Characterizing Fronto-Amygdala Functional Connectivity Across Adolescent Development: A High-Field Longitudinal Investigation

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Introduction

Adolescent Affective Development

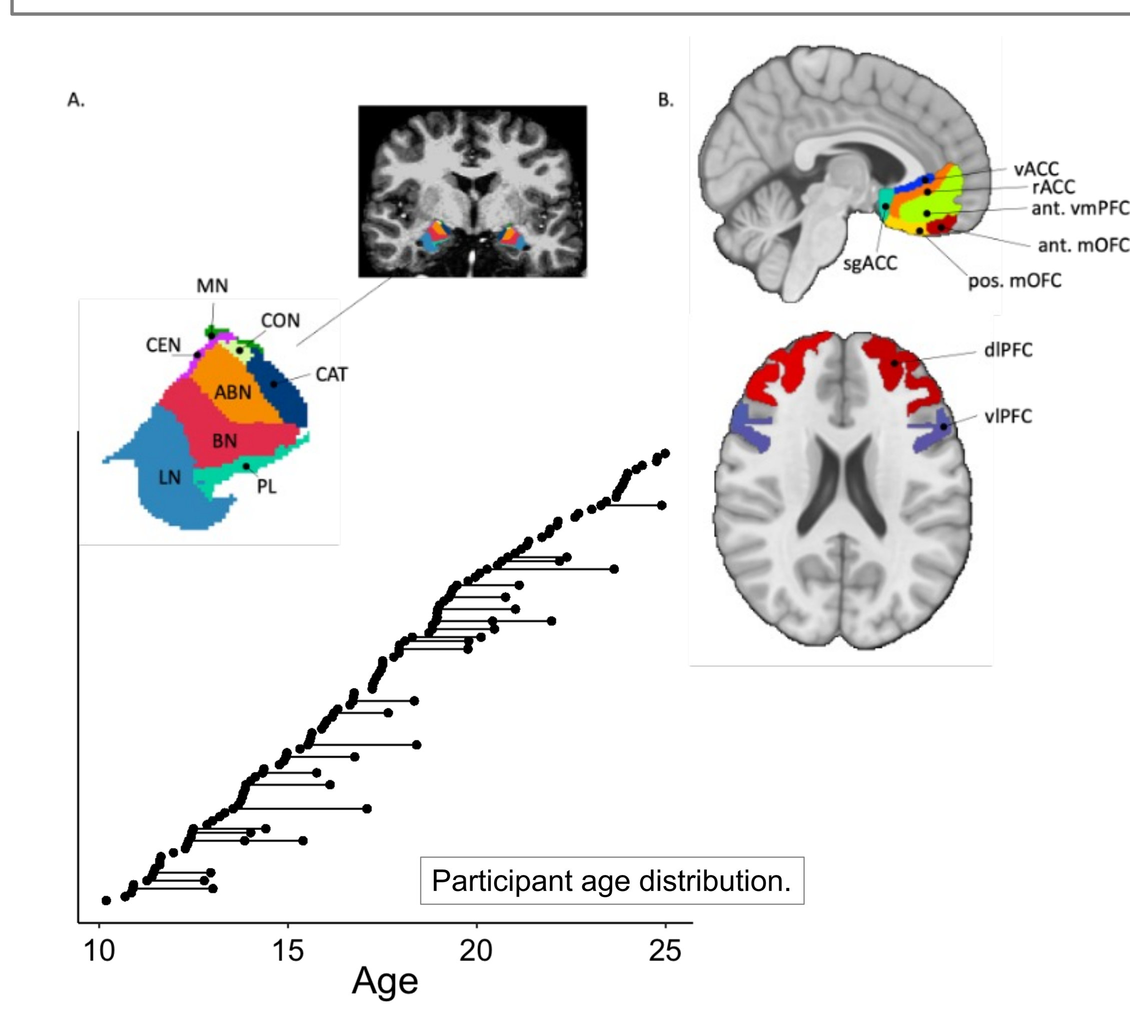
- Adolescence is marked by significant affective development[1], supported by neural refinements of fronto-amygdala regions and their connectivity[2] during a time for increased risk for the emergence of major psychopathology[3,4,5], exemplified by internalizing and externalizing phenotypes.
- Initial results from fronto-amygdala developmental studies, however, are inconsistent likely due to the complexity of amygdala organization composed of subnuclei with unique functional and connectional profiles[6].
- Here, we characterize developmental changes in prefrontal connectivity to amygdalar nuclei at rest and during a cognitive state as well as associations with internalizing/externalizing phenotypes in healthy adolescents.

Hypothesis

Given past findings, we hypothesize that fronto-amygdala functional connectivity supporting cognitive control will increase with age and be associated with externalizing disorders while those supporting affect will decrease with age and be associated with internalizing disorders.

Study Design & Analyses

- We collected 7 Tesla fMRI data in 113 healthy participants (51.3% F) ages 10-25, scanned 1-3 times for a total of 140 scans.
- We extracted indices of resting-state and background connectivity from a memory-guided saccade task to represent cognitive states with task-evoked activity removed prior to computing functional connectivity (FC).
- Amygdala nuclei were segmented using subject-specific anatomical definitions from FreeSurfer 7.2[7,8].
- Normative variation in internalizing and externalizing was assessed using the Adult/Youth Self-Report (ASR/YSR) measures[9,10].
- Generalized additive mixed models (GAMMs)[11] characterized development of fronto-amygdala connections and linear mixed effects models were used to test associations between connectivity and ASR/YSR while controlling for inverse age (age^{-1}).
- Relative connectivity strengths of background vs. resting-state was computed as the difference of z-scored FC values to provide an index of state-based modulation.
- Statistical tests were Bonferroni-corrected to account for multiple comparisons.



	TR (ms)	TE (ms)	Voxel size (mm)	Total duration (min:sec)
Rest	48	23	2 x 2 x 2	8:03
MGS	48	23	2 x 2 x 2	7:03
T1w	6000	2.47	1 x 1 x 1	5:14

Fronto-amygdala ROIs

AMYG

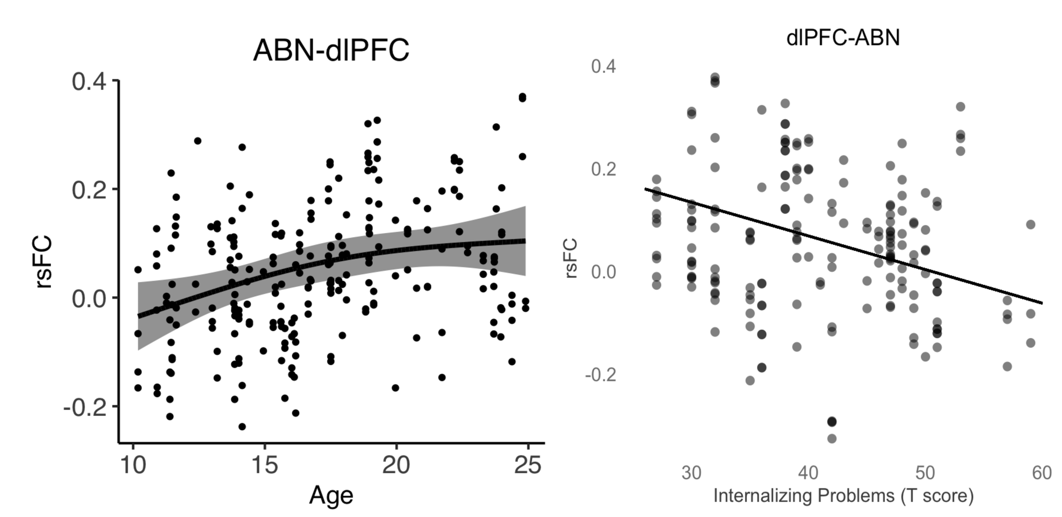
ABN, accessory basal nucleus; **BN**, basal nucleus; **LN**, lateral nucleus; **PL**, paralaminar nucleus; **CAT**, corticoamygdaloid transition area; **CON**, cortical nucleus; **MN**, medial nucleus; **CEN**, central nucleus

PFC

vmPFC, ventromedial prefrontal cortex; **sgACC/vACC/rACC**, subgenual/ventral/rostral anterior cingulate cortex; **mOFC**, medial orbitofrontal cortex; **vlPFC**, ventrolateral PFC, **dlPFC**, dorsolateral PFC.

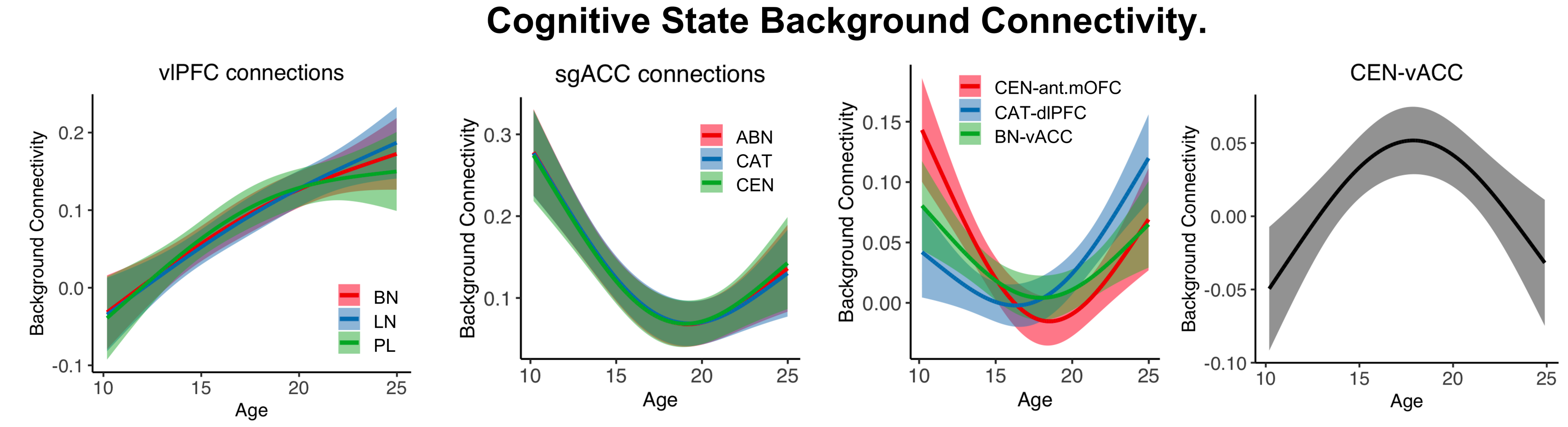
Results

Resting-State Functional Connectivity.

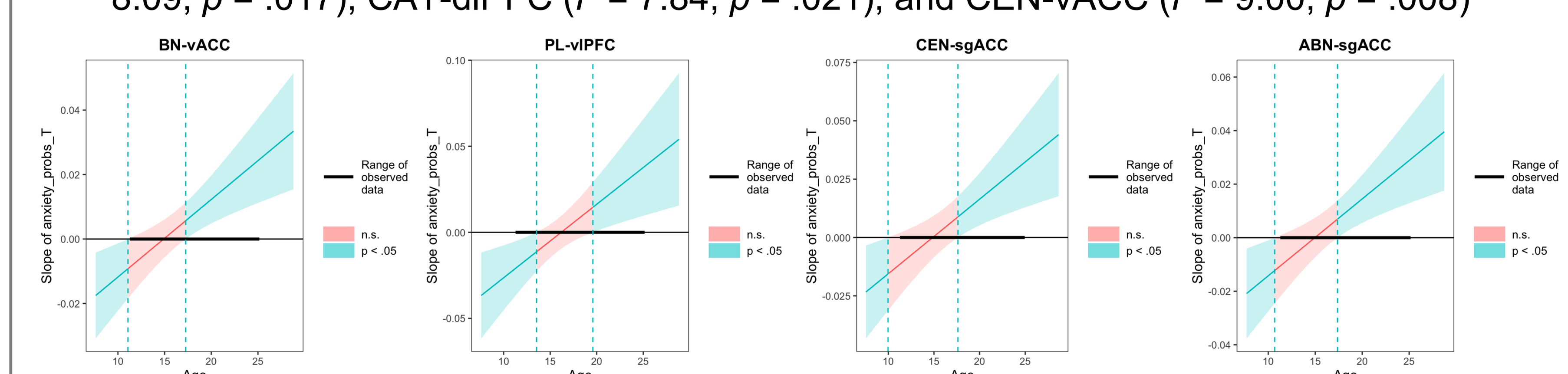


- ABN-dlPFC rsFC significantly increased across adolescence ($F = 6.96$, $p = .048$).
- Stronger ABN-dlPFC rsFC was associated with fewer internalizing problems after controlling for age^{-1} effects ($\beta = -.005$, $p = .022$).

Cognitive State Background Connectivity.

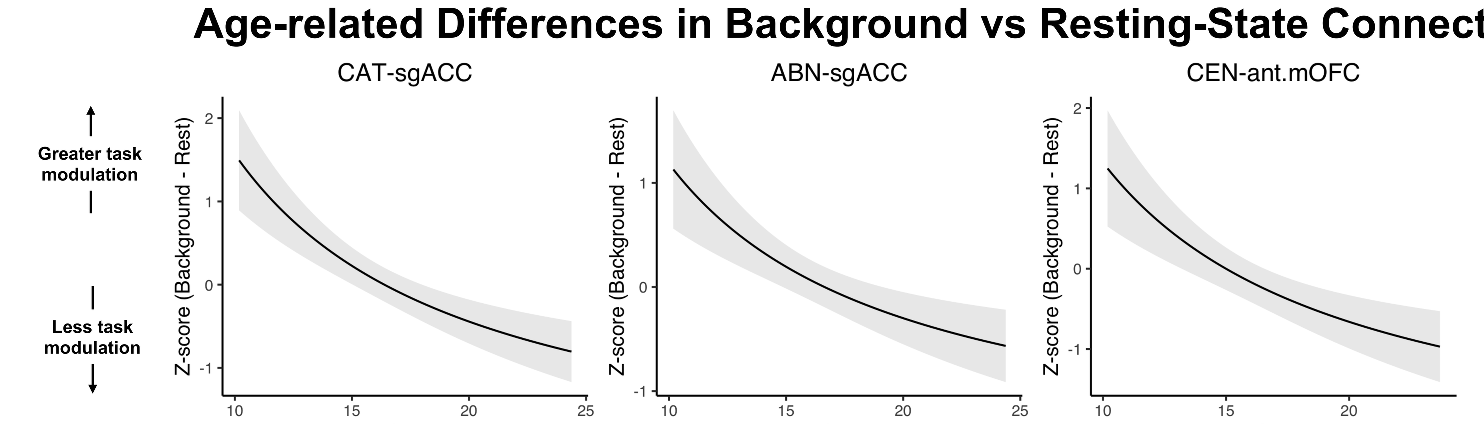


- Background connectivity **increased** with age in connectivity with the **vlPFC** in the BN ($F = 11.23$, $p = .001$), LN ($F = 15.76$, $p = .00005$), and PL ($F = 6.85$, $p = .048$).
- Background connectivity **decreased** with age in connectivity with the **sgACC** in the CEN ($F = 7.44$, $p = .033$), ABN ($F = 11.16$, $p = .001$), and CAT ($F = 12.77$, $p = .0002$).
- Quadratic associations were found for CEN-ant.mOFC ($F = 7.18$, $p = .042$), BN-vACC ($F = 8.09$, $p = .017$), CAT-dlPFC ($F = 7.84$, $p = .021$), and CEN-vACC ($F = 9.00$, $p = .008$)

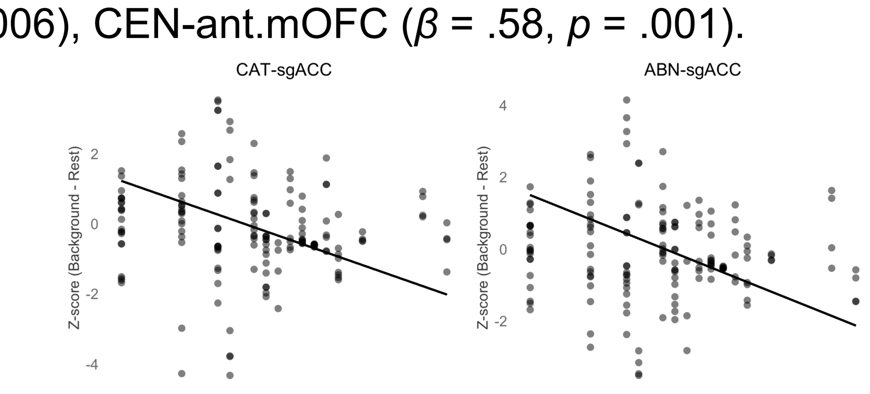


- Cognitive state background connectivity was significantly associated with anxiety symptoms as a function of age in four connections: BN-vACC ($\beta = .002$, $p = .007$), PL-vlPFC ($\beta = .004$, $p = .033$), CEN-sgACC ($\beta = .003$, $p = .022$), and ABN-sgACC ($\beta = .003$, $p = .011$).

Age-related Differences in Background vs Resting-State Connectivity



- Cognitive state background FC was greater than resting state FC in youth and became more similar into adulthood in CAT-sgACC ($\beta = .049$, $p = .002$), ABN-sgACC ($\beta = .47$, $p = .006$), CEN-ant.mOFC ($\beta = .58$, $p = .001$).



- Less sgACC cognitive state FC (relative to rest) with the CAT ($\beta = -.48$, $p = .048$) and ABN ($\beta = -.59$, $p = .006$) was associated with more externalizing problems after controlling for age^{-1}.

Discussion

- Background FC during a cognitive state differed from resting-state FC in youth compared to adults, suggesting developmental decreases in cognitive effort.
- Age-related changes in **resting-state FC** were only evident in increases in dlPFC-ABN suggesting a foundational maturation in executive control over affect supporting fewer internalizing features.
- **During cognitive state**, further developmental increases in FC were evident in executive PFC including dlPFC-CAT and vlPFC-BN, -LN, -PL and anterior mOFC-CEN suggesting a need to engage executive systems at a higher level through adolescence. In contrast, decreases were found for ventral frontal regions of vACC-CEN, sgACC-CAT, -ABN and -CEN, suggesting developmental attenuation of executive affective/motivational frontal systems with amygdala nuclei.
- Positive associations with anxiety were found in ventral frontal regions with amygdala nuclei suggesting a contribution of these circuits in aversive associative learning-related processes during mid-adolescence and into early adulthood.
- **Taken together**, our findings indicate that fronto-amygdala coupling differs by amygdala nuclei with those coupling with dorsal executive regions strengthening with development while those coupled with more ventral frontal affective regions weakening suggesting a transition to more top-down executive control as affective influences are attenuated with deviations associated with markers of affective disorders.

Future Directions

- Although our study leveraged high-field resting-state fMRI data at 7T, future work should leverage Big Data, include additional emotional assessments, and investigate these circuits in adolescent populations with greater psychopathological variability, such as in individuals with depression and/or anxiety disorders.
- Better understanding of the unique processes of amygdala nuclei is needed.
- Understanding the plasticity mechanisms underlying these changes in fronto-amygdala connectivity are also needed.

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