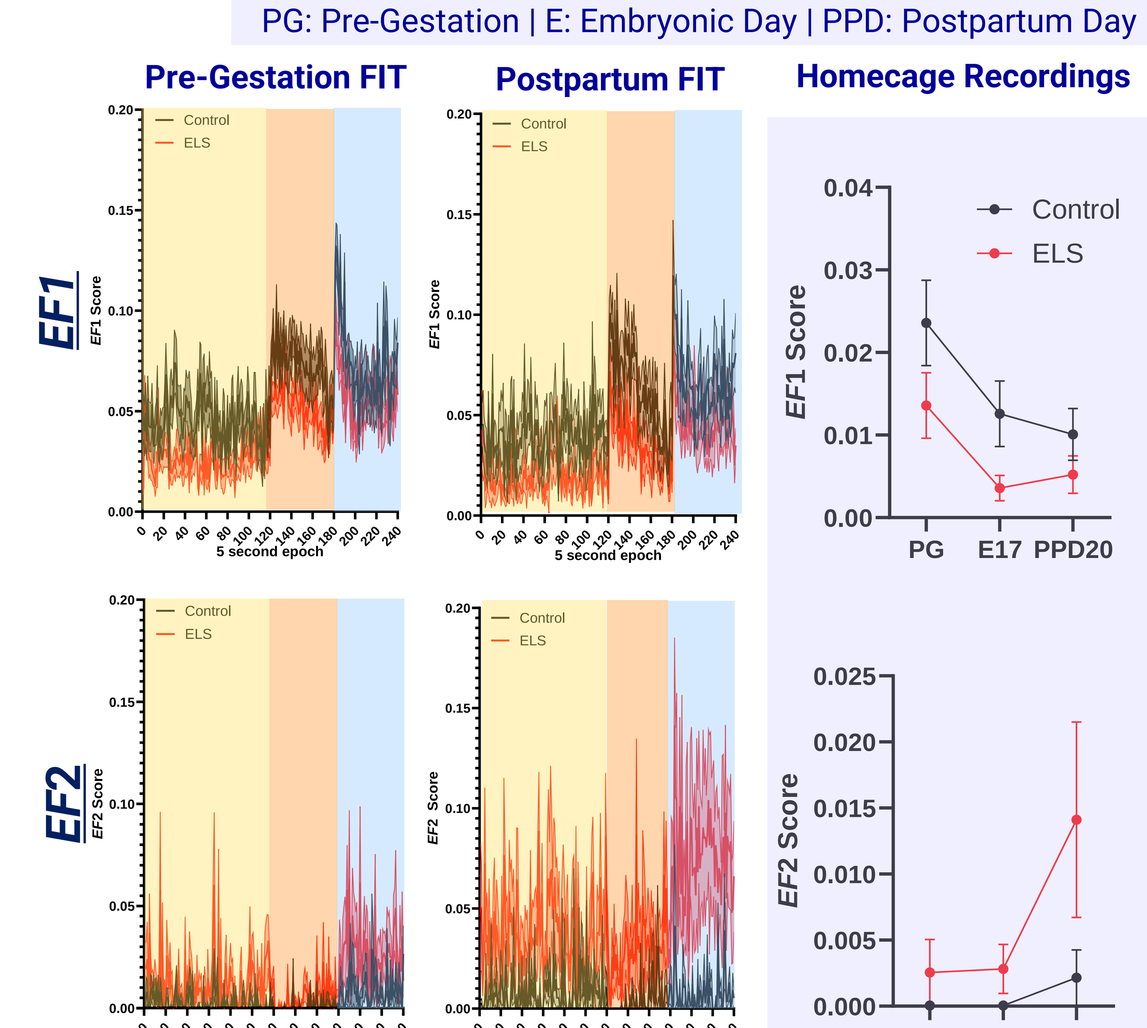
Forced Interaction Test



AUC Measurements	Homecage	FIT-empty	FIT-aggressor
***EF*1-pre**	0.6272	0.6391	0.5872
***EF*1-post**	0.6389	0.6661	0.6218
***EF*2-pre**	0.5530	0.5538	0.6064
***EF*2-post**	0.6373	0.6320	0.7647

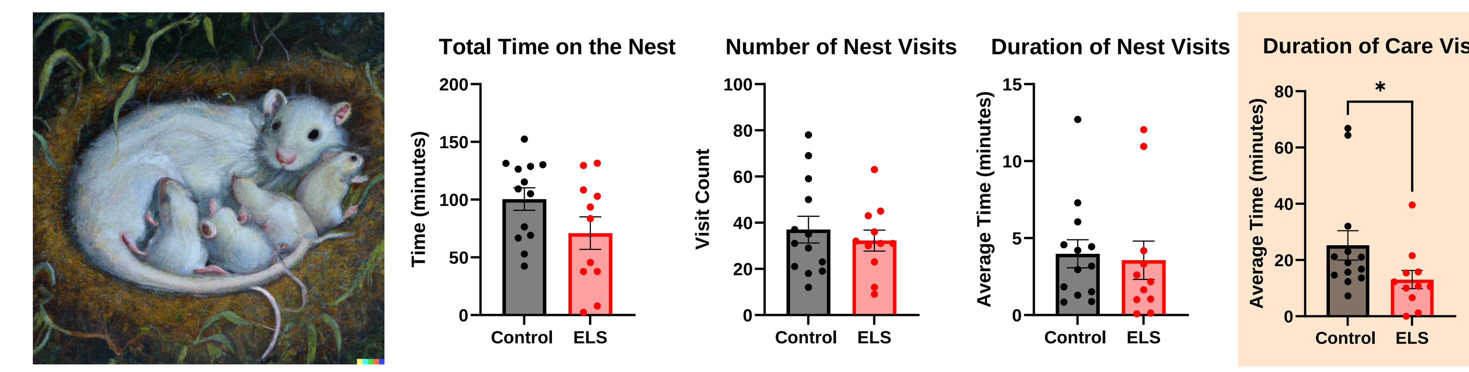
- ***EF*1**: Significant effect of time and trending stress effect (0.0522).
- ***EF*2**: Trending effects of time (0.0853) and stress (0.0747).

PG: Pre-Gestation | E: Embryonic Day | PPD: Postpartum Day



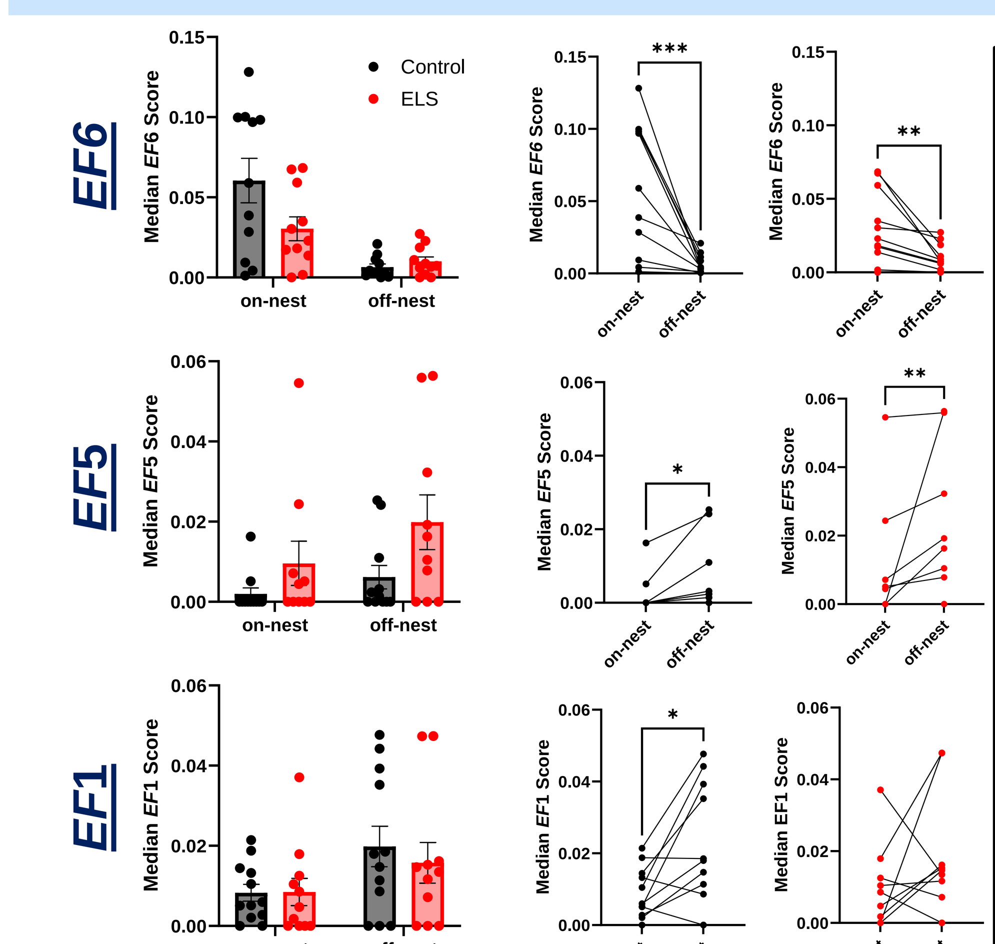
Stress-associated *electome factors* (*EFs*) and basic maternal behavior

A history of ELS alters patterns of maternal care.



Over a 3-hour observation at P3, there are significant alterations in patterns of maternal care visits to the nest for dams with exposure to ELS. No change is observed when including all nest visits. No change in duration of care visits was observed at P8.

Links between maternal on-nest behavior and activity within stress-associated network signatures.



- ***EF6***: Significant effect of nesting behavior (decrease off-nest), with an interaction for nesting behavior and stress.
- ***EF5***: Significant effect of nesting behavior (increase off-nest).
- ***EF1***: Significant effect of nesting behavior (increase off-nest). Wilcoxon test does not show a significant difference for ELS animals; consider off-nest state as a negative affect response?

Future Directions

- **Continue detailed assessment of maternal care focused on early PPDs.**
- **Further investigate the relationships amongst network characteristics, negative affect responses, and maternal care.**
- **Evaluate maternal network dynamics while on the nest → model building to identify networks of maternal care/engagement.**
- **Record while manipulating maternally-targeted variables: pup-retrieval task, ultrasonic vocalization playback, oxytocin administration...**
- **Could an *EF* relevant to maternal care and engagement really exist?**
- **How might the activity of this network be altered in ELS-exposed dams?**

References and Acknowledgements

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(4) Figure adapted from Schaich Borg, J. and Vu, M. et al. eNeuro, 2015).
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(9) Schematic figures prepared using BioRender.
(10) Mouse art generated using DALL – E via openai.com

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