Stress and Anxiety Impact Maturation of Adolescent Neural Circuitry Involved in Emotion and Reward Processing

Candace Killian-Farrell[1,2,3], Ashley Williams[2,3], Joshua Bizzell[2,3], Jessica Graham[2,3], Alana Campbell[1,2,3], Hannah Waltz, MA[2], Elizabeth Andersen[2], Jens Pruessner[4], & Aysenil Belger[1,2,3]

1 Carolina Institute for Developmental Disabilities, 2 Department of Psychiatry, University of North Carolina at Chapel Hill, 3Duke-UNC Brain Imaging and Analysis Center, Duke University Medical Center, [4]McGill Centre for Studies in Aging, McGill University

- **Background and Purpose:** Adolescence is a critical period for neurodevelopment related to stress regulation, emotional processing, and reward, and a time of increased vulnerability for psychiatric symptoms and disorders. Understanding how these neural circuits develop and are influenced by environmental factors such as stress is crucial in developing novel prevention and intervention strategies to provide adequate treatment for disadvantaged adolescents at increased risk for psychiatric problems. Our study examined the impact of stress and trait anxiety on adolescent neurodevelopment and hypothesized that age and trait anxiety are significantly associated with atypical development of neural circuits involved in stress regulation, emotion, and reward.

- **Methods:** 73 participants aged 9-13 y/o were recruited from the community, hospital system and local mental health clinics for a large neuroimaging study. Clinical data and fMRI data from 30 of the typically developing participants was analyzed for this study. All participants underwent clinical assessment and completed the Montreal Imaging Stress Task (MIST) in a 3T GE MRI scanner . The MIST task employs challenging mental math with negative social feedback to induce performance and social evaluative stress in participants. The State-Trait Anxiety Inventory–Child version (STAI-C) was administered to measure anxiety. FMRIB Software Library (FSL) was used to analyze fMRI data and perform covariate analyses which were corrected using a familywise error (FWE) at $z>2.3$ ($p<.01$ cluster threshold).

- **Results:** Our data revealed that stress blocks significantly activated a network of cortical regions involved in emotion regulation including the insula, frontal operculum, and paracingulate regions. Results showed deactivation of limbic and reward circuitry, including the amygdala and nucleus accumbens (NA). Males were demonstrated significantly greater activation in reward circuitry during stress. Covariate analyses revealed significant age-dependent maturational changes in stress activation in fronto-limbic circuitry including the inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG). Significant correlations were found between trait anxiety scores and stress-induced activation in the IFG, superior frontal gyrus (SFG) and ventral anterior cingulate.

- **Conclusion and Implications:** Our study reveals the novel finding that the neural circuits of stress response and regulation show significant age-dependent maturation during adolescence and significant covariation with trait anxiety. This suggests that age-dependent and anxiety-sensitive neural nodes may play key roles in the emergence of psychiatric disorders during adolescence. Our gender results suggest that adolescent males may be more sensitive to reward under stress which may contribute to higher levels of externalizing and reward seeking behaviors. Future research is needed to replicate these findings in a larger sample and to link these neurodevelopmental findings to behavior. Ultimately, further investigation of the link between these regions, their clinical correlates, and how this may develop in individuals with chronic stress or trauma history could provide important information for the development of preventative screening and secondary prevention initiatives to identify adolescents at increased neurodevelopmental risk for specific psychiatric symptoms and late onset psychiatric disorders.

Candace Killian-Farrell, PhD, LCSW

Stress and Anxiety Impact Maturation of Adolescent Neural Circuitry Involved in Emotion and Reward Processing

Candace Killian-Farrell[1,2,3], Ashley Williams[2,3], Joshua Bizzell[2,3], Hannah Waltz, MA[2], Elizabeth Andersen[2], Jens Pruessner[4], & Aysenil Belger[1,2,3]

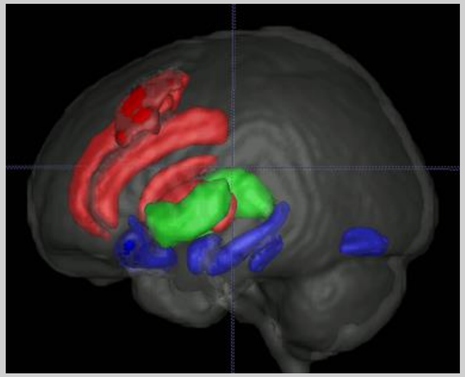
Background

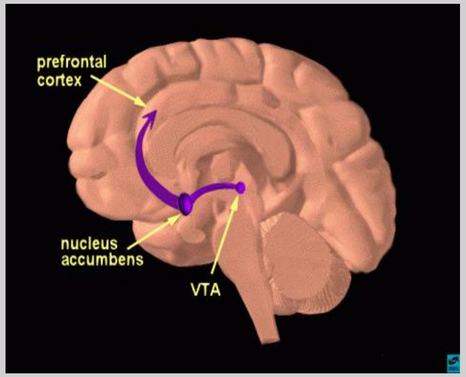
- Adolescence is a risk period for the onset of many psychiatric disorders
- Aberrant stress reactivity and regulation have been linked to clinical psychiatric symptoms (1) and may increase risk for psychiatric disorders
- Adolescence is a critical period for the maturation of frontal and limbic brain circuits implicated in emotional processing and reward sensitivity
- Frontal and limbic brain circuits are also critical for regulation of the stress response and are associated with emotional regulation, impulsivity, and behavioral control
- Neural reward circuitry has been associated with symptoms including anhedonia, amotivation, substance use, and risk-taking behavior

Hypotheses

H1: Limbic regions will show increased activation while executive regions will show decreased activation during stress.
H2: Aberrant stress reactivity and regulation in fronto-limbic and reward circuitry will demonstrate significant age and gender related effects.
H3: Fronto-limbic and reward circuits will be significantly associated with trait anxiety measures

Fronto-Limbic Circuitry Reward Circuitry





Stress and Anxiety Impact Maturation of Adolescent Neural Circuitry Involved in Emotion and Reward Processing

Candace Killian-Farrell[1,2,3], Ashley Williams[2,3], Joshua Bizzell[2,3], Hannah Waltz, MA[2], Elizabeth Andersen[2], Jens Pruessner[4], & Aysenil Belger[1,2,3]

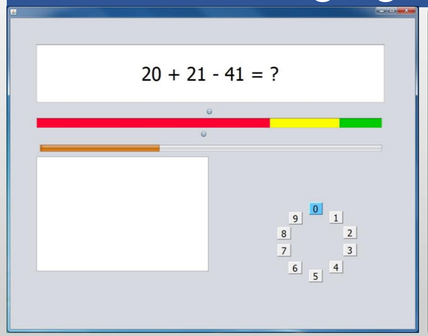
Methods

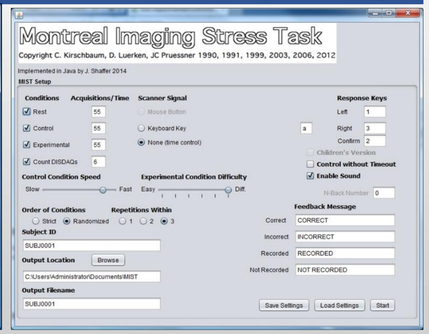
- **Participants:** N=30 typically developing adolescents aged 9-16 years old recruited from the community.
  - Mean age = 12.8(2.3),
  - 56.7% Female, 43.3% Male
  - Mean Trait Anxiety Score = 30.7(5.3), Range=21-41

- **Protocol:** All participants completed 3 visits for data collection: Clinical, EEG, fMRI protocol

- **Trait Anxiety Measure:** State-Trait Anxiety Inventory for children (STAI-CH) administered at fMRI visit prior to entering scanner

Montreal Imaging Stress Task (MIST)





- **Montreal Imaging Stress Task:**
  - 3 Mental Math runs, 5 min each
  - Negative feedback between runs
  - Button response to all stimuli

- **Functional imaging parameters:**
  - GE MR750 3T Scanner
  - Spiral acquisition sequence:
    - TR=2000ms;TE=30ms; Flip angle=60°
  - Voxel size 3.75 * 3.75 * 4 mm;
  - 34 oblique-axial slices (FOV=24 cm)

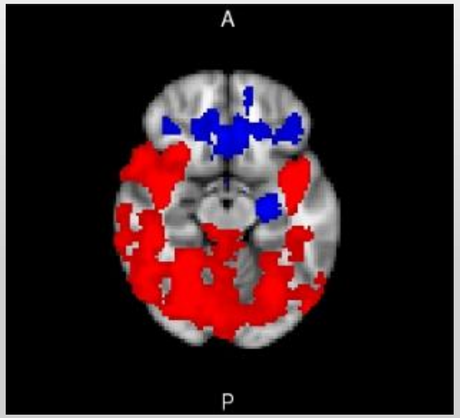
- **Image analysis:**
  - •Whole-brain voxel-based analyses of activation using FSL version 5.0.10
  - •ROI analyses using anatomical (Wake Forest Pick Atlas) and functional masks
  - •Covariate analyses corrected using a FWE at z>2.3 (p<.01 cluster threshold)

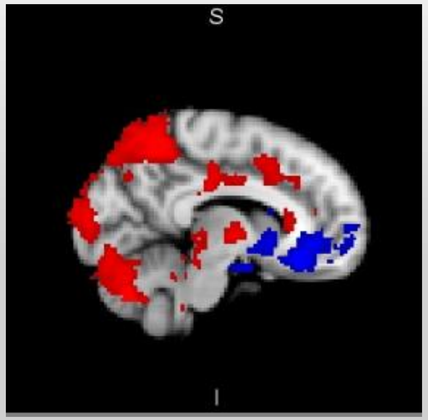
Stress and Anxiety Impact Maturation of Adolescent Neural Circuitry Involved in Emotion and Reward Processing

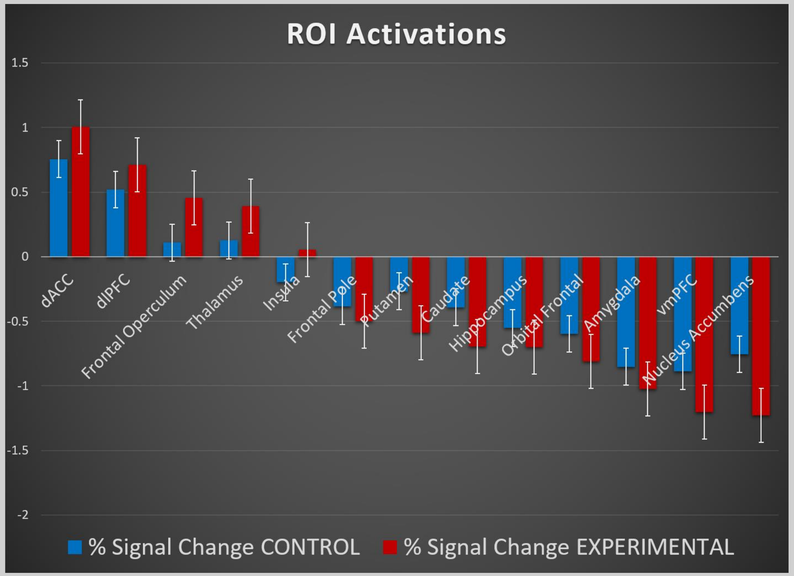
Candace Killian-Farrell[1,2,3], Ashley Williams[2,3], Joshua Bizzell[2,3], Hannah Waltz, MA[2], Elizabeth Andersen[2], Jens Pruessner[4], & Aysenil Belger[1,2,3]

Results: Brain Activation During Stress

Stress blocks significantly activated multiple regions including the insula, thalamus, frontal operculum,and anterior cinculate cortex, supporting findings in adults from Dedovic et al. (2009). Other areas were significantly deactivated during stress, including the nucleus accumbens, putamen, and orbito-frontal regions.

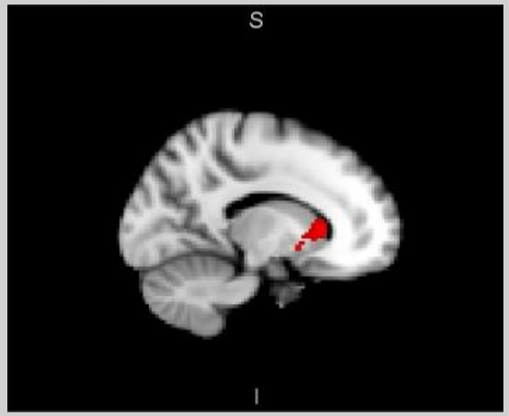






Results: Gender Differences

Male participants demonstrated significantly greater activation in reward circuitry including the nucleus accumbens, caudate, and putamen during stress

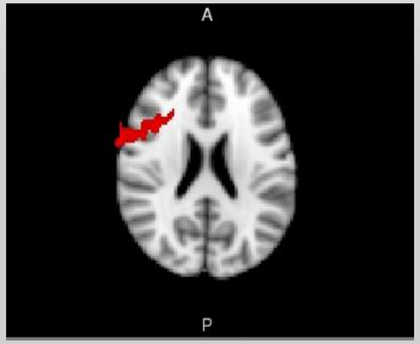


Stress and Anxiety Impact Maturation of Adolescent Neural Circuitry Involved in Emotion and Reward Processing

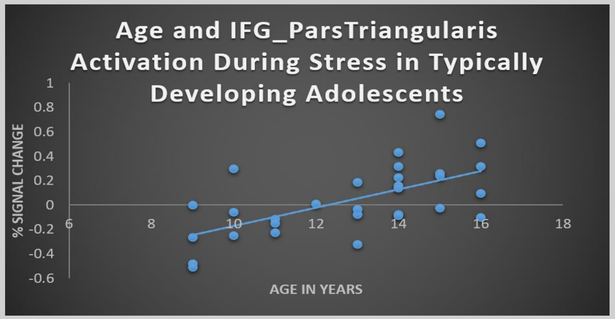
Candace Killian-Farrell[1,2,3], Ashley Williams[2,3], Joshua Bizzell[2,3], Hannah Waltz, MA[2], Elizabeth Andersen[2], Jens Pruessner[4], & Aysenil Belger[1,2,3]

Results: Age Dependent Activations

- Significant correlations were found between participants' age and brain activation during stress in the right inferior frontal gyrus (IFG), a brain region associated with impulse control and risk aversion.

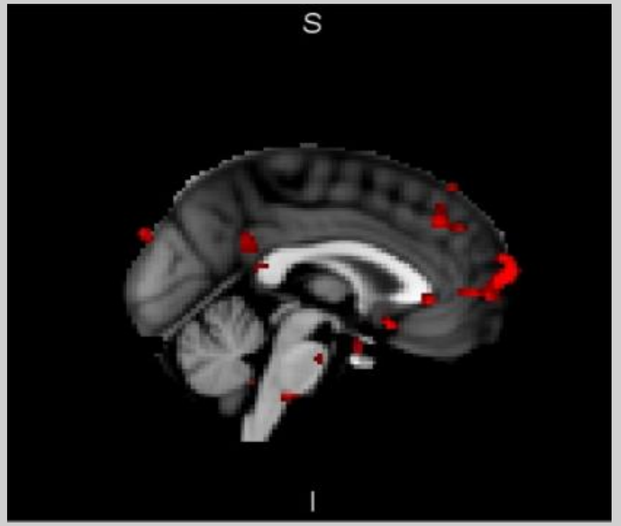


- Both the right IFG pars opercularis (r^2=0.561, p<.01) and right IFG pars triangularis (r^2=0.624, p<.001_ were significantly correlated with age



Results: Effects of Trait Anxiety

- Correlations were found between trait anxiety scores and brain activation during stress in several regions in preliminary, uncorrected results.
  - IFG pars triangularis (r2=.445, p<0.05)
  - Anterior cingulate gyrus (r2=0.416, p<0.05)
  - Superior frontal gyrus (r2=0.381, p<0.05)
  - Paracingulate region (r2=0.487, p<0.01)



Stress and Anxiety Impact Maturation of Adolescent Neural Circuitry Involved in Emotion and Reward Processing

Candace Killian-Farrell[1,2,3], Ashley Williams[2,3], Joshua Bizzell[2,3], Hannah Waltz, MA[2], Elizabeth Andersen[2], Jens Pruessner[4], & Aysenil Belger[1,2,3]

Discussion

•Stress may cause domain effects: increases cognition in some areas but inhibit others

•Deactivation of amygdala and NA during stress: temporary blunting of emotional response to reward?

•Age-dependent maturation during adolescence: Significantly increased activation of IFG may indicate increased ability to inhibit risky behavior during stress

•Age-dependent neural nodes may play key roles in the emergence of adolescent psychiatric disorders

•Multiple nodes of stress-related circuitry may covary with trait anxiety: Activation of ACG under stress covaries with trait anxiety and may indicate hyperreactivity or greater intolerance to task uncertainty among individuals with more anxious baselines

•Decreased suppression of the IFG with increased trait anxiety levels may be linked to increased behavioral inhibition in highly anxious adolescents

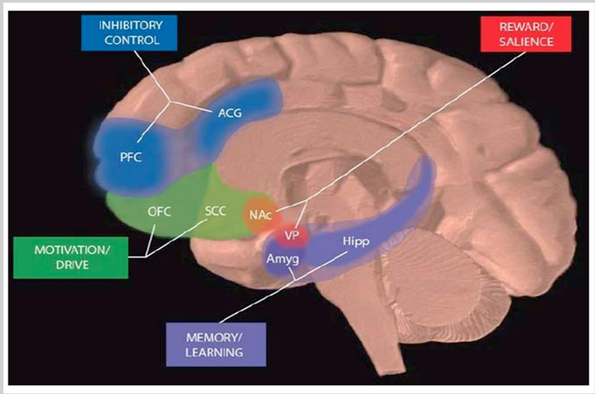
Next Steps

•How will adolescents with psychopathology diverge from these results?

• What is the functional connectivity associated with these regional activation differences?

• Are there any correlations with other clinical measures? How are these findings linked to specific behaviors?

•What are potential neurodevelopmental implications for chronic stress exposure in childhood and adolescence?



References

1. Dedovic, K., Duchesne, A., Engert, V., Lue, S.D., Andrews, J., Efanov, S., Beaudry, T. & Pruessner, J. (2014). Psychological, endocrine and neural responses to social evaluation in subclinical depression, *SCAN, 9,* 1632-1644.
2. Dedovic, K., Rexroth, M., Wolff, E., Duchesne, A. Scherling, C., Beaudry, T., Lue, S.D., Lord, C., Engert, V., & Pruessner, J. (2009). Neural correlates of processing stressful information: An event-related MRI study, *Brain Research, 1293,* 49-60.

Support: NIH -R01 MH103790-01A1, NICHD NRSA Training Grant, #T32-HD40127