Nuclei-Specific Functional Maturation of Fronto-Amygdala Circuitry Through Adolescence: Longitudinal Insights from 7 Tesla fMRI

Amar Ojha[1,2]; Valerie J. Sydnor[3], Will Foran[3], Natalie Phang[4], Arshia Sista[4], Shawn F. Sorrells[4], Ashley C. Parr[3], Finnegan J. Calabro[3,5], Beatriz Luna[1-3,5,6]

1. Center for Neuroscience; 2. Center for Neural Basis of Cognition; 3. Department of Psychiatry;
4. Department of Neuroscience; 5. Department of Bioengineering, 6. Department of Radiology, University of Pittsburgh.

Laboratory of Neurocognitive Development

CNBC Center for the Neural Basis of Cognition

Background & Motivation

Adolescent Affective Development

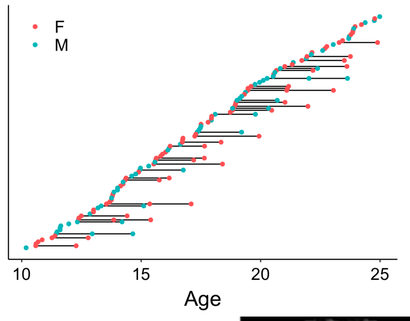
- Adolescence is a period of marked affective development[1], supported by neural refinements of fronto-amygdala circuitry[2] whose alterations are implicated across several major psychopathological disorders[3,4], which typically emerge during adolescence[5].
- Past research has generated mixed developmental findings, which may be due in part to collapsing across amygdala nuclei with unique functional and connectional profiles[6] whose maturation *in vivo* in human adolescents has not yet been investigated.
- Here, we characterize developmental changes in connectivity at the amygdalar nuclei level, associations with externalizing behaviors, and involvement of cortical circuitry across various cognitive domains.

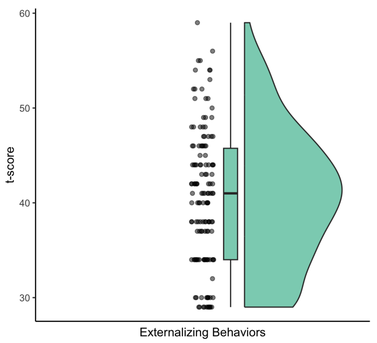
Hypothesis

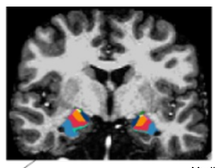
Protracted development of fronto-amygdala functional connectivity will be evident in nuclei known to have continued maturational processes through adolescence.

Study Design & Analyses

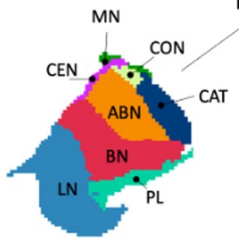
- We collected 7 Tesla resting-state fMRI data in 156 healthy participants ages 10-25, scanned 1-3 times for a total of 221 scans.
- Amygdala nuclei were segmented using subject-specific anatomical definitions from FreeSurfer[7,8]. Medial PFC ROIs were defined with the Mackey and Petrides atlas[9] and lateral PFC ROIs were determined using the Brainnetome atlas[10].
- Generalized additive mixed models (GAMMs)[11] were used to characterize non-linear development of fronto-amygdala resting-state functional connectivity, (task-regressed) cognitive state background connectivity, and intrinsic (combined) functional connectivity.
- Statistical tests were Bonferroni-corrected to account for multiple comparisons.
- Externalizing behaviors were assessed using the YSR[12] and ASR[13].
- Finally, we performed a cognitive domain decoding analysis[14] to better understand the cortical circuitry associated with amygdala nuclei undergoing protracted maturation in adolescence.

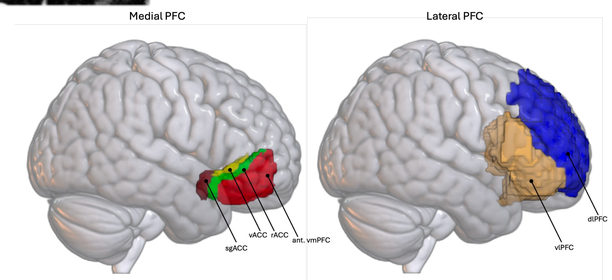






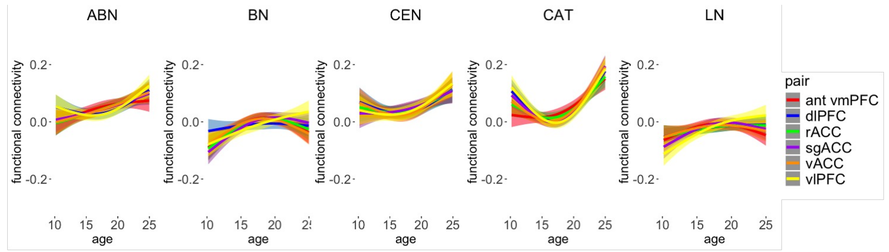
Fronto-amygdala regions of interest (ROIs). ABN, accessory basal nucleus; BN, basal nucleus; LN, lateral nucleus; PL, paralaminar nucleus; CAT, corticoamygdaloid transition area; CON, cortical nucleus; MN, medial nucleus; CEN, central nucleus; vmPFC, ventromedial prefrontal cortex; sgACC/vACC/rACC, subgenual/ventral/rostral anterior cingulate cortex; d/vlPFC, dorso/ventrolateral PFC.



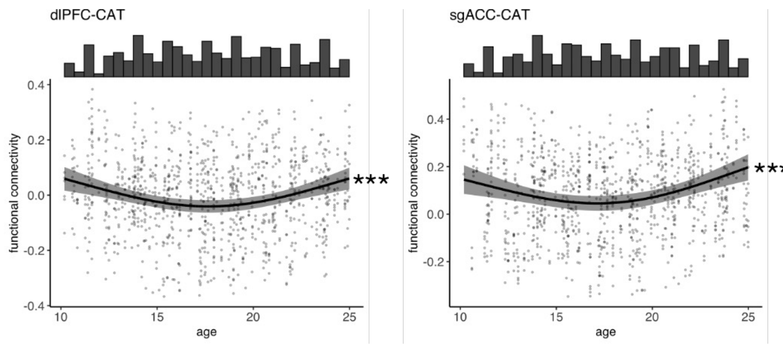


Results

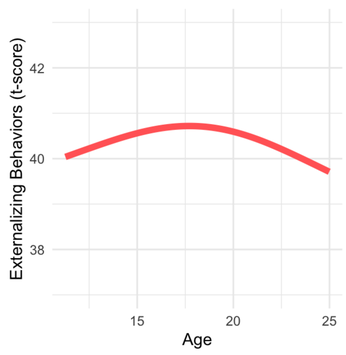
Most Fronto-Amygdala Connections Do Not Significantly Change with Age.

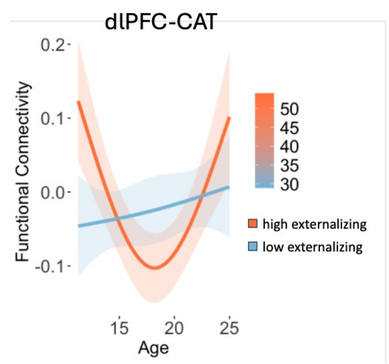


Corticoamygdala Transition Area (CAT) PFC Connectivity Changed with Age.

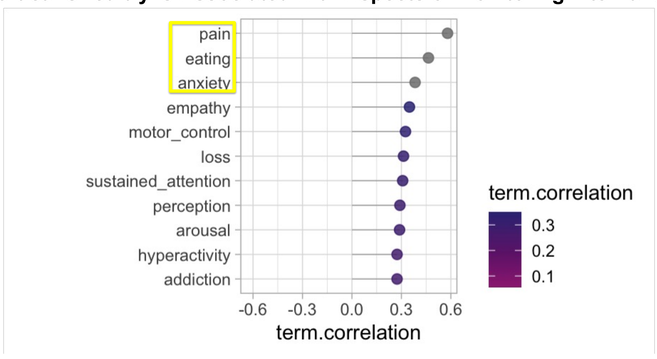


Mid-Adolescent FC Troughs are Driven by Individuals with More Externalizing Behaviors.





CAT Cortical Circuitry is Associated with Aspects of Monitoring Internal States.



Discussion

- Consistent with our hypothesis, we found robust PFC FC age effects with the CAT, which contains neurons that mature in adolescence[18].
- Developmental changes showed a mid-adolescent trough that may reflect dampened PFC influence on amygdala function, which parallel teen increases in emotional reactivity, and are reflected in externalizing phenotypes driving this age effect.
- CAT cortical circuitry was specifically related to pain, eating, and anxiety, all of which relate to monitoring one's internal state (i.e., introspection), which may undergo specific maturation during adolescence.
- Evidence from animal models suggests that the CAT is critical for social behaviors[13] and expresses hormone receptors[16], both predominant in adolescence, and connectivity to the ventral hippocampus[17,18], may reflect a period of imbuing memories with emotional significance.
- **Together, our findings suggest that fronto-amygdala coupling may be well established by adolescence, except for CAT connectivity, which may specifically underlie the peak in specific emotional processes including introspection and related social-processing in adolescence**.

Future Directions

- Our sample was limited to adolescents with no psychopathology. Characterizing development of amygdala nuclei connectivity in psychopathology could inform etiology and interventions.
- Amygdala circuitry maturation begins early in life, thus future work should expand age ranges to understand developmental trajectories across amygdala nuclei earlier in childhood.
- Examining amygdala nuclei activation/connectivity during an emotional task would inform functional properties of structures, such as the CAT, in affective processes.
- While we examined amygdala connectivity to PFC, connectivity to other structures undergoing maturation through adolescence and implicated in psychopathology, including the anterior insula[19], ventral striatum[20], and hippocampus[21] should be investigated.

References

1. Silvers, J.A., (2022). *Current Opinion in Psychology*, *44*, 258-263.
2. Silvers J.A., Insel C., et al. (2017). *Cerebral Cortex*, *27*(7), 3502-3514.
3. Jalbrzikowski, M., Larsen, B., et al. (2017). *Biological Psychiatry*, *82*(7), 511-521.
4. Anticevic, A., Brumbaugh, M.S., et al. (2013). *Biological Psychiatry*, *73*(6), 565-573.
5. Paus, T., Keshavan, M., Giedd, J.N. (2008). *Nature Reviews Neuroscience*, *9*(12), 947-957.
6. Gabard-Durnam, L.J., O'Muircheartaigh, J., et al. (2018). *Developmental Cognitive Neuroscience*, *34*, 63-74.
7. Fischl, B. (2012). *NeuroImage*, *62*(2), 774-781.
8. Saygin, Z.M., Kliemann, D., et al. (2017). *NeuroImage*, *155*, 370-382
9. Mackey, S. & Petrides, M. (2014). *European Journal of Neuroscience*, *40*(5), 2777-2796.
10. Fan, L., Li, H., et al. (2016). *Cerebral Cortex*, *26*(8), 3508-3526.
11. Wood, S.N. (2017). *Generalized Additive Models: An Introduction with R*.
12. Achenbach, T.M. & Rescorla, L.A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*.
13. Achenbach, T.M. & Rescorla, L.A. (2003). *Manual for the ASEBA Adult Forms & Profiles*.
14. Shafiei, G., Markello, R.D., et al. (2020). *eLife*, *9*, e62116.
15. Yamaguchi, T., Wei, D., et al. (2020). *Nature Neuroscience*, *23*(9), 1111-1124.
16. Canteras, N.S., Simerly, R.B., & Swanson, L.W. (1992). *Journal of Comparative Neurology*, *324*(*2*), 143-179.
17. Sedwick, V.M. & Autry, A.E. (2022). *Neuroscience & Biobehavioral Reviews*, *142*, 104893.
18. Fudge, J.L., deCampo, D.M., & Becoats, K.T. (2012). *Neuroscience*, *212*, 104-119.
19. Smith, A.R., Steinberg, L., & Chein, J. (2014). *Developmental Neuroscience*, *36*(*3-4*), 196-209.
20. Cardinal, R.N., Parkinson, J.A., et al. (2002). *Neuroscience & Biobehavioral Reviews*, *26*(*3*), 321-352.
21. Calabro, F.J., Murty, V.P., et al. (2020). *Cerebral Cortex*, *30*(*3*), 1548-1558.

Acknowledgements

The authors thank the participants and their families for participating in the study and the staff and students at the Laboratory of Neurocognitive Development (LNCD) for making this research possible. This research was supported by funding from Staunton Farm Foundation (BL), R01MH080243 (BL), R01MH067924 (BL), and T32GM081760 (AO).

Contact: amo80@pitt.edu