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

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

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

Introduction

Adolescent Development and Fronto-Amygdala Circuitry

- Adolescence involves significant cognitive[1] and affective development[2], supported in part by neural refinements of fronto-amygdala circuitry[3,4] during a time for increased risk for the emergence of major psychopathology[5], exemplified by internalizing and externalizing phenotypes related to this circuitry[6,7].
- Initial results from fronto-amygdala developmental studies, however, are inconsistent[8-10] likely due to the complexity of amygdala organization[11], which is composed of several (sub)nuclei with unique functional and connectional profiles[12].
- Here, we characterize developmental changes in amygdala nuclei functional connectivity with prefrontal cortex (PFC) during resting- and cognitive-state in healthy adolescents.

Amygdala Subdivisions and Associated Functions

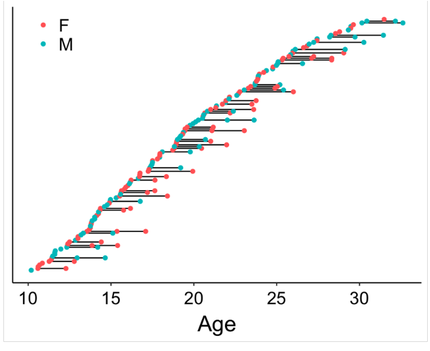
- Functional and connectivity analyses, largely from animal research, has demonstrated that the basolateral amygdala (BLA) is associated with associative learning[13], the centromedial amygdala (CMA) with affective responsivity[14], and the superficial amygdala (SFA) with social cognitive processing[15].

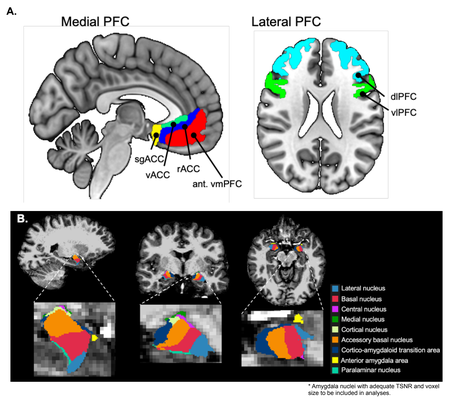
Hypothesis

Given continued improvements in cognition and amelioration of affect, we hypothesized that connectivity of nuclei in the BLA (i.e., ABN, BN, LN) and SFA (i.e., CAT) with the lateral PFC would increase with age, whereas CMA (i.e., CEN) connectivity with medial PFC would decrease with age.

Study Design & Analyses

- We collected ultra high-field 7 Tesla fMRI data in 143 healthy participants (52.4% F) ages 10-30, scanned 1-3 times for a total of 198 scans.
- We computed functional connectivity from resting-state[16] and cognitive-state[17] (task-regressed background connectivity from a memory-guided saccade [MGS] task[18]). We combined both measures to generate a single index of *intrinsic* functional connectivity (while covarying for 'context' in analyses).
- Amygdala nuclei were segmented using subject-specific anatomical definitions from FreeSurfer 7.4.1[19,20].
- Affective measures were assessed using normative variation in internalizing and externalizing behaviors using the Adult/Youth Self-Report (ASR/YSR)[21,22].
- Cognitive measures included MGS accuracy and latency and variability of each.
- Big additive (mixed) models (BAMs) were used to characterize the development of fronto-amygdala connections.
- Linear associations within a GAMM framework were used to test associations between functional connectivity and affective/cognitive measures, controlling for non-linear age effects in developmental connections.
- All statistical tests were Bonferroni-corrected to account for multiple comparisons.

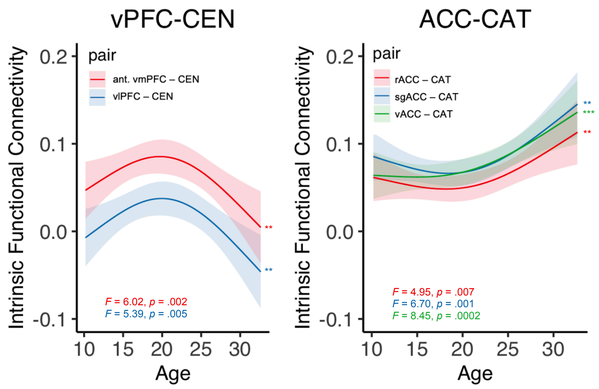




Results

Age-Related Changes in Fronto-Amygdala Connectivity

- Most fronto-amygdala connections did not significantly change with age following Bonferroni corrections (*p*s > .0083) suggesting maturation by adolescence.
- Specific connections for each major amygdala subdivision showed unique changes with age, suggesting peaks in affect and increases in cognitive processes.

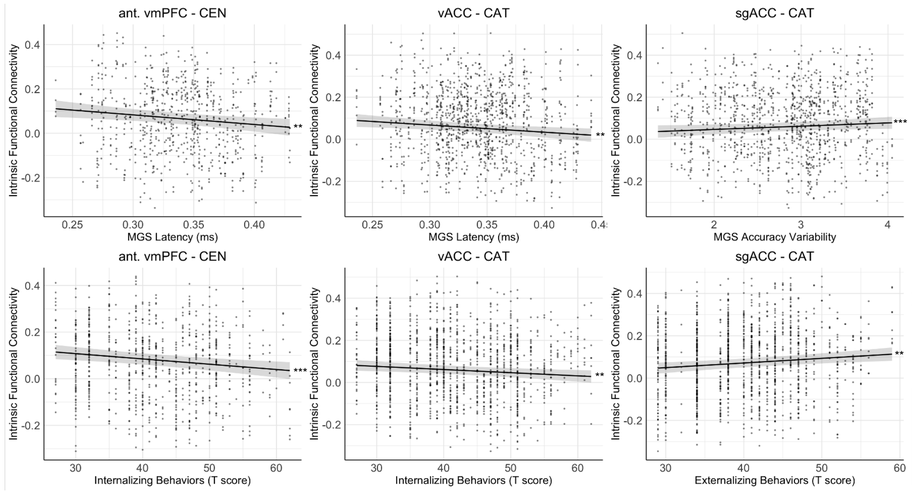


Associations with Cognitive Measures (beyond non-linear age effects)

- Weaker connectivity in two connections were associated with slower MGS performance on correct trials: anterior vmPFC – CEN (β = -0.43, p = .003), vACC – CAT (β = -0.34, p = .003).
- Stronger connectivity in social cognitive circuitry (sgACC – CAT) was associated with increased variability on MGS accuracy (β = 0.03, p = .0001).
- Weaker connectivity in fronto-amygdala circuitry related to executive functioning and associative learning processes (vlPFC – LN) was associated with increased variability on MGS latency on correct trials (β = -0.76, p = .00003).

Associations with Affective Measures (beyond non-linear age effects)

- Stronger connectivity in affective and cognitive connections were associated with fewer internalizing behaviors: anterior vmPFC – CEN (β = -0.002, p = .0007), vACC – CAT (β = -0.002, p = .005). In contrast, stronger sgACC – CAT connectivity was uniquely associated with more externalizing behaviors (β = 0.002, p = .001).



Discussion

- The present study provides novel evidence for mature and protracted functional maturation of anatomically precise fronto-amygdala circuitry through adolescence into early adulthood.
- The CEN—critical for canonical fight, flight, freeze affective responses[23]—with ventral PFC circuitry—important for value assignment[24] and self-referential processing[25]—peaked in connectivity decreasing into early adulthood, where it was related to fewer internalizing characteristics, suggesting maturation of affective control.
- ACC – CAT circuitry exhibited increases in connectivity through adolescence, possibly reflecting ongoing maturation of social cognitive processing into early adulthood. These results suggest a link to social behaviors, given its association with externalizing (e.g., antisocial) behaviors, which may be related to limitations in self-regulatory (affective and cognitive) neurodevelopment[26].
- Lateral PFC circuitry—critical for higher-order cognition[27] and top-down regulation[28]—increasingly coordinates its activity with the BLA, crucial for valence assignment[29] and associative learning[30], suggesting a possible role of experiential influences and emotional learning on decision-making processes.
- **Together, these findings suggest that core aspects of affect and cognition may be established by adolescence while circuits that support more specialized affective/cognitive processes may continue to mature into adulthood.**

Future Directions

- Future studies should probe the distinct processes underlying each of these amygdala nuclei to PFC regions to better understand the nature of the circuitry that has prolonged maturation and plasticity and its association with normative and atypical development.

References

1. Luna et al. (2004), *Child Development*
2. Silvers (2022), *Current Opinion in Psychology*
3. Casey et al. (2019), *Neuroscience Letters*
4. Dixon & Dweck (2022), *Psychological Review*
5. Dalsgaard et al. (2020), *JAMA Psychiatry*
6. Burghy et al. (2012), *Nature Neuroscience*
7. Thijssen et al. (2020), *Journal of Child Psychology & Psychiatry*
8. Jalbrzikowski et al. (2017), *Biological Psychiatry*
9. Gee et al. (2013), *Journal of Neuroscience*
10. Gabard-Durnam et al. (2014), *NeuroImage*
11. McDonald (1998), *Progress in Neurobiology*
12. Roy et al. (2009), *NeuroImage*
13. Wassum & Izquierdo (2015), *Neuroscience & Biobehavioral Reviews*
14. Warlow et al. (2020), *Nature Communications*
15. Goossens et al. (2009), *Human Brain Mapping*
16. Hallquist, Hwang, & Luna (2013), *NeuroImage*
17. Fair et al. (2007), *NeuroImage*
18. McKeon et al. (2023), *NeuroImage*
19. Fischl (2012), *NeuroImage*
20. Saygin et al. (2017), *NeuroImage*
21. Achenbach & Rescorla (2001), *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment*
22. Achenbach & Rescorla (2003), *Handbook of Psychological and Educational Assessment of Children*
23. Fadok et al. (2017), *Nature*
24. Smith et al. (2010), *Journal of Neuroscience*
25. Philippi et al. (2012), *Journal of Cognitive Neuroscience*
26. Posner et al. (2007), *Cognitive, Affective, & Behavioral Neuroscience*
27. Miller & Wallis (2009), *Executive Function and Higher-Order Cognition*
28. Nee & D'Esposito (2016), *eLife*
29. Zhang & Li (2018), *Nature Communications*
30. Gründemann & Lüthi (2015), *Current Opinion in Neurobiology*

Acknowledgements

The authors thank the participants and their families for participating in the studies 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), and R01MH067924 (BL).

Twitter: @aojha7
Contact: amo80@pitt.edu