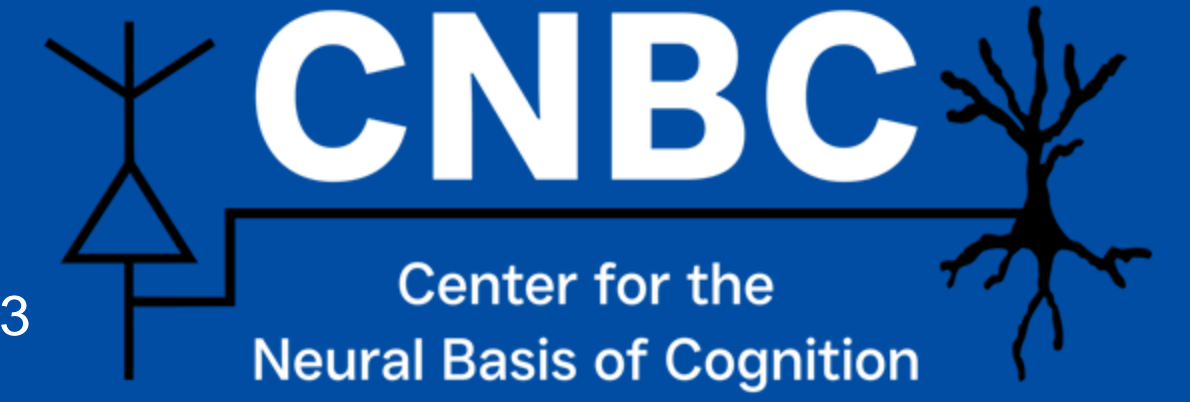# Nuclei-Specific Functional Maturation of Fronto-Amygdala Circuitry Through Adolescence: Longitudinal Insights from 7 Tesla fMRI

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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 BLA and SFA nuclei connectivity with the lateral PFC would increase with age, whereas CMA nuclei 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.
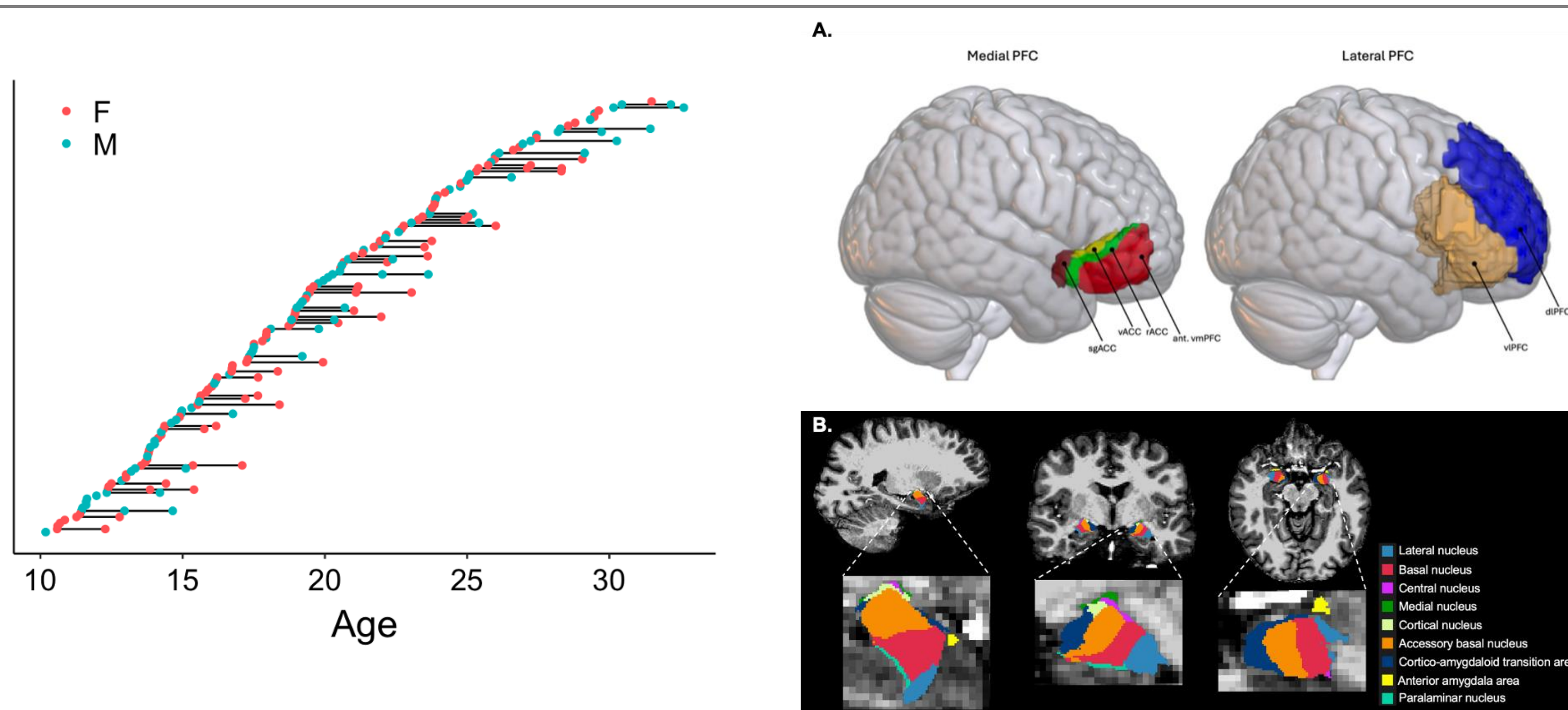

Results

Age-Related Changes in Fronto-Amygdala Connectivity

- Most fronto-amygdala connections did not significantly change with age following Bonferroni corrections ($ps > .0083$) suggesting maturation by adolescence.
- Specific connections (n=8) for each major amygdala subdivision showed unique changes with age, suggesting peaks in affect and increases in cognitive processes.
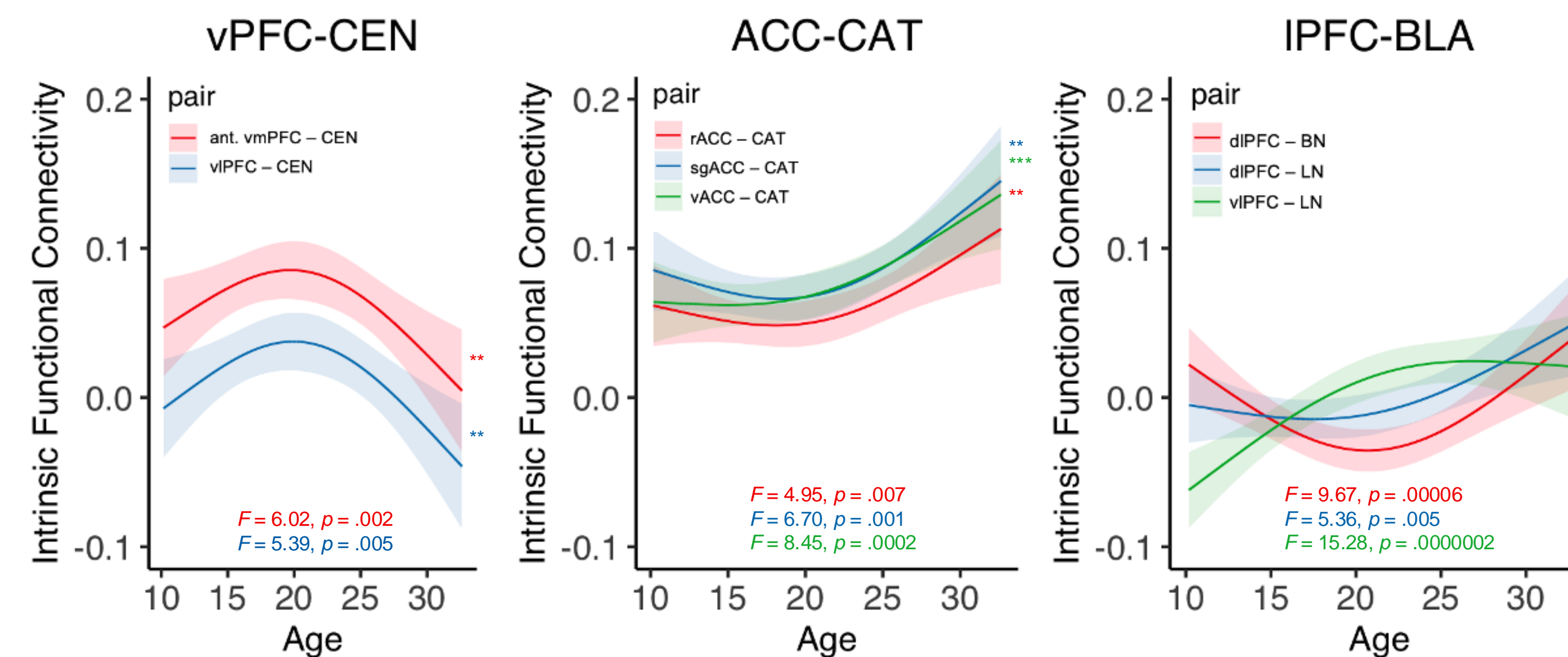

Associations with Affective Measures (beyond non-linear age effects)

- Stronger connectivity in affective and cognitive connections were associated with fewer internalizing behaviors: anterior vmPFC – CEN ($\beta = -0.002$, $p = .0007$), vACC – CAT ($\beta = -0.002$, $p = .005$). In contrast, stronger sgACC – CAT connectivity was uniquely associated with more externalizing behaviors ($\beta = 0.002$, $p = .001$).
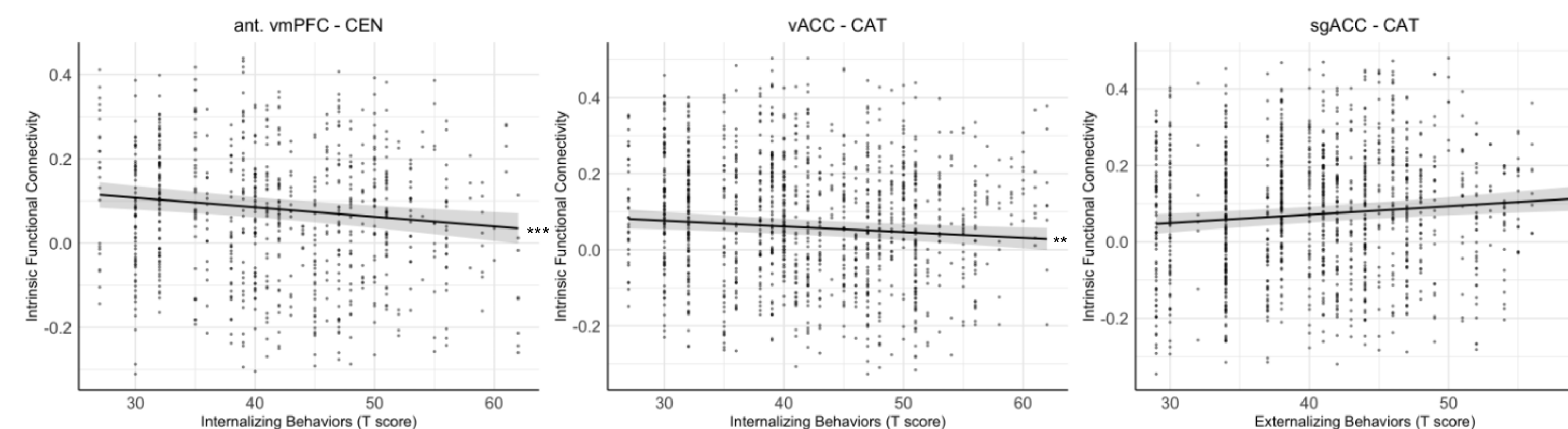
Associations with Cognitive Measures (beyond non-linear age effects)

- Stronger connectivity in two connections, both related to fewer internalizing behaviors, were associated with faster MGS performance on correct trials: anterior vmPFC – CEN ($\beta = -0.43$, $p = .003$), vACC – CAT ($\beta = -0.34$, $p = .003$).
- Stronger connectivity in social cognitive circuitry (sgACC – CAT), related to more externalizing behaviors, was associated with increased variability on MGS accuracy ($\beta = 0.03$, $p = .0001$).
- Stronger connectivity in fronto-amygdala circuitry related to executive functioning and associative learning processes (vlPFC – LN) was associated with reduced variability on MGS latency on correct trials ($\beta = -0.76$, $p = .00003$).
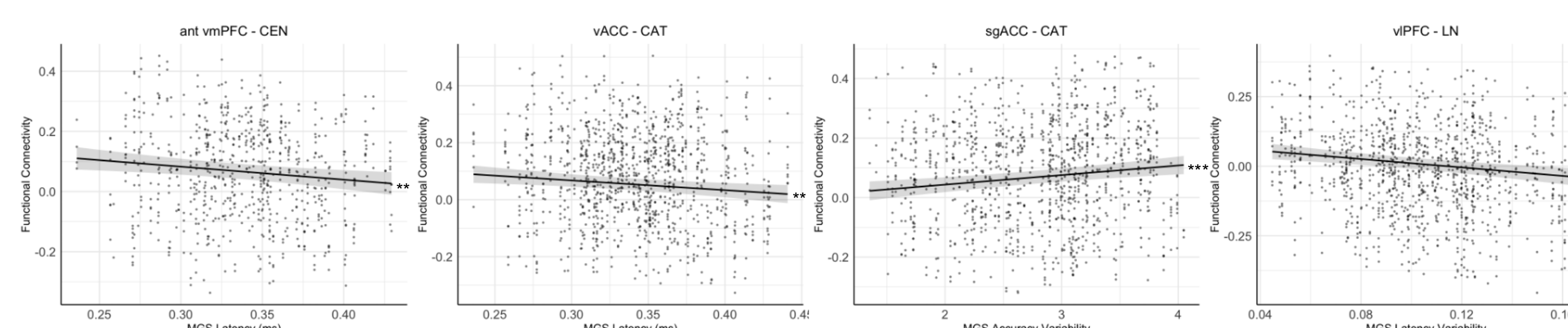
Discussion

- The present study provides novel evidence for mature and protracted functional maturation of anatomically precise fronto-amygdala circuitry through adolescence into early adulthood.
- Ventral PFC circuitry—important for value assignment[23] and self-referential processing[24]—with the CEN—critical for canonical fight, flight, freeze affective responses[25]—broadly decreased in connectivity across adolescent development and into early adulthood, possibly suggesting maturation of affective control; stronger coupling in one of these connections was related to fewer internalizing problems, underscoring a potential role for this connection in emotion regulation.
- 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 deficits 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, our findings show establishment of core aspects of affect and cognition by adolescence while identifying unique specialization of higher-order affective/cognitive functional integration into adulthood.**

Future Directions

- Future work should utilize structural connectivity measures, include additional emotional assessments, and investigate these circuits in adolescent populations with greater psychopathological variability, such as in populations with depression and/or anxiety disorders.

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Acknowledgements

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