Human Amygdala Nuclei Show Distinct Developmental Trajectories from Adolescence to Adulthood in Functional Integration with Prefrontal Circuitry

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

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

Laboratory of Neurocognitive Development

Center for the Neural Basis of Cognition

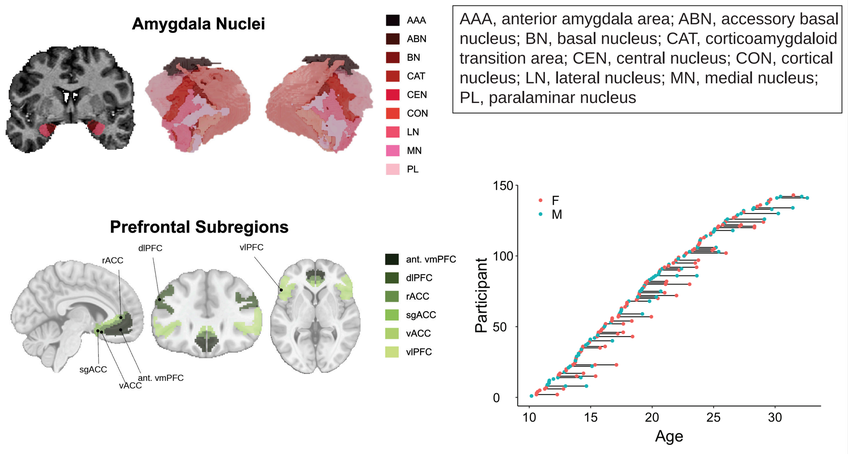
Background & Motivation

- Adolescence, a critical period of neurodevelopment, is characterized by marked improvements in affective and cognitive control to support adaptive adult functioning and altered transdiagnostically.[1]
- Changes in prefrontal cortex (PFC) and amygdala connectivity support behavioral improvements but may increase psychiatric risk.[2]
- Evidence from human studies have yielded mixed findings,[3,4] possibly due to functional heterogeneity of amygdala nuclei, anatomical heterogeneity between participants, and technical challenges related to neuroimaging.
- Preliminary work suggests distinct maturational trajectories for amygdala subregions,[5] which include the basolateral (BLA), centromedial (CMA), and superficial amygdala (SFA), each comprised of diverse nuclei.
- BLA nuclei exhibit strong cortical connectivity, support cognitive processes (e.g., associative learning, memory),[6] and are predominantly comprised of cortical-like glutamatergic pyramidal neurons.[7]
- CMA nuclei densely project to the brainstem and hypothalamus,[8] mediate rapid affective responses (e.g., flight-or-flight, appetitive and aversive behaviors, physiological responses), and include striatal-like GABAergic medium spiny neurons.[9]
- SFA nuclei remain poorly characterized but have been implicated in social information processing via chemoreception and affective salience detection.[10,11]

Hypotheses:
- **Age-related increases in lateral PFC – BLA nuclei, which will support cognitive control.**
- **Adolescent-specific peak in medial PFC – CMA nuclei, which will support affective responsivity.**
- **Age-related increases in ACC – SFA nuclei, which will support socioemotional functioning.**

Study Design & Analysis

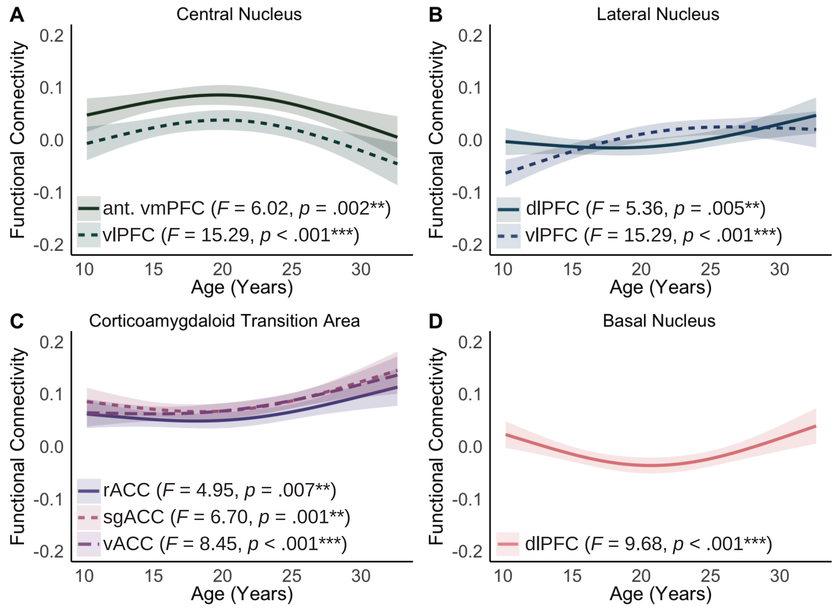
- **Participants and scan acquisitions**: Longitudinal 7T fMRI data from 143 healthy participants (75 F, 52.4%), ages 10-32 years, with up to 3 visits each (198 total visits). T1w: voxel size = 1x1x1mm, total duration = 5m14s. T2* BOLD: voxel size = 2x2x2mm, rest duration = 8m, task duration = 21m.
- **Region-of-interest (ROI) definitions**: amygdala nuclei were segmented using FreeSurfer 7.4.1. Medial PFC subregions were defined using Mackey & Petrides and lateral subregions using Brainnetome.
- **Functional connectivity**: time courses were extracted using the first PCA component within each ROI and Pearson correlation coefficients computed between ROI pairs were normalized using Fisher's z transformation. Task-regressed and resting-state fMRI data were combined in analyses while controlling for scan context (rest or task).
- **Behavioral measures**: Affective measures included internalizing and externalizing behaviors from the Youth/Adult Self-Report (YSR/ASR) and total difficulties in emotion regulation from the DERS. Cognitive measures from a memory guided saccade (MGS) task included accuracy, accuracy variability, correct trial latency, and correct trial latency variability.
- **Psychological domain decoding**: Glasser atlas determined ROI activation probability maps were obtained for terms present in Neurosynth and the Cognitive Atlas. Association tests (z) quantified the extent to which cortical activations were consistently found in previous studies mentioning a given term.
- **Statistical approach**: Generalized additive mixed models (GAMMs) were used to characterize non-linear developmental trajectories. Brain-behavior associations were tested linearly while controlling for non-linear age effects. Statistical tests were Bonferroni-corrected.



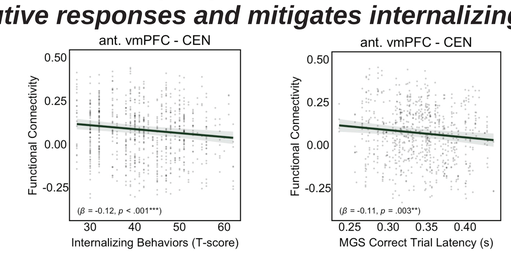
AAA, anterior amygdala area; ABN, accessory basal nucleus; BN, basal nucleus; CAT, corticoamygdaloid transition area; CEN, central nucleus; CON, cortical nucleus; LN, lateral nucleus; MN, medial nucleus; PL, paralaminar nucleus

Results

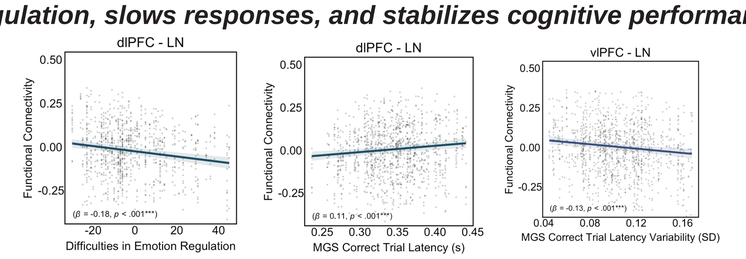
Amygdala nuclei follow distinct developmental trajectories



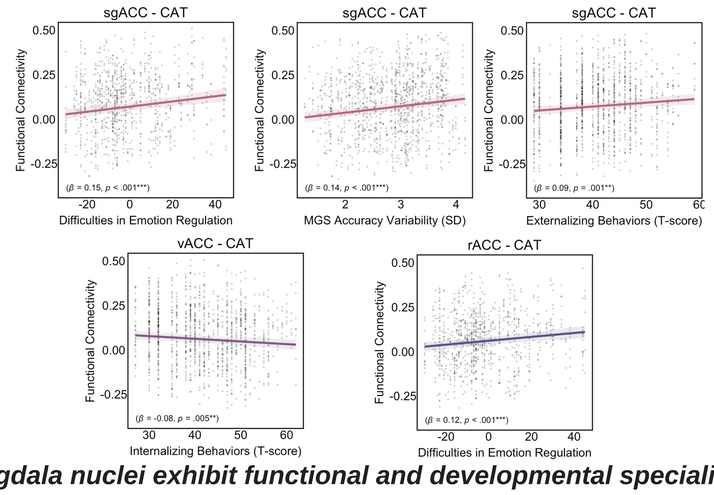
Central nucleus coupling with anterior vmPFC supports rapid executive responses and mitigates internalizing behaviors



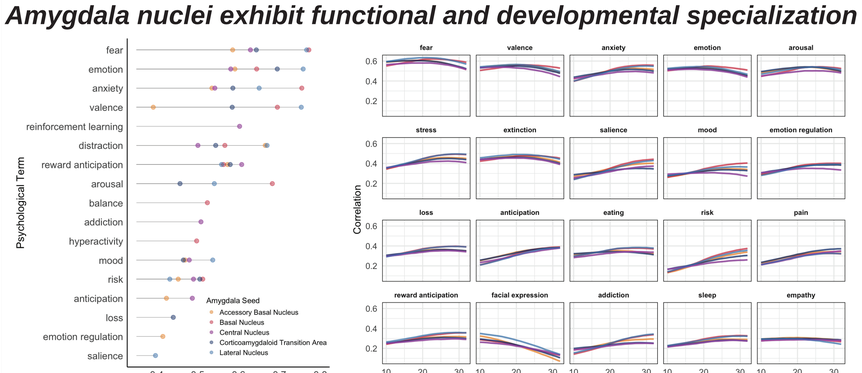
Lateral nucleus coupling with lateral PFC supports emotion regulation, slows responses, and stabilizes cognitive performance



Corticoamygdaloid transition area coupling with sgACC and rACC may increase emotion dysregulation while vACC may attenuate it



Amygdala nuclei exhibit functional and developmental specialization



Discussion

- As hypothesized, we observed distinct maturational trajectories for functional connectivity between amygdala nuclei and PFC regions across adolescent development, consistent with past work examining amygdala development by subregion.[5]
- Unexpectedly, both better and worse affective and cognitive control were related to fronto-amygdala functional connectivity, challenging prominent neurodevelopmental models of adolescence[12] that propose PFC maturation to downregulate amygdala activity to facilitate age-related behavioral improvements.
- Finally, our psychological domain decoding analysis using meta-analytic data revealed that cortical connectivity of human amygdala nuclei exhibit functional and developmental specialization, underscoring the need for future studies to consider a subregional or nuclei-based approach rather than treating the structure as functionally monolithic.
- The present study's results, which indicate dissociable developmental patterns and behavioral associations, clarify contradictory findings from previous studies that have often treated the amygdala as a functionally monolithic structure.

Conclusion

Together, our findings suggest that functional maturation of amygdala nuclei integration with prefrontal structures from adolescence to adulthood follows a driven dual systems model with connections involved in cognitive and social processing strengthening in functional coupling through adolescence and into adulthood while connections related to affective processing dampen in their coordinated activity through development.

Future Directions

- Our study sample was limited to healthy participants. Future work is needed in more psychiatrically diverse samples to advance our understanding of psychopathological etiologies and developmentally timed interventions.
- Evidence suggests that amygdala circuitry development begins far earlier in life,[4] indicating a need to recruit younger study participants to more comprehensively characterize amygdala circuitry development.
- Future work is needed to examine amygdala nuclei activity in response to various stimuli, which may inform our understanding of development and psychiatric risk.
- Finally, specific neurobiological mechanisms supporting the maturation of this circuitry in humans remains. Possible factors supporting fronto-amygdala maturation may include adolescent changes in the balance of cortical excitatory/inhibitory (E/I) neurotransmission, puberty-related changes in sex hormones, and/or elevated dopaminergic signaling through mesocorticolimbic circuitry during adolescence.

References

1. Larsen, B. & Luna, B. (2018), *Neuroscience & Biobehavioral Reviews*; 2. Paus, T., Keshavan, M., & Giedd, J. N. (2008), *Nature Reviews Neuroscience*; 3. Gee, D.G., et al. (2013), *Journal of Neuroscience*; 4. Gabard-Durnam, L.J., et al. (2014), *NeuroImage*; 5. Alarcón, G., et al. (2015), *NeuroImage*; 6. Gründemann, J. & Lüthi, A. (2015), *Current Opinion in Neurobiology*; 7. Muller, J.F., Mascagni, F., & McDonald, A.J. (2006), *Journal of Comparative Neurology*; 8. Price, J. & Amaral, D. (1981), *Journal of Neuroscience*; 9. McDonald, A.J. (1982), *Journal of Comparative Neurology*; 10. Goossens, L., et al. (2009), *Human Brain Mapping*; 11. Dulac, C. & Torello, A.T. (2003), *Nature Reviews Neuroscience*; 12. Casey, B.J., Jones, R.M., & Somerville, L.H. (2011), *Journal of Research on Adolescence.*

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), the National Institutes of Health (T32MH016804 to VJS; T32AA007453 to DJP; R01MH0607924 to BL; 5R37MH080243-14 to BL), and CTSI (UL1TR001857).

National Institutes of Health

Staunton farm foundation EST. 1937

Contact: amo80@pitt.edu
Bluesky: @amarojha.bsky.social