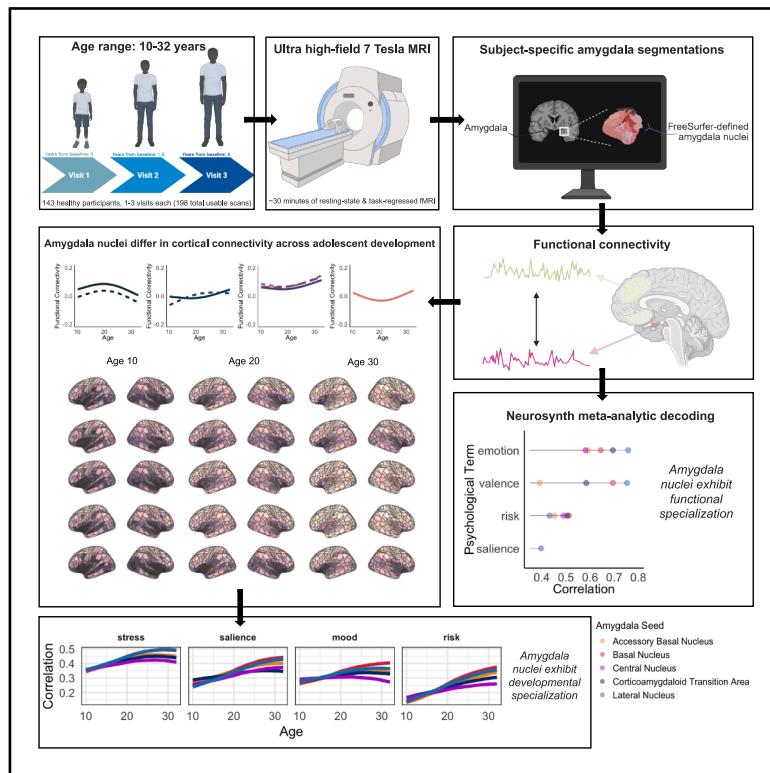


Human amygdala nuclei show distinct developmental trajectories from adolescence to adulthood in functional integration with prefrontal circuitry

Graphical abstract



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In brief

Ojha et al. use longitudinal 7 T neuroimaging to characterize distinct developmental trajectories of fronto-amygdala connectivity across nuclei through adolescence. They identify how age-related connections support affective and cognitive control and find amygdala nuclei to exhibit functional and developmental specialization.

Highlights

- Ultra-high-field 7 T fMRI was used to segment amygdala nuclei
- Fronto-amygdala functional connections develop along distinct trajectories
- Age-related connections relate to affective and cognitive control
- Amygdala nuclei exhibit developmental and functional specialization



Article

Human amygdala nuclei show distinct developmental trajectories from adolescence to adulthood in functional integration with prefrontal circuitry

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SUMMARY

Adolescent neurodevelopment of affective and cognitive control, crucial for healthy functioning and impaired transdiagnostically, is supported by refinements between the amygdala and prefrontal cortex (PFC). Due to technical limitations, fronto-amygdala connectivity remains poorly characterized. Here, we leverage multimodal longitudinal 7 T neuroimaging data in 143 healthy participants aged 10–32 to examine developmental trajectories between subject-specific amygdala nuclei and PFC subregions. We find age-related functional connectivity changes between the lateral PFC and basolateral amygdala, ventral portions of the PFC and central amygdala, and the anterior cingulate cortex and corticoamygdaloid transition area. Variability in connectivity strength relates to individual differences in affective and cognitive control. Using a data-driven meta-analytic decoding approach, we find functional specialization across nuclei and development. Together, these data recapitulate amygdala heterogeneity from animal models and inform how diverse subcircuits support adaptive functioning and confer psychiatric risk during developmental windows of heightened plasticity.

INTRODUCTION

Adolescence is a period of neurodevelopmental refinement and specialization^{1–3} characterized by marked improvements in diverse functions (e.g., working memory and emotion regulation),^{4,5} which coincide with the maturation of neural systems involved in cognitive and affective processing.⁶ Neurodevelopmental frameworks of adolescence (e.g., the driven dual systems model)^{7,8} propose that adolescent behavioral phenotypes (including increased risk-taking and exploration) may be explained by differences in the engagement of executive and affective systems in adolescence. Specifically, it posits that executive cortical regions, important for cognitive control functions, such as working memory and inhibitory control, protractedly mature through adolescence before stabilizing into adulthood.^{9,10} On the other hand, subcortical systems, involved in affective processing functions, such as reward processing and socioemotional sensitivity, exhibit a developmental peak in functioning in adolescence before declining.^{11–13} This unique balance between executive control and affective systems in adolescence can drive decision-making systems to pursue rewards, contributing

to prototypical motivated behaviors observed in adolescents. These behaviors, though sometimes risky, are thought to be crucial for specializing experience-dependent neural circuitry supporting behaviors adapted to increasingly complex environmental demands. The triadic model, another influential neurodevelopmental model,¹⁴ posits that motivated behaviors in adolescents can be understood in the context of interactions between three mesocorticolimbic structures—an approach (e.g., reward) system involving the nucleus accumbens, an avoidance (e.g., fear) system involving the amygdala, and a regulatory system involving the prefrontal cortex (PFC).

Previous neuroimaging work suggests that the amygdala is a central node, or anchor, across multiple large-scale networks (e.g., perception, affiliation, and aversion) supporting complex social functioning in animals such as primates.¹⁵ The unusually protracted maturation of PFC circuitry, unique to humans,¹⁶ including its functional integration with the amygdala, represents a neurobiological substrate of experience-dependent plasticity reflecting our species' extended altriciality.¹⁷ Circuit-level interactions between the PFC and amygdala support aspects of cognitive and affective development (e.g., decision-making



and emotion regulation).^{18,19} Disruptions of these interactions are implicated across psychopathologies with adolescent onset, including depression, anxiety, and substance use disorders.^{20–22} To better understand the functional relevance of this circuitry, it is crucial to investigate specific connections within fronto-amygdala pathways. These connections support myriad psychological functions, and deviations from normative developmental trajectories may confer psychiatric risk and explain the circuitry's near-ubiquitous involvement across disorders. However, previous research examining the development of fronto-amygdala connectivity has been inconclusive, with mixed findings showing strengthening or weakening of functional connectivity across adolescent development.^{23–25}

One possible reason for these discrepancies may be due to the structural and functional heterogeneity of the amygdala itself, which broadly modulates neural processing²⁶ but includes several substructures that follow distinct developmental trajectories.²⁷ The amygdala is comprised of interconnected subregions supporting associative learning,²⁸ affective responsiveness,²⁹ and socio-emotional processing.³⁰ These subregions are characterized by discrete morphological, functional, and connectional properties^{31–33} and express rich transcriptomic diversity³⁴ as well as heterogeneity in cytoarchitecture and receptor densities.³⁵ Subregions include the basolateral amygdala (BLA), centromedial amygdala (CMA), and superficial amygdala (SFA).²⁸ However, each subregion is further comprised of anatomically and functionally distinct nuclei: the anterior amygdaloid area (AAA), accessory basal nucleus (ABN), basal nucleus (BN), cortico-amygdaloid transition area (CAT), central nucleus (CEN), cortical nucleus (CON), lateral nucleus (LN), medial nucleus (MN), and paralamellar nucleus (PL). BLA nuclei (ABN, BN, and LN) have been linked to associative learning, value updating, encoding of stimulus-outcome associations, and goal-directed behaviors.^{36–40} CMA nuclei (CEN and MN) coordinate autonomic and behavioral responses to threats, mediate arousal, and initiate rapid emotional responses.^{41–43} Finally, SFA nuclei (AAA, CAT, CON, and PL), the most understudied subregion, are associated with social information processing, olfactory cues, and affective salience detection.^{30,44–46} However, limitations in further segmenting amygdala subregions in neuroimaging data have precluded associating more specific functions with individual nuclei.

Although the complexity of amygdala circuitry is well established in animal models,⁴⁷ developmental neuroimaging studies in humans have almost exclusively examined whole-amygdala or subregional connectivity due to technical limitations on typical 3 Tesla (T) MRI scanners. These limitations include the relative size of amygdala nuclei and low temporal signal-to-noise ratio (tSNR) in temporal regions, complicating developmental *in vivo* studies in humans.⁴⁸ Advances in ultra-high-field neuroimaging (e.g., 7 T human fMRI) provide a unique opportunity to investigate relatively smaller subcortical structures like amygdala nuclei^{49,50} that require greater tSNR. Recent work comparing 3 to 7 T shows marked tSNR improvements in the amygdala at higher field strengths.⁵¹ Investigators have also suggested examining amygdala connectivity heterogeneity for neuroimaging-based precision psychiatry approaches,⁵² with emerging evidence identifying amygdala nucleus-based func-

tional connectivity associations with dimensions of mental health.⁵³ This underscores a need to chart normative maturational trajectories to contextualize developmental deviations in cases of psychopathology.

BLA nuclei share strong bidirectional connections with the cortex⁵⁴; play a role in higher-order cognitive processes, including associative learning and memory^{36–38}; and predominantly feature glutamatergic pyramidal neurons resembling cortical circuitry.⁵⁵ In contrast, CMA nuclei densely project to the brain stem and hypothalamus,^{56,57} mediate rapid behavioral responses and autonomic processes (e.g., fight-or-flight and freeze responses, appetitive and aversive behaviors, and physiological reactivity),^{41–43} and are characterized by a preponderance of GABAergic medium spiny neurons resembling striatal circuitry.⁵⁸ These features suggest that the BLA may be more closely related to "cognitive" processes (e.g., coordination with the cortex and a role in associative learning and memory processes) and the CMA with "affective" processes (e.g., coordination with the subcortex and brain stem and a role in physiological responses and rapid behavioral responses).

Guided by this framework of the "cortical" BLA and "subcortical" CMA, we hypothesized that fronto-amygdala circuitry would exhibit dissociable developmental trajectories reflecting cognitive and affective specialization, respectively. Based on the driven dual systems model,^{7,8} which posits that affective functioning peaks in adolescence while cognitive processes stabilize into adulthood, we make the following predictions. We expect to observe age-related increases in functional coupling, reflecting greater coordinated activity, between the lateral PFC, involved in executive functioning (e.g., cognitive control)⁵⁹ and BLA nuclei, important for associative learning.⁶⁰ In contrast, we expect connectivity between the medial PFC, involved in context-specific valuation of stimuli and self-referential processing, among other functions,^{61,62} and CMA nuclei important for affective (e.g., reward-related and socioemotional) processes, to peak in mid-adolescence before weakening into adulthood, reflecting normative developmental changes in reward responsibility, motivated behaviors, and affective reactivity.^{63–68} SFA nuclei, the most understudied of the major amygdala subdivisions, are more difficult to categorize in this "cortical/subcortical" schema; however, some evidence suggests a role in socio-affective functions, including processing facial expressions and chemosensory signals in humans.^{30,44} Given striking changes in adolescents' socio-affective sensitivity, experiences, and processing,^{69,70} we hypothesize protracted functional integration of the "social" SFA with brain structures, such as anterior cingulate cortex (ACC) subregions, that are involved in multimodal integration of intrinsic and extrinsic cues, social-emotional responsivity, and self-regulation.^{71,72} Finally, we expect fronto-amygdala connections that exhibit age-related changes through adolescence to be related to individual differences in cognitive and affective measures: PFC-BLA connectivity will be associated with cognitive (working memory task) performance and PFC-CMA with (self-reported) affective regulation. Given that the functional maturation of circuitry between the PFC and amygdala nuclei remains unknown in humans, we are limited in our ability to hypothesize at the nucleus level.

Table 1. Demographic characteristics of the study sample

| | Participants (<i>n</i> = 143) |
|----------------------------------|--------------------------------|
| Sex assigned at birth (% female) | 75 (52.45%) |
| Race (%) | |
| Native American/Alaska Native | 0 (0%) |
| Asian | 12 (8.39%) |
| Black/African American | 24 (16.78%) |
| Native Hawaiian/Pacific Islander | 0 (0%) |
| White | 95 (66.43%) |
| More than one race | 8 (5.59%) |
| Unknown/Missing | 4 (2.80%) |
| Ethnicity (%) | |
| Hispanic | 5 (3.50%) |
| Not Hispanic | 136 (95.10%) |
| Unknown/Missing | 2 (1.40%) |
| Highest parental education | |
| Less than ninth grade | 1 (0.70%) |
| Partial high school | 1 (0.70%) |
| High school | 14 (9.79%) |
| College | 60 (41.96%) |
| Postgraduate | 63 (44.06%) |
| Unknown/missing | 4 (2.80%) |
| Highest annual parental income | |
| <\$25,000 | 6 (4.20%) |
| \$25,000–\$50,000 | 15 (10.49%) |
| \$50,000–\$75,000 | 29 (20.28%) |
| \$75,000–\$100,000 | 37 (25.87%) |
| \$100,000–\$250,000 | 35 (24.48%) |
| >\$250,000 | 12 (8.39%) |
| Unknown/missing | 9 (6.29%) |

To address these gaps, the present study leverages recent advances in ultra-high-field 7 T human fMRI and subject-specific amygdala nuclei segmentations to characterize developmental trajectories of fronto-amamygdala functional connectivity at the nucleus level across adolescence and into early adulthood. Using a longitudinal, multimodal study design, we aim to (1) characterize age-related functional connectivity changes between PFC structures and anatomically defined amygdala nuclei; (2) relate age-related connections to measures of cognitive and affective control; and (3) leverage a meta-analytic data-driven approach to identify potential psychological functions shared among or unique to each amygdala nucleus connectivity pattern in adults and through adolescent development. This work charts the development of functional integration of amygdala nuclei with prefrontal circuitry to understand how these connections support healthy functioning and how deviations may confer psychiatric risk.

RESULTS

To characterize how amygdala nuclei develop in their functional connectivity with PFC circuitry to support aspects of cognitive

and affective control, we segmented amygdala nuclei from ultra-high-field anatomical scans at 7 T in a subject-specific manner and collected nearly 30 min of fMRI data per person at each visit. In a sample of 143 healthy participants ages 10–32 years assessed longitudinally, we (1) identified shared and distinct age-related changes in functional connectivity across development at the level of amygdala nuclei, (2) tested the extent to which connectivity strength in maturing fronto-amamygdala connections was related to aspects of affect (internalizing, externalizing, and emotion regulation) and cognition (working memory accuracy, latency on correct trials, and variability of each), and (3) performed a psychological domain decoding analysis to associate amygdala nuclei seeded connectivity patterns across the cortex with meta-analytic phenotype data derived from previous neuroimaging studies.

Distinct developmental trajectories of fronto-amamygdala connectivity across nuclei

To investigate which fronto-amamygdala circuits significantly changed with age at the nuclei level, we analyzed intrinsic (combined resting-state and background) functional connectivity data in 143 adolescents and young adults (sample demographic characteristics are presented in Table 1). FreeSurfer-defined amygdala nuclei regions of interest (ROIs) are presented in Figures 1A and 1B, PFC ROIs in Figure 1C, and a distribution of study participants by age, sex, and visit in Figure 1D. Bonferroni corrections ($p < 0.008$) for multiple comparisons revealed that developmental changes in fronto-amamygdala circuitry are specific to a subset of functional connections: dorsolateral PFC (dIPFC)-BN ($F = 9.68$, $p < 0.001$), dIPFC-LN ($F = 5.36$, $p = 0.005$), and ventrolateral PFC (vIPFC)-LN ($F = 15.29$, $p < 0.001$) increased in connectivity strength through adolescence before either stabilizing or continuing to increase into early adulthood. The anterior ventromedial PFC (vmPFC)-CEN ($F = 6.02$, $p = 0.002$) and vIPFC-CEN ($F = 5.39$, $p = 0.005$) exhibited a peak in connectivity strength before decreasing through the third decade of life. Finally, rostral ACC (rACC)-CAT ($F = 4.95$, $p = 0.007$), subgenual ACC (sgACC)-CAT ($F = 6.70$, $p = 0.001$), and ventral ACC (vACC)-CAT ($F = 8.45$, $p < 0.001$) exhibited a transient dip in connectivity strength before increasing through the third decade of life. See Figure 2 for age-related model fits and Table 2 for statistical model details. Significant age-related model fits with individual data points and derivative bars indicating periods of significant change are presented in Figure S1. No other fronto-amamygdala ROI pair was significantly associated with age (all $p > 0.008$). All (significant and non-significant) fronto-amamygdala connections across development are presented in Figure S2 for illustrative purposes. These results suggest that developmental changes in fronto-amamygdala functional connectivity are specific to a subset of circuits.

Sensitivity analyses performed to test for potential confounds (sex, ROI tSNR, ROI size, and motion) in age-related associations yielded results largely consistent with our main findings. All but one age-related connection remained significant at $p < 0.05$ following sensitivity analyses, with most remaining significant at the Bonferroni correction level ($p < 0.008$), suggesting that most of our developmental findings are robust to potential confounds; covarying for PFC and amygdala nucleus ROI sizes

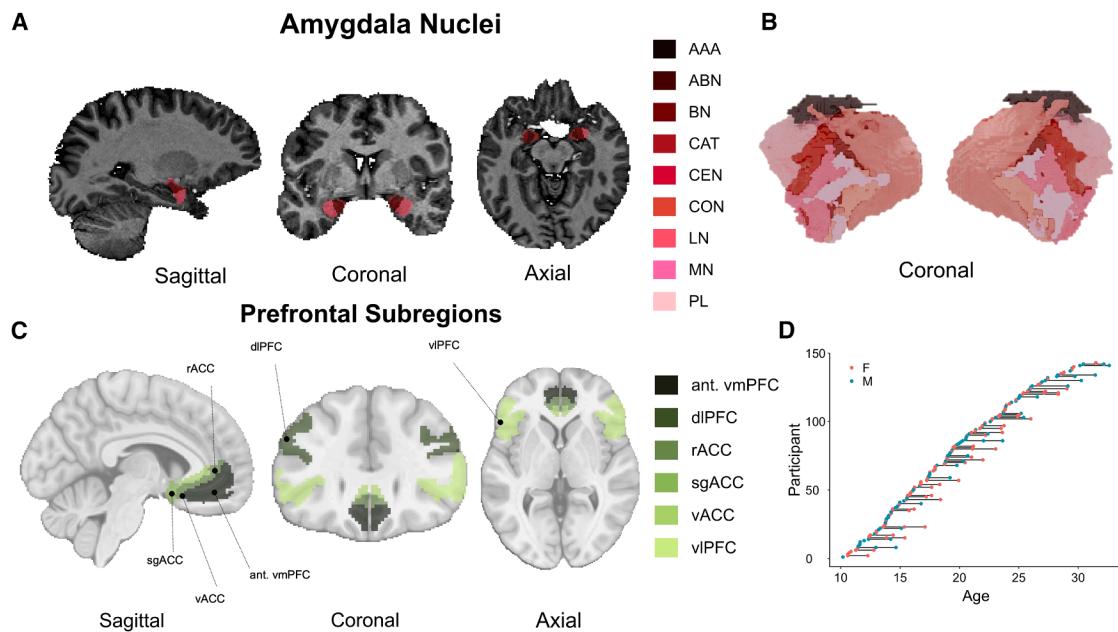


Figure 1. Amygdala and prefrontal ROIs and participant distribution by age at scan, sex assigned at birth, and visit

(A) FreeSurfer-derived amygdala nuclei segmentations (all nine nuclei) overlaid on an example participant's skull-stripped T₁-weighted structural image (sagittal, coronal, and axial views). Although all nine nuclei are shown here, only five were retained for further analysis—accessory basal nucleus (ABN), basal nucleus (BN), central nucleus (CEN), corticoamygdaloid transition area (CAT), and lateral nucleus (LN)—due to exclusions based on insufficient temporal signal-to-noise (tSNR) or ROI volume size. Excluded amygdala nuclei included the anterior amygdala area (AAA), cortical nucleus (CON), medial nucleus (MN), and paralaminar nucleus (PL).

(B) Three-dimensional rendering of amygdala nuclei (coronal view), reconstructed in Blender; colors correspond to each nucleus.

(C) Prefrontal cortical ROIs overlaid on a structural template (sagittal, coronal, and axial views). Medial PFC ROIs (sagittal view) were defined using the Mackey & Petrides atlas and included the anterior ventromedial prefrontal cortex (ant. vmPFC), rostral anterior cingulate cortex (rACC), subgenual anterior cingulate cortex (sgACC), and ventral anterior cingulate cortex (vACC). Lateral PFC ROIs included the dorsolateral prefrontal cortex (dIPFC), defined using the Glasser atlas, and ventrolateral prefrontal cortex (vIPFC), defined using the Brainnetome atlas.

(D) Participant distribution by age at scan, sex assigned at birth, and scan visit. Each dot represents one MRI session; lines connect visits from the same individual (F, female; M, male).

See Figures S6 and S7 for fronto-amamygdala ROI size by number of voxels and tSNR, respectively.

rendered dIPFC-BN age effects no longer significant ($p = 0.068$). See Table S1 for statistical model details for each sensitivity test for each age-related connection.

To determine whether separating age effects by amygdala nuclei for each PFC ROI improved model fits, we compared Akaike information criteria (AICs) derived from models with and without the factor-smooth (“by” term) for amygdala nuclei. We found that including the factor-smooth amygdala nucleus term improved model fits (i.e., lower AICs) for the sgACC (AIC difference between models = 1.641) and vIPFC (AIC difference between models = 42.696), suggesting that separating age effects by amygdala nuclei produces models that better fit the data than models that did not separately evaluate age effects by amygdala nuclei for these two PFC structures.

To investigate the impact of sex assigned at birth on age-related changes in fronto-amamygdala functional connectivity, we performed post hoc moderation analyses, which revealed three connections that significantly ($p < 0.05$) differed by sex in their age-related connectivity changes between males and females: anterior vmPFC-CEN ($F = 3.04, p = 0.048$), dIPFC-LN ($F = 5.34, p = 0.005$), and vIPFC-LN ($F = 11.94, p < 0.001$). Further inspection of these age-related sex differences using models run sepa-

rately in males and females revealed sex-specific trajectories. In males, anterior vmPFC-CEN significantly changed with age ($F = 8.95, p < 0.001$), exhibiting an inverted U shape, but did not change in females ($F = 0.07, p = 0.928$). In contrast, dIPFC-LN connectivity significantly changed with age in females ($F = 8.75, p < 0.001$), continuing to strengthen through the third decade of life, which was not observed in males ($F = 0.36, p = 0.700$). Finally, vIPFC-LN connectivity significantly increased with age in females before plateauing ($F = 22.67, p < 0.001$), which was absent in males ($F = 1.97, p = 0.140$). Full results from these age-related post hoc sex tests are reported in Table S2 and plotted in Figure S3.

Fronto-amamygdala connectivity predicts individual differences in effect and cognitive performance

Affective and cognitive control processes—such as emotional regulation and working memory—are refined during adolescent neurodevelopment.^{5,73,74} We focused our brain-behavior tests on fronto-amamygdala connections exhibiting significant developmental effects to understand the extent to which these circuits are associated with our affective and cognitive measures. For each of the eight age-related fronto-amamygdala connections, we

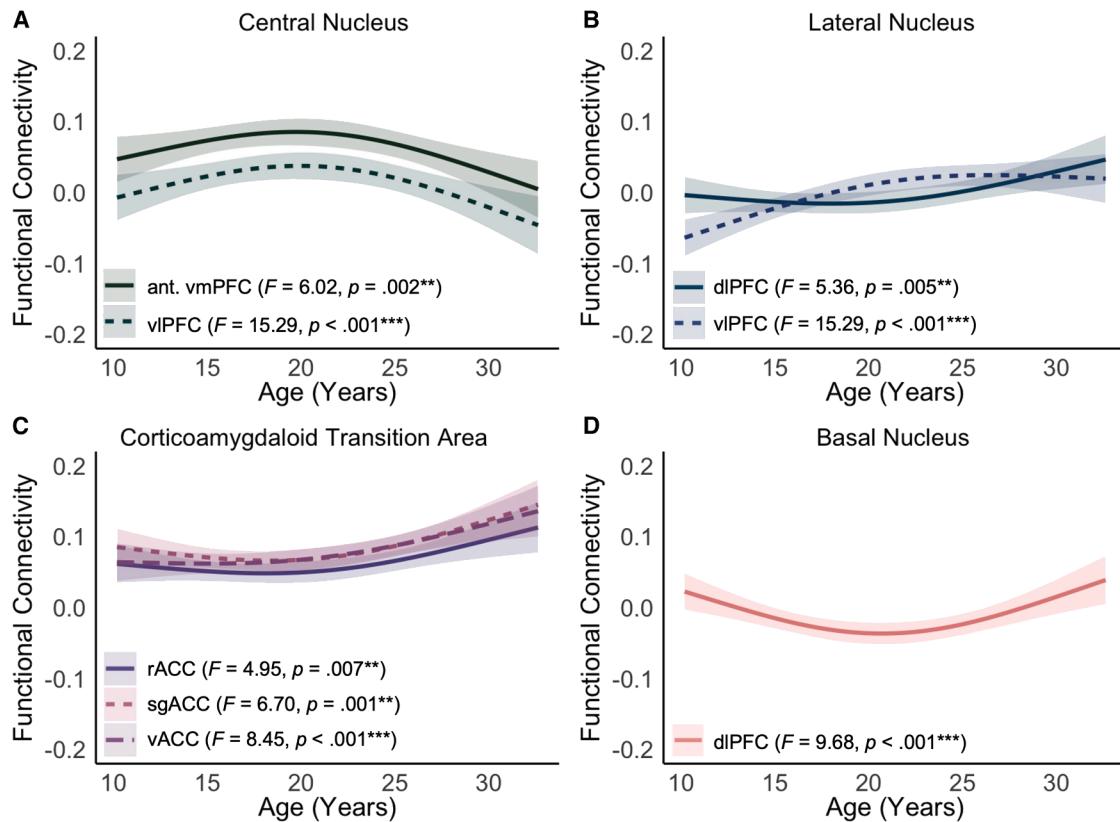


Figure 2. Developmental trajectories of fronto-amamygdala functional connectivity

Generalized additive mixed model (GAMM) fits show age-related changes in intrinsic functional connectivity (combined resting state and task regressed) between amygdala nuclei and PFC regions. The model included laterality, ROI side, and context as covariates, with random effects for participant ID and visit. The solid line shows the predicted relationship between age and intrinsic functional connectivity, with the shaded area representing 95% confidence intervals. Each graph represents a different amygdala nucleus, with separate curves showing connectivity with different PFC regions. Functional connectivity values are Fisher z-transformed Pearson correlation coefficients.

(A) CEN connectivity with the anterior vmPFC (solid line) and vIPFC (dashed line).

(B) LN connectivity with the dIPFC (solid line) and vIPFC (dashed line).

(C) CAT connectivity with the rACC (solid blue line), sgACC (dashed red line), and vACC (dashed purple line).

(D) BN connectivity with the dIPFC.

All connections shown exhibited significant age effects ($p < 0.008$). Raw data and derivative plots indicating specific developmental periods of change for these connections are presented in Figure S1. GAMM fits from all fronto-amamygdala connections tested, including those with non-significant age effects, are presented in Figure S2. GAMM fits from sex-by-age analyses for the significant fronto-amamygdala age-related connections displayed here are presented in Figure S3.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

sought to identify how that circuit's connectivity strength, beyond age effects, was related to various aspects of affective and cognitive processing. Therefore, we treated each connection as a separate hypothesis for the brain-behavior relationships tested and applied a Bonferroni correction of $p < 0.006$ (0.05/8). We additionally characterized age-related changes in affective and cognitive measures in our sample, presented in Table S3 and Figure S4.

After controlling for non-linear age effects, stronger functional connectivity in two fronto-amamygdala connections was related to fewer internalizing behaviors: anterior vmPFC-CEN ($\beta = -0.12, p < 0.001$) and vACC-CAT ($\beta = -0.08, p = 0.005$). Stronger sgACC-CAT functional connectivity was related to more externalizing behaviors ($\beta = 0.09, p = 0.001$). Stronger dIPFC-LN functional connectivity was related to fewer diffi-

culties in emotion regulation ($\beta = -0.18, p < 0.001$). In contrast, stronger connectivity in the following was related to more difficulties in emotion regulation: rACC-CAT ($\beta = 0.12, p < 0.001$) and sgACC-CAT ($\beta = 0.15, p < 0.001$). After controlling for non-linear age effects, stronger sgACC-CAT functional connectivity was also related to greater variability in accuracy on a (working) memory-guided saccade (MGS) task ($\beta = 0.14, p < 0.001$). Further, stronger dIPFC-LN functional connectivity was related to longer latencies (slower response) on correct MGS trials ($\beta = 0.11, p < 0.001$). In contrast, stronger anterior vmPFC-CEN functional connectivity was related to shorter latencies (faster response) on correct trials ($\beta = -0.11, p = 0.003$). Finally, stronger vIPFC-LN functional connectivity was related to less latency variability on correct MGS trials ($\beta = -0.13, p < 0.001$). Model parameters from all brain-behavior

Table 2. Age-related changes in fronto-amygdala functional connectivity

| PFC ROI | Amygdala ROI | Intrinsic functional connectivity | |
|------------|--------------|-----------------------------------|-----------|
| | | F | p Value |
| ant. vmPFC | ABN | 2.03 | 0.131 |
| | BN | 1.11 | 0.329 |
| | CAT | 2.92 | 0.054 |
| | CEN | 6.02 | 0.002** |
| | LN | 2.14 | 0.117 |
| dIPFC | ABN | 2.99 | 0.050 |
| | BN | 9.68 | <0.001*** |
| | CAT | 1.87 | 0.154 |
| | CEN | 0.74 | 0.476 |
| | LN | 5.36 | 0.005** |
| rACC | ABN | 0.73 | 0.482 |
| | BN | 0.07 | 0.482 |
| | CAT | 4.95 | 0.007** |
| | CEN | 0.18 | 0.837 |
| | LN | 0.08 | 0.924 |
| sgACC | ABN | 0.49 | 0.613 |
| | BN | 3.75 | 0.024* |
| | CAT | 6.70 | 0.001** |
| | CEN | 0.73 | 0.481 |
| | LN | 2.99 | 0.051 |
| vACC | ABN | 1.36 | 0.256 |
| | BN | 1.02 | 0.360 |
| | CAT | 8.45 | <0.001*** |
| | CEN | 0.16 | 0.848 |
| | LN | 0.97 | 0.381 |
| vlPFC | ABN | 1.13 | 0.323 |
| | BN | 1.24 | 0.290 |
| | CAT | 3.97 | 0.019* |
| | CEN | 5.39 | 0.005** |
| | LN | 15.29 | <0.001*** |

Reported statistics from big (generalized) additive (mixed) models refer to smoothed age effects from the models. Bonferroni-corrected significant *p* values (<0.0083) are bolded. **p* < 0.05, ***p* < 0.01, ****p* < 0.001. ROI, region of interest; PFC, prefrontal cortex; ABN, accessory basal nucleus; BN, basal nucleus; CAT, corticoamygdaloid transition area; CEN, central nucleus; LN, lateral nucleus; ant. vmPFC, anterior ventromedial prefrontal cortex; dIPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; vACC, ventral anterior cingulate cortex; vlPFC, ventrolateral prefrontal cortex.

tests above are reported in [Table 3](#), and significant associations are presented in [Figure 3](#).

Exploratory post hoc tests examined the moderating effects of sex assigned at birth on brain-behavior relationships. Significant interactions (*p* < 0.05) were further interrogated by performing brain-behavior tests separately in males and females. Sex differences in the relationships between age-related fronto-amygdala functional connectivity and self-reported affective behaviors included stronger ACC-CAT functional connectivity being related to less internalizing in females (rACC: $\beta = -0.11$, *p* =

0.006; sgACC: $\beta = -0.13$, *p* < 0.001; vACC: $\beta = -0.17$, *p* < 0.001) but with more internalizing (rACC: $\beta = 0.14$, *p* = 0.009; sgACC: $\beta = 0.10$, *p* = 0.026) and greater difficulties in emotion regulation in males (sgACC: $\beta = 0.25$, *p* < 0.001; vACC: $\beta = 0.14$, *p* = 0.007). Stronger dIPFC/vlPFC-LN connectivity in females was related to fewer difficulties in emotion regulation (dIPFC: $\beta = -0.20$, *p* < 0.001; vlPFC: $\beta = -0.14$, *p* = 0.001). Stronger anterior vmPFC-CEN connectivity was related to greater difficulties in emotion regulation in females ($\beta = 0.21$, *p* < 0.001) but with less externalizing in males ($\beta = -0.17$, *p* < 0.001). Sex differences in the relationships between age-related fronto-amygdala functional connectivity and cognitive task performance included stronger anterior vmPFC-CEN connectivity being related to more MGS accuracy variability in females ($\beta = 0.19$, *p* < 0.001) but the opposite in males ($\beta = -0.12$, *p* = 0.019). Stronger ACC-CAT connectivity was related to more latency variability on correct MGS trials in males (rACC: $\beta = 0.13$, *p* = 0.008; sgACC: $\beta = 0.25$, *p* < 0.001; vACC: $\beta = 0.13$, *p* = 0.008) but the opposite in females (rACC: $\beta = -0.13$, *p* = 0.003; sgACC: $\beta = -0.11$, *p* = 0.018; vACC: $\beta = -0.19$, *p* < 0.001). Finally, stronger sgACC-CAT connectivity was related to increased latency (slower response times) on correct MGS trials in males ($\beta = 0.17$, *p* < 0.001), whereas stronger vACC-CAT connectivity was related to reduced latency (faster response times) on correct MGS trials in females ($\beta = -0.15$, *p* < 0.001). Complete results, including significant and non-significant findings from these analyses, are reported in [Table S4](#).

Amygdala nuclei exhibit functional specialization across psychological domains and development

To investigate shared and distinct functions of cortico-amygdala connectivity patterns, we performed two psychological domain decoding analyses using resting-state fMRI data. Whole-brain resting-state functional connectivity (RSFC) maps seeded in each amygdala nucleus were parcellated using the Glasser atlas ([Figure S5](#)) before examining psychological term correlations for each amygdala nucleus' cortical connectivity. We focus on positive correlations between connectivity and psychological terms to identify which connectivity patterns are related to promoting, rather than inhibiting, a given psychological process.

The first analysis, limited to data from adult participants only (ages 18–32) in the top 10% of cortical regions with the strongest connectivity to each amygdala nucleus ([Table S5](#)), was performed to identify potentially stable psychological processes associated with connectivity patterns for amygdala nuclei seeds. Results from this analysis (depicted in [Figure 4A](#)) revealed that, while some putative functions may be shared across amygdala nuclei (such as those involving fear, emotion, and anxiety), albeit to varying extents, others (including reinforcement learning, hyperactivity, and salience) may be specific to certain nuclei.

The second analysis, which included all study participants, examined how the correlation between a seed region's cortical connectivity map was related to psychological processes across development (depicted for several of the top terms in [Figure 4B](#)). This broadly revealed age-related differentiation, such that earlier in development, amygdala nuclei were similarly related to a psychological term, whereas later in development, they increasingly diverged from each other in correlational strength,

Table 3. Brain-behavior relationships between age-related fronto-amamygdala intrinsic functional connectivity and affective/cognitive behaviors

| PFC ROI | Amygdala ROI | Internalizing | | | Externalizing | | | Difficulties in emotion regulation | | | MGS accuracy variability | | | MGS latency variability | | |
|------------|--------------|---------------|---------------------|---------|----------------|---------|---------------------|------------------------------------|---------|---------|--------------------------|---------|---------------------|-------------------------|---------------------|---------|
| | | ROI | β | p Value | ROI | β | p Value | ROI | β | p Value | ROI | β | p Value | ROI | β | p Value |
| ant. vmPFC | CEN | -0.12 | <0.001*** | -0.09 | 0.009** | 0.09 | 0.044* | -0.05 | 0.190 | 0.01 | 0.749 | -0.11 | 0.003** | 0.09 | 0.030* | |
| dIPFC | BN | 0.002 | 0.941 | 0.004 | 0.885 | -0.07 | 0.043* | 0.05 | 0.095 | 0.03 | 0.314 | 0.08 | 0.008** | 0.01 | 0.653 | |
| dIPFC | LN | -0.02 | 0.418 | 0.05 | 0.097 | -0.18 | <0.001*** | 0.01 | 0.666 | -0.02 | 0.592 | 0.11 | <0.001*** | 0.04 | 0.262 | |
| rACC | CAT | -0.01 | 0.643 | 0.05 | 0.051 | 0.12 | <0.001*** | 0.05 | 0.114 | 0.08 | 0.012* | 0.002 | 0.011* | -0.02 | 0.566 | |
| sgACC | CAT | -0.05 | 0.110 | 0.09 | 0.001** | 0.15 | <0.001*** | 0.08 | 0.013* | 0.14 | <0.001*** | 0.0078 | 0.818 | 0.06 | 0.065 | |
| vACC | CAT | -0.08 | 0.005** | 0.01 | 0.654 | 0.05 | 0.157 | -0.006 | 0.847 | 0.06 | 0.046* | -0.07 | 0.014* | -0.05 | 0.105 | |
| vIPFC | CEN | -0.01 | 0.727 | -0.03 | 0.338 | 0.01 | 0.880 | 0.07 | 0.070 | 0.07 | 0.063 | -0.01 | 0.769 | 0.04 | 0.356 | |
| vIPFC | LN | 0.05 | 0.112 | 0.03 | 0.227 | -0.07 | 0.050 | -0.007 | 0.816 | -0.04 | 0.149 | 0.01 | 0.625 | -0.13 | <0.001*** | |

Big additive (mixed) models were fitted to characterize and control for non-linear age-related effects on connectivity. Reported statistics are from linear associations between fronto-amamygdala functional connectivity strength and self-reported affective measures (internalizing behaviors, externalizing behaviors, and difficulties in emotion regulation) and cognitive performance (accuracy, accuracy variability, latency on correct trials, and latency variability on correct trials) on an MGS task. Though presented together here, we considered each age-related fronto-amamygdala connection separately (each connection being a separate family of tests) in its relevance to the affective and cognitive measures above. Thus, following Bonferroni corrections for multiple comparisons, associations were only considered significant at $p < 0.006$ ($0.05/8$), which are bolded. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. MGS, memory-guided saccade; CEN, central nucleus, BN, basal nucleus; LN, lateral nucleus; CAT, cortico-amygdaloid transition area; ant. vmPFC, anterior ventromedial prefrontal cortex; dIPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; vIPFC, ventrolateral prefrontal cortex.

possibly reflecting age-related functional specialization. Additionally, whereas certain terms remained relatively stable in rank order across ages for some amygdala nuclei (e.g., “fear” was most strongly correlated with most seeded RSFC maps across ages), others were more unstable, or dynamic, exhibiting age-related changes in rank order (e.g., though ranked lower early in adolescence, “salience” becomes increasingly correlated with most RSFC maps with age). Rank orders of terms by age are presented in Figure S6.

DISCUSSION

In this study, we report evidence of specific fronto-amamygdala connections at the anatomical nucleus level exhibiting developmental changes in a large well-characterized sample of healthy adolescents and young adults, using multimodal human neuroimaging data collected longitudinally at ultra-high-field 7 T. The unusually protracted maturation of PFC circuitry, unique to humans,¹⁶ including in its functional integration with the amygdala as shown here, may represent a neurobiological substrate of experience-dependent plasticity reflecting our species’ extended altriciality.¹⁷ We relate individual variations in connectivity strength within these circuits to developmentally relevant aspects of affect (i.e., internalizing/externalizing characteristics and emotion regulation) and cognition (i.e., working memory processes). To delineate distinct and shared patterns and functions of the amygdala nuclei, we performed a seeded RSFC analysis and leveraged a psychological domain decoding technique to identify meta-analytic phenotypes from previous neuroimaging experiments associated with cortical activation patterns in structures most strongly connected to each amygdala nucleus. Taken together, our findings (1) reveal developmentally distinct trajectories of anatomically specific fronto-amamygdala connections using subject-specific amygdala nuclei segmentations through adolescence and into early adulthood; (2) characterize the strength of connectivity within these age-related circuits relates to individual differences in aspects of affective and cognitive processing maturing through adolescence; and (3) identify functional and developmental specialization of psychological processes related to amygdala nuclei’s cortical circuitry. We arranged the following sections by amygdala subregional groups (BLA, CMA, and SFA).

Increased coordinated activity between the lateral PFC and BLA across adolescence might reflect higher-order cognitive processing. The BLA (ABN, BN, and LN), conserved across various species but expanded in primates with complex social structures and dynamics,^{75–77} including disproportionately more neurons in the LN in humans than in other primates,⁷⁸ mediates processes like associative learning, important for fear and anxiety, commonly attributed to the amygdala.⁷⁹ This is supported by findings from our psychological domain decoding analysis, which identified greater involvement of BLA circuitry in fear and anxiety than cortical circuitry of the other amygdala nuclei examined. The BLA’s role in associative learning may be explained in part by rapid processing of incoming sensory information from various streams.⁸⁰ Signals carrying information about environmental stimuli arrive through the BLA—specifically the LN, the “sensory interface” of the amygdala, which, with

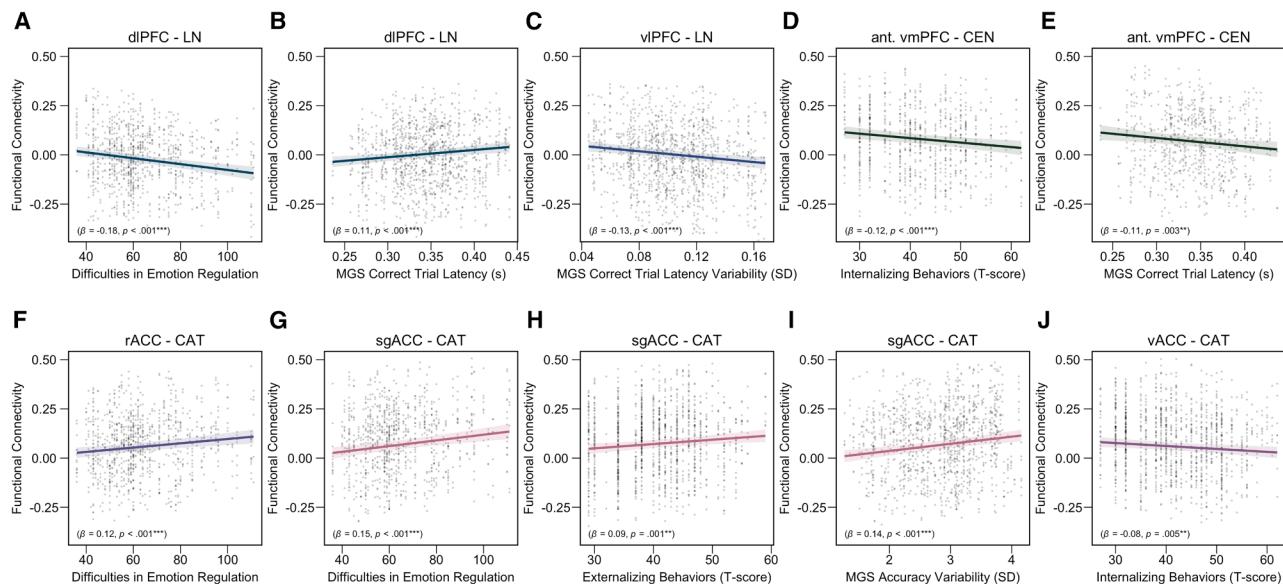


Figure 3. Associations between fronto-amamygdala connectivity and behavioral measures, controlling for age effects

Shown are linear relationships between fronto-amamygdala functional connections exhibiting age effects (identified in Figure 2) and behavioral measures. All analyses control for non-linear age effects using GAMMs. Additional covariates included laterality, ROI side, and context, with random effects for participant ID and visit. Solid lines display age-adjusted connectivity strength (y axis) plotted against behavioral scores (x axis), with the shaded area representing 95% confidence intervals. Connectivity values represent Fisher z-transformed correlation coefficients from combined resting-state and task-regressed background connectivity data. Each point represents one participant at one time point for one fronto-amamygdala ROI pair, each including four laterality permutations (combinations: left-left, left-right, right-left, and right-right). Regression lines depict best-fit linear associations; standardized beta coefficients (β) and p values for brain-behavior associations are shown. Age-related changes for all tested behavioral measures are presented in Figure S4. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

(A–C) Brain-behavior associations for age-related BLA nuclei.

(A) Emotion regulation difficulties (Difficulties in Emotion Regulation Scale [DERS] total) vs. dIPFC-LN connectivity.

(B) Correct trial latency (in seconds) on MGS task vs. dIPFC-LN connectivity.

(C) Correct trial latency variability (standard deviation) on MGS task vs. vIPFC-LN connectivity.

(D and E) Brain-behavior associations for age-related CMA nuclei.

(D) Internalizing behaviors (youth self-report [YSR]/adult self-report [ASR] T scores) vs. ant. vmPFC-CEN connectivity.

(E) Correct trial latency (in seconds) on the memory-guided saccade (MGS) task vs. ant. vmPFC-CEN connectivity.

(F–J) Brain-behavior associations for age-related SFA nuclei.

(F) Emotion regulation difficulties (DERS total) vs. rACC-CAT connectivity.

(G) Emotion regulation difficulties (DERS total) vs. sgACC-CAT connectivity.

(H) Externalizing behaviors (YSR/ASR T scores) vs. sgACC-CAT connectivity.

(I) Accuracy variability (standard deviation) on MGS task vs. sgACC-CAT connectivity.

(J) Internalizing behaviors (YSR/ASR T-scores) vs. vACC-CAT connectivity.

adjoining nuclei,^{81,82} is critical for emotional learning⁸³—either directly from sensory systems or indirectly by way of the thalamus, hippocampus, or frontal regions, such as the orbitofrontal cortex (OFC).⁸⁴ Whether information streams are processed by amygdala nuclei serially or in parallel remains unclear.⁸⁵ Cellular properties of the BLA and interactions with the PFC⁸⁶ enable the amygdala to compute valence—supported by our psychological domain decoding analysis indicating BN and LN's cortical circuitry being more strongly related to valence relative to other nuclei examined—across sensory modalities to support associative learning,⁸⁷ which undergoes specialization through adolescence.⁸⁸ Notably, lateral PFC projection neurons to the amygdala, insofar as they exist, appear to somewhat selectively target the BLA.⁸⁹ Although direct connections between the amygdala and dIPFC appear to be sparse (albeit present) in non-human primates,^{90,91} both are heavily innervated by fibers coursing through the medial PFC, including ACC subre-

gions,^{21,92} one plausible pathway connecting the dIPFC to the amygdala. In humans, dIPFC-amygdala connectivity has been implicated in emotion regulation,^{93–96} consistent with our finding that stronger dIPFC-LN connectivity is associated with fewer difficulties in emotion regulation and with evidence demonstrating that successful cognitive reappraisal recruits lateral PFC regions and dampens amygdala responses.¹⁹ Lateral PFC regulation of amygdala activity is corroborated by transcranial direct current stimulation of the human dIPFC reducing amygdala threat reactivity.⁹⁷ Separate evidence from a multimodal study in humans incorporating transcranial magnetic stimulation (TMS), fMRI, and diffusion MRI corroborates this line of reasoning; TMS pulses applied to the vIPFC decreases amygdala blood-oxygen-level-dependent activity, which is mediated by fiber density in a direct vIPFC-amygdala pathway.⁹⁸ Our observation that stronger vIPFC-LN functional connectivity was related to reduced MGS latency variability (consistently faster responses)

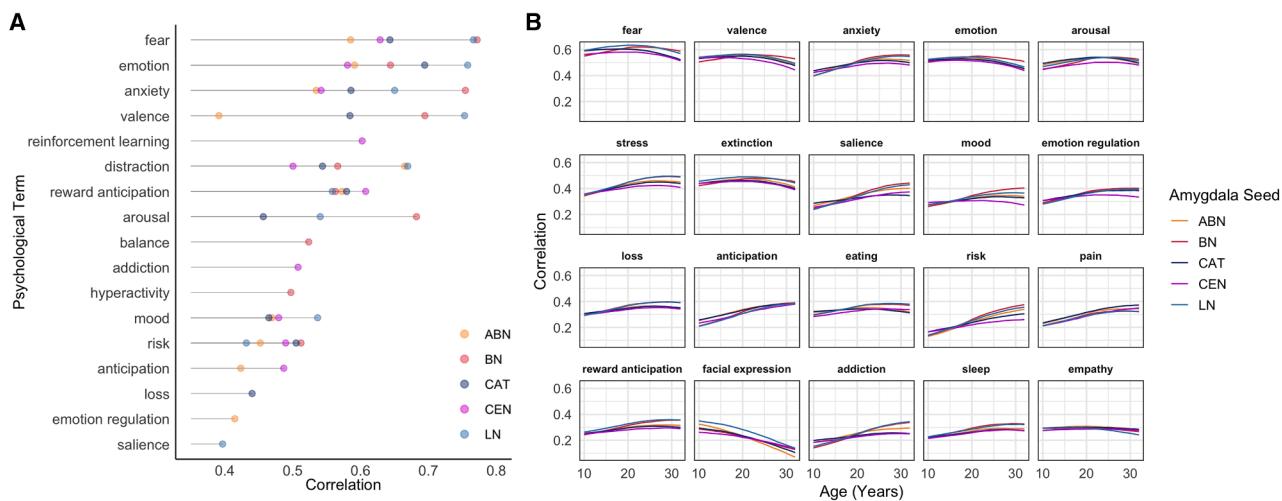


Figure 4. Psychological term associations with amygdala nuclei connectivity patterns in adults and across development

The psychological domain decoding analysis examines how amygdala nuclei resting-state functional connectivity (RSFC) patterns relate to psychological constructs from the Cognitive Atlas by comparing connectivity maps with meta-analytic brain activation patterns from neuroimaging studies via Neurosynth. Higher correlations indicate that an amygdala nucleus connects to brain regions consistently activated in studies of that psychological domain. Amygdala nuclei RSFC maps were correlated with meta-analytic activation maps from Neurosynth for terms also present in the Cognitive Atlas (124 total terms). RSFC maps were parcellated using the Glasser atlas before performing correlation analyses.

(A) Adult connectivity-term associations. One RSFC map was computed for each amygdala seed region by averaging across adult participants (ages 18–32) using 3dmean from the Analysis of Functional Neurolimages (AFNI). Each dot represents the correlation between one amygdala seed's RSFC pattern and one psychological term's meta-analytic activation map in adults (ages 18–32). Colors indicate different amygdala nuclei. Only terms showing positive associations and correlations >0.4 for at least one amygdala nucleus are displayed.

(B) Developmental changes in term associations. RSFC data from the full sample (ages 10–32) were fitted using AFNI's 3dLMEr and connectivity maps at each age were estimated using linear mixed-effects models controlling for sex, hemisphere, visit, and included random intercepts. Plots show how connectivity-term correlations change across development for psychological terms with the strongest positive correlations. Each colored line represents a different amygdala nucleus (same color scheme as in A).

See [Figure S6](#) for developmental changes in psychological term rank order for amygdala nuclei connectivity patterns.

on correct trials can be interpreted to suggest that signaling in this pathway may facilitate goal-directed decision-making speeds. That is, vIPFC-LN circuitry may support rapid processing of sensory information, consistent with our previous work linking vIPFC function to latency on cognitive tasks.^{99–101} Therefore, the BLA—the multi-layered “cortex” of the amygdala¹⁰²—may be increasingly coordinating neural activity with lateral PFC structures (i.e., dIPFC and vIPFC) important for higher-order executive functioning to guide aspects of decision-making¹⁸ as one matures into early adulthood. Interestingly, and in contrast to the BN and LN, ABN connectivity with the PFC does not change with age, suggesting that these connections may be online by age 10, in line with evidence of frontoamygdala reorganization prior to this age.¹⁰³ The lack of continued maturation suggests that certain aspects of fronto-amygdala integration, such as those involving the ABN, may already be present in childhood. Together, these findings speak to the maturation of lateral PFC-BLA circuitry in early adulthood and its involvement in emotion regulation and information processing.

The CMA (CEN and MN), known as the “striatum” of the amygdala due to its fast-spiking GABAergic medium spiny neurons,¹⁰⁴ supports value attribution (e.g., reward estimates), motivational salience, and rapid affective responses, such as behaviors directed toward or away from a stimulus.¹⁰⁵ This characterization is supported by our psychological domain decoding analysis

findings showing CEN-cortical circuitry to be uniquely related to reinforcement learning and more closely associated with reward anticipation than patterns of cortical connectivity of any other amygdala nuclei examined. Rodent studies indicate that the CMA can amplify or narrow reward salience,^{106,107} which may influence incentive motivation,¹⁰⁵ known to be undergoing maturation through adolescence.¹⁰⁸ Ventral portions of the PFC have been implicated in value assignment, self-referential processing, and aspects of emotion regulation.^{109–113} CEN connectivity with the anterior vmPFC and vIPFC, which we observed to peak in functional connectivity strength in late adolescence and is associated with value-based (e.g., reward-related) information processing,^{105,114} may guide behavioral responses via modulation of the CEN, which projects heavily to the brain stem, hypothalamus, autonomic nervous system, and motor output regions.^{115–117} This connectivity profile supports our finding of stronger anterior vmPFC-CEN coupling being related to faster performance (reduced latency) on correct MGS trials beyond age-related effects; dense projections from the CEN to structures involved in facilitating rapid behavioral responses may underlie this observed effect. Our observation of stronger anterior vmPFC-CEN functional connectivity (increased coordinated activity), related to less internalizing, may reflect down-regulation of aversive affective responses (e.g., freeze, fight, or flight).^{118,119} The CMA's involvement in reward-related (e.g., eating and

substance use) disorders¹⁰⁵ is consistent with our psychological domain decoding analysis showing CEN-cortical connectivity to be uniquely associated with addiction. Our finding of increased integration of CEN with ventral portions of the PFC is consistent with evidence of a peak in reward processing,¹²⁰ sensation seeking, and risk-taking,^{12,13}—possibly via heightened CEN-related dopaminergic function¹²¹—in adolescence,¹²² extending our understanding of the adolescent phenotype by revealing a potential role for CEN circuitry.

Another pattern we observed was protracted plasticity (i.e., continued strengthening) of functional connectivity between the SFA—specifically the CAT, which contains immature neurons similar to those described in the PL¹²³ that mature during adolescence¹²⁴—with ACC subregions through adolescence and into adulthood. Whereas the dorsal ACC is involved in cognitive control, effort-based decision-making, and expectancy violation detection,¹²⁵ ventral subdivisions of the ACC (i.e., ventral, rostral, and subgenual) constitute core corticolimbic circuitry and are associated with socio-affective processes,¹²⁶ including socio-emotional pain processing,¹²⁷ physiological regulation,¹²⁸ and emotion generation.¹²⁹ Although dense fibers connect the ACC to the amygdala,¹³⁰ previous work has demonstrated that the BLA, not SFA, shares the strongest connections with the ACC.¹³¹ The SFA (AAA, CON, CAT, and PL), arguably the least well-understood of the amygdala subregions,¹³² is primarily characterized by its connections with the olfactory cortex, insula, ventral striatum, and (para)hippocampal gyri.^{133–135} Abutting the piriform and entorhinal cortices,¹³² SFA nuclei detect emotionally salient information (e.g., via pheromone chemoreception),⁴⁵ resemble the olfactory cortex,¹³⁶ and have been implicated in social cognitive processing in humans,³³ which undergoes refinement in adolescence.¹³⁷ The SFA, of which the CAT comprises a large portion, has been linked to social cognitive processes not only in humans,³⁰ findings in mice corroborate a role for the CAT (or posterior amygdala) in social behaviors (e.g., aggression and mating).⁴⁶ Work in rodents investigating CAT circuitry has demonstrated strong projections to the infralimbic PFC,¹³⁸ which roughly corresponds to BA25 (i.e., sgACC), a possible direct anatomical pathway connecting the CAT to the sgACC. This is consistent with separate retrograde labeling work demonstrating connectivity between ACC subregions and the periamygdaloid cortex (i.e., the CAT).¹³⁰ Previous work in rhesus macaques has demonstrated more afferent projections from cingulate areas BA24 and BA25 (corresponding to the vACC and sgACC, respectively) to the amygdala⁸⁹ relative to efferent projections, suggesting that the functional ACC-CAT connections we observed here may originate in the cingulate. This is consistent with neuroimaging work in 5- to 11-year-old humans examining effective connectivity indicating that the ACC increasingly downregulates the amygdala during emotion regulation with age.¹³⁹ Increased interactions between the vACC and CAT, both implicated in social cognitive processes,^{140,141} might reflect healthy development, supported by our finding of fewer internalizing behaviors in individuals with stronger vACC-CAT functional connectivity. Further, stronger connectivity between these structures was associated with faster performance (reduced latency) on correct MGS trials beyond age-related effects, possibly via strong connections be-

tween the CAT and hippocampus.¹²³ The trough in ACC-CAT functional connectivity in mid-adolescence could reflect a transient period of reorganization or relatively uncoordinated neural activity whereby ACC circuitry—which undergoes substantial refinement in adolescence¹⁴²—does not sufficiently (down)regulate the CAT, important for emerging socio-sexual behaviors¹⁴¹ and potentially underlying risky social behaviors prevalent during this period of development.¹⁴³ Indeed, elevated connectivity between the sgACC and CAT—both strongly connected to the midbrain and hypothalamus,^{138,144,145} which is involved in aggression¹⁴⁶—was related to more externalizing behaviors in our sample. The sgACC, a corticolimbic “autonomic control center” that modulates internal states to match environmental demands of emotionally salient situations,¹⁴⁷ is associated not only with emotionality¹⁴⁸ but also with monitoring and controlling physiological arousal.¹⁴⁹ Increased coupling between the CAT, involved in social behaviors, and the sgACC, involved in autonomic processing, may, as observed in our sample, contribute to greater externalizing characterized by behavioral dysregulation and heightened autonomic reactivity¹⁵⁰ and more variable goal-directed behavior (i.e., greater MGS accuracy variability). Together, these results advance our understanding of social neurodevelopment, which undergoes extended refinements into adolescence,¹⁵¹ by elucidating protracted functional interactions between the CAT and neural structures supporting self-regulatory socio-affective development (i.e., ACC subregions).

Our longitudinal models also revealed three significant age-by-sex interactions in fronto-amygdala connectivity. Anterior vmPFC-CEN functional connectivity followed an inverted U-shaped trajectory that peaked in males in mid-adolescence before declining into adulthood, whereas this connection was largely stable across age in females. In contrast, females exhibited age-related strengthening of LN connectivity with both dlPFC and vIPFC, which was absent in males. These findings suggest that functional refinements within certain circuits in fronto-amygdala pathways occur across distinct timelines for males and females.

We additionally identified sex-specific brain-behavior relationships. Specifically, anterior vmPFC-CEN connectivity may have asymmetric effects by sex, with stronger connectivity advantageous in males (reduced externalizing behaviors and decreased accuracy variability) but disadvantageous for females (more difficulties in emotion regulation and increased accuracy variability). Stronger LN connectivity with the dlPFC/vIPFC, however, might be uniquely protective against difficulties in emotion regulation in females, converging with previous evidence linking lateral PFC thinning with emotion regulation in adolescent females but not males;¹⁵² however, this is speculative and would require dedicated testing to determine the extent to which such neurodevelopment supports emotion regulation in a sex-specific manner. Finally, whereas stronger ACC-CAT connectivity is related to less internalizing and enhanced cognitive processing (reduced latency and latency variability on correct MGS trials) in females, the opposite is true for males; stronger ACC-CAT connectivity in males is related to more internalizing and difficulties in emotion regulation as well as to reduced cognitive processing (increased latency and latency variability on

correct MGS trials). Some of these observed sex differences may be related to differences in pubertal timing (e.g., changes in sex hormones associated with reactivation of the hypothalamic-pituitary-gonadal axis).^{153–155} Sex differences in the neurodevelopmental timing of maturational events, which can be affected by environmental factors such as adversity related to minoritized identities, socioeconomic disadvantage, and other life stressors,^{156–165} may result in distinct fronto-amygdala circuits optimized to support various aspects of affective and cognitive processing in males and females. These differences in pubertal timing, stress responsivity, and affective and cognitive strategies to navigate changing and often challenging environments are likely relevant to sex differences in psychiatric risk that emerge during this period of neurodevelopment^{166–169} and warrant longitudinal investigations that incorporate dense multimodal sampling across diverse study samples to identify person-specific puberty-related risk related to psychopathology. Our developmental psychological domain decoding analysis further suggests a potential age-related differentiation or possibly specialization of each amygdala nucleus' correlation with various psychological processes with age. That is, whereas psychological functions were more similar across amygdala nuclei in younger participants, they increasingly diverged in their respective associations in older participants. This may suggest age-related increases in functional specialization in amygdala nuclei connectivity that occur through adolescent development.

Ultra-high-field neuroimaging (e.g., 7 T) affords increased signal-to-noise and contrast-to-noise ratios, critical for imaging and partitioning the amygdala into its separate nuclei and demarcating the structural border separating the amygdala from surrounding regions such as the hippocampus.¹⁷⁰ Leveraging this enhanced specificity, our results provide critical information bridging the gap between animal studies that have demonstrated the functional roles and anatomical connections of amygdala nuclei using labeling, tracing, and behavioral techniques and human studies reporting adolescent development of fronto-amygdala connections and implicating this circuitry across several psychiatric disorders with adolescent onsets. In a large longitudinal cohort of adolescents and young adults scanned using multimodal neuroimaging at 7 T, we segmented amygdala nuclei using subject-specific anatomical definitions, which allowed us to robustly describe functional connectivity age effects across this circuitry, previously uncharacterized in humans, possibly due to limited age ranges, treatment of the (heterogeneous) amygdala as a functionally monolithic structure, and relatively low-field imaging techniques.

Limitations of the study

We used a convenience sample that may not be fully representative of varied demographic backgrounds, limiting us from generalizing to more diverse samples. Because our study design excluded participants who met clinical criteria based on symptom endorsements on the youth self-report (YSR)/adult self-report (ASR), we caution against extrapolating these findings to infer how functional pathways in fronto-amygdala circuitry are altered in neuropsychiatric disorders. Instead, we examined associations between (subclinical) variability in internalizing/externalizing features and brain connectivity, following previous ap-

proaches²⁵ and consistent with recent dimensional models of psychopathology (e.g., research domain criteria and hierarchical taxonomy of psychopathology)^{171,172} rather than dichotomous diagnostic categorizations. Nevertheless, we underscore the potential relevance of certain circuits, including those identified here, in neuropsychiatric variability and possibly vulnerability and encourage future investigations to draw from and test our findings in more clinically diverse study samples. Despite the spatial resolution afforded to us by 7 T neuroimaging, we were still unable to examine several amygdala nuclei that remain poorly characterized in the developing human, including the AAA, CON, MN, and PL. Further, some fronto-amygdala connections associated with age became statistically insignificant at the Bonferroni-corrected level following sensitivity tests, underscoring the importance of considering covariates when performing such analyses. Finally, the psychological domains we associated with Neurosynth-derived meta-analytic activation patterns were primarily sourced from neuroimaging studies in adult participants. Therefore, developmental associations should be interpreted with greater caution than those in the adult sample.

Future directions

Our findings generate several exciting avenues for future research into potential cellular and molecular mechanisms underlying the maturation of this circuitry. Amygdala neurons are studded with various receptors, making them ideal candidates for neuromodulation. These include androgen and estrogen receptors sensitive to sex hormones¹⁷³ as well as diverse receptors sensitive to various neurotransmitters and neuropeptides—including glutamate, γ -aminobutyric acid, dopamine, serotonin, acetylcholine, vasopressin, oxytocin, and corticotrophin-releasing factor—that differ in population density across amygdala nuclei.^{42,133,174,175} The timing of fronto-amygdala circuitry development and possible sex differences we observed, both developmentally and in brain-behavior relationships, may be associated with pubertal maturation, which warrants future investigation. Furthermore, although the present study investigated participants between the ages of 10 and 32, amygdala circuitry maturation begins far earlier in life^{176,177} and may continue through early adulthood.¹⁷⁸ Therefore, studies that recruit younger and older study participants may be able to extend our results and more comprehensively characterize developmental trajectories of amygdala circuitry maturation. Future studies should also assess the extent to which clinical samples exhibit deviations from normative fronto-amygdala connectivity development, which may become most apparent in the context of evocative tasks that engage specific circuits, which we did not employ here. Model comparisons indicated that separating the amygdala by nuclei improved age-related model fits the most for the sgACC and vIPFC; as such, we suggest future investigators examining development of sgACC/vIPFC-amygdala circuitry in particular consider deconstructing the amygdala into its constituent parts if possible. Finally, our study focused on fronto-amygdala circuitry, which, based on effect sizes observed here, is modestly related to aspects of affect and cognition. White matter tracts connect several additional cortical regions to the amygdala, including the OFC, dorsomedial PFC, and inferior frontal gyrus (BA47),^{179,180} among others beyond the scope

of this study (e.g., the dorsal ACC) but likely important for modulating amygdala activation.¹⁷⁹ Investigation of functional interactions with more distributed circuitry is likely to advance our understanding of how the human amygdala supports myriad functions beyond affective and cognitive control investigated here, including aspects of pain,^{29,181} reward,¹⁸² and social processing.¹⁸³ Future work leveraging approaches optimized for imaging regions with relatively lower tSNR (e.g., the OFC) is also needed to comprehensively characterize the functional neurodevelopment of frontoamygdala circuitry, including by using various experimental paradigms. Although the amygdala has been classically considered a core constituent of the brain's fear and/or emotion circuitry, evidence from lesion^{184,185} and multivariate neuroimaging studies^{186,187} compellingly demonstrates that fear, or emotions more broadly, cannot be reduced to or localized in the amygdala alone, especially in humans. Whereas affective responses are intimately tied to direct perceptual processing of environmental inputs in non-human animals, neocortical expansion in primates may support internal abstract representations of affective contingencies that contribute to the complexity of subjective experiences in humans.¹⁸⁴ Therefore, evidence supports a psychological constructionist hypothesis wherein a host of distributed neural structures likely supports affective phenomena in humans. Several of these structures are connected to the amygdala and undergo protracted functional maturation through adolescence, including the anterior insula,^{188–190} ventral striatum,^{191–193} and hippocampus,^{194,195} which warrants further investigation. Together, these observations narrow the gap between neuroimaging studies in humans and findings from animal models to advance our understanding of how subcortical structures, like the amygdala, support functions related to both affective and cognitive control processes undergoing refinement during critical periods of neurodevelopment and commonly impacted across numerous neuropsychiatric disorders with adolescent onset.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Amar Ojha (amo80@pitt.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The code to replicate the results and figures is available at <https://doi.org/10.5281/zenodo.16690846>. All deidentified neuroimaging and behavioral data and any additional information required to reanalyze the data reported in this paper will be made available by the lead contact upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization, A.O.; data curation, W.F.; methodology, A.O., W.F., F.J.C., V.J.S., D.J.P., and A.C.P.; software, A.O., W.F., F.J.C., V.J.S., D.J.P., and A.C.P.; validation, A.O., N.P., and A.S.; formal analysis, A.O.; investigation, A.O. and A.F.; resources, W.F. and A.F.; writing – original draft, A.O.; writing – review & editing, A.O., W.F., F.J.C., V.J.S., D.J.P., A.C.P., A.F., N.P., A.S., S.F.S., and B.L.; visualization, A.O. and V.J.S.; project administration, F.J.C. and B.L.; supervision, F.J.C., S.F.S., and B.L.; funding acquisition, B.L.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|--|---|---|
| Software and algorithms | | |
| R 4.0.3 | R Foundation | https://cran.r-project.org/src/base/R-4/R-4.0.3.tar.gz |
| RStudio 2022.12.0 | Posit | https://posit.co/download/rstudio-desktop/ |
| fMRI processing scripts | Laboratory of Neurocognitive Development | https://zenodo.org/records/8320245 |
| FreeSurfer 7.4.1 | Laboratory for Computational Neuroimaging | https://surfer.nmr.mgh.harvard.edu/ |
| Data analysis and figure generation code | Study authors | https://doi.org/10.5281/zenodo.16690846 |

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Participants

Data from 143 participants (75 F, 10-32-years-old) were analyzed in the present study, with participants completing 1–3 visits approximately 18 months apart for a total of 198 scans (sample demographics are presented in [Table 1](#); see [Figure 1D](#) for distributions of age and sex at each visit). Each visit comprised a neurocognitive battery and MRI scan session completed on different days. MRI scans were performed at the University of Pittsburgh Magnetic Resonance Research Center (MRRC). Participants were recruited from the local population and screened for exclusion criteria including a history of loss of consciousness due to head injury, a history of substance abuse, a history of major psychiatric or neurological conditions in either the participant or a first-degree relative, and MRI contraindications (e.g., nonremovable metal in body). Participants were screened for psychiatric symptoms using the Youth (<18yo) and Adult (>18yo) Self-Report (YSR, ASR respectively) assessments. Participants were excluded if they scored in the clinical range for internalizing, externalizing, or total problems (scores >65) subscales. Participants returning for follow-up visits that had been diagnosed with psychiatric illness were excluded from further study. The University of Pittsburgh's Institutional Review Board (IRB) approved the study. Participants or the parents of minors provided informed consent, while those under 18 years of age also provided assent. Participants over 18 years of age provided written consent. Participants were compensated for their participation.

METHOD DETAILS

Magnetic resonance imaging (MRI) data acquisition and processing steps

MR data were acquired on a Siemens 7T scanner (methods have been reported elsewhere¹⁹⁶) at the University of Pittsburgh's MRRC (RRID: SCR_025215). Structural images were collected using a Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) sequence (1mm isotropic resolution, TR = 6000ms, TE = 2.87ms, INV1 = 800ms, INV2 = 2700ms, flip angle 1 = 4°, flip angle 2 = 5°, voxel size = 1 × 1 × 1mm; total duration = 5m 14s, which were used for alignment and parcellation. With MP2RAGE sequences, two gradient-recalled echo (GRE) images with short (INV1) and long (INV2) inversion times are combined to derive a T1-weighted Uniform (UNI) image that is relatively free of B1-, proton density, and T2* effects. To leverage the maximal amount of data, resting-state functional MRI (rsfMRI) data and (task-regressed) background connectivity from a Memory-Guided Saccade (MGS) fMRI task obtained in the same session were combined to derive a measure of “intrinsic” functional connectivity and a factor for ‘context’ (“rest” or “task”) was included in statistical tests. rsfMRI was acquired using a T2*-weighted scan sensitive to the BOLD contrast with the following sequence: TR = 2.18, TE = 23ms, voxel size = 2 × 2 × 2mm, total duration was 479.6s (approximately 8 min). During the rsfMRI scan, participants were instructed to keep their eyes open while presented with a black screen and to remain still and awake. Background connectivity derived from the MGS task (details below) used the same sequence as the rsfMRI scan, but the total task duration varied between 418.56s and 422.4s (approximately 7 min per run, 3 runs).

fMRI data were preprocessed using the following steps designed to minimize the effects of head motion¹⁹⁷ (<https://zenodo.org/records/8320245>) using functions from multiple software packages, including AFNI, FSL, ANTs, and NiPype. These steps included head motion correction, wavelet despiking, intensity normalization, nuisance regression based on head motion and non-gray matter signal (white matter and CSF, and their derivatives), and bandpass filtering between 0.009 and 0.08Hz. Notably, we did not apply spatial smoothing given the small size of the amygdala nuclei ROIs. Frame-wise motion estimates were computed and volumes with frame-wise displacement (FD) > 0.3mm were censored from connectivity analyses.

Region of interest (ROI) definitions

Amygdala nuclei ROIs were defined in a subject-specific manner using FreeSurfer-derived segmentations ([Figures 1A and 1B](#)). UNI images were corrected for residual B1+ bias field inhomogeneities using the unified segmentation algorithm from SPM.^{198,199} This

was implemented using a containerized version of SPM12 (<https://hub.docker.com/r/bids/spm/tags>) with default parameters. Following bias correction, FreeSurfer's longitudinal processing stream was run on UNI images (including cross-sectional, template, and longitudinal steps) using the containerized FreeSurfer BIDS app version 7.4.1 (<https://hub.docker.com/r/bids/freesurfer/tags>).^{200,201} Participants' FreeSurfer-generated amygdala ROIs were then visually inspected by three members of the research team (AO, NP, AS) for quality checks to confirm accurate anatomical reconstructions. This process included independently examining the reconstructed amygdala nuclei in three views (sagittal, coronal, axial) using FreeSurfer's Freeview. Ratings were made based on a scale of '2' (pass), '1' (questionable), or '0' (fail). To ensure all raters shared an understanding of what constituted a 'pass,' 'questionable,' or 'fail' rating, we discussed the criteria and reconstruction examples for each rating level to ensure consistency prior to assessment. Discrepancies in ratings were discussed to achieve a consensus. We excluded the AAA, CON, MN, and PL from functional connectivity analyses given that their relatively small size (<10 voxels bilaterally) would not provide reliable measures. Despite its small size (Figure S7), we included the CEN given its relatively high tSNR, the highest of the 9 amygdala nuclei (>200 per hemisphere) (Figure S8). As such, the final amygdala nuclei ROI list included the ABN, BN, CAT, CEN, and LN. FreeSurfer-derived amygdala nuclei reconstructions were affine transformed (6 degrees of freedom) from T1w alignment to a motion corrected mean native functional space reference. This transformation utilized FreeSurfer's 'mri_convert,' AFNI's '3dresample,' FSL's 'applywarp,' with the functional reference generated by the 'preprocessFunctional' pipeline (<https://zenodo.org/records/8320245>).

Given our interest in optimizing anatomical precision of our ROIs and reducing atlas-specific biases, we employed multiple anatomically informed atlases to define our PFC ROIs, consistent with our previous approach.⁹⁹ Validated for detailed parcellation of medial cortical structures, we used the Mackey and Petrides vmPFC atlas²⁰² to define medial PFC ROIs. We focused on the ventral medial PFC given that the amygdala shares the strongest connections with this portion of the medial PFC. Retrograde tracer studies performed in macaques has shown that the densest amygdala connections with the mPFC are specific to ventral portions of this subregion,^{203,204} including areas 14, 24, 25, and 32, which we include in the present study. Further, functional neuroimaging studies in humans have reported fluctuations in amygdala activity to positively correlate with vmPFC but negatively with dmPFC.^{205,206} These ROIs included the anterior ventromedial PFC (vmPFC) (BA 14m), rostral ACC (rACC) (BA 32), subgenual ACC (sgACC) (BA 25), and ventral ACC (vACC) (BA 24) (Figure 1C). Despite strong projections between the orbitofrontal cortex (OFC) and amygdala,²⁰⁷ we excluded anterior and posterior medial OFC subregions (BAs 11m, 14rr, 14c, and 14r) from analyses due to relatively low tSNR (see Figure S8). As the Mackey and Petrides atlas does not include more lateral PFC structures of interest, we used the Glasser and Brainnetome atlases, which offer complementary strengths in segmenting these ROIs, to define the dorsolateral PFC (dlPFC; BAs 9, 46) and ventrolateral PFC (vlPFC; BAs 44, 45) (Figure 1C), respectively.^{208,209} Though some include BA 47 as part of vlPFC, evidence suggests that BA 47 may be more evolutionarily homologous with BA 12/47 in macaque, which is classified as part of the posterolateral orbitofrontal cortex rather than vlPFC proper.²¹⁰ Indeed, the brain atlas we used for our vlPFC ROIs, the Brainnetome atlas,²⁰⁹ pairs BA 47 with BA 12 and classifies the region within the orbital gyrus. Further, the proximity of BA 47 to air-filled cavities (e.g., sinuses) increases susceptibility to imaging artifacts when using typical acquisition parameters.²¹¹ The MNI-aligned PFC ROIs were nonlinear registered to each participant's visit-specific T1w-native alignment using FSL's 'applywarp' with inverted T1w to MNI warp coefficients. See Table S6 for anatomical nomenclature for atlas-derived PFC ROIs.

Functional connectivity analyses

Consistent with our previous approaches,^{99,197} time courses were extracted for each ROI from each participant by taking the first principal component across all voxels within the ROI from the preprocessed and head motion scrubbed voxel-wise time courses. Pearson correlation coefficients were computed between the amygdala nuclei and PFC subregions and normalized using Fisher's z transformation. In addition to resting-state functional connectivity (RSFC) analyses, we also performed background connectivity analyses from the Memory-Guided Saccade (MGS) task. Participants performed 3 runs of the MGS task while undergoing fMRI scanning, each with 24 trials. To measure background connectivity, we regressed out task-related trial level BOLD responses from the time series using a generalized linear model (GLM). The three 7-min runs were concatenated to optimally estimate and remove task-evoked BOLD responses. Task-evoked events were modeled with a TENT function to estimate the hemodynamic responses (using '3dDeconvolve' in AFNI). Compared to the canonical hemodynamic response function (HRF), the TENT function makes no assumptions about the shape of HRF responses, thereby removing more variability due to task-evoked signals from the time series.²¹² Our research group has previously used this approach of calculating background connectivity to investigate functional connectivity development in adolescents.^{191,213}

Affective measures

Internalizing and externalizing characteristics were assessed via the Youth Self-Report (YSR) and Adult Self-Report (ASR).^{214,215} The YSR was administered to participants under 18, whereas the ASR was administered to participants over 18. These self-report measures consist of questions pertaining to one's emotional and behavioral problems over the past 6 months. The YSR has a total of 112 items whereas the ASR has a total of 126 items. Responses range from 0 ("Not true") to 2 ("Very true or often true"). Although scoring the YSR/ASR generates several subscores, we focused our analyses on the internalizing and externalizing subscales.

Emotion regulation was assessed using the Difficulties in Emotion Regulation Scale (DERS).²¹⁶ The DERS is a 36-item self-report questionnaire assessing aspects of emotion dysregulation across various domains. Responses can range from 1 to 5, where 1 is "Almost never" and 5 is "Almost always". The scale includes 11 reverse-scored items that require recoding before calculating total

scores. Although several subscores can be derived from the measure, we focused our analyses on total scores, with higher scores indicating more difficulties in emotion regulation. An example item from the DERS is, “When I’m upset, I have difficulty controlling my behaviors.”

Cognitive measures

The Memory-Guided Saccade (MGS) task was performed during both the fMRI and EEG sessions, each conducted on separate visits. However, while the resting-state fMRI data was necessarily used for functional connectivity analyses, we limited behavioral analyses to data collected during the EEG session due to optimal quality eye tracking compared to the fMRI session. EEG signals were recorded and have been previously reported.^{217,218} Trials began with participants fixating on a blue cross in the center of the screen for 2s. Once fixation was extinguished, participants were to saccade to a peripheral cue that was presented in an unknown location along the horizontal midline (12.5 or 22.2° from central fixation to left or right of center). Once the cue disappeared, participants were to return their gaze to the central fixation cross for a variable delay epoch (6-10s) during which participants were to maintain the location of the peripheral target in working memory. Once the central fixation disappears, the participants performed a memory-guided saccade (MGS) to the recalled location of the previous target. The trial ended when participants were presented with a white fixation cross (i.e., variable ITI) that remained for 2-8s. Horizontal electrooculogram (hEOG) channels recorded from facial muscles were used to derive eye position and resulting performance measures.²¹⁷ Participants fixated on locations across the screen for calibration that was used to identify fixation locations during the task itself. We focused our analyses on four output measures from the MGS task: accuracy, correct response latency, accuracy variability, and correct response latency variability.

QUANTIFICATION AND STATISTICAL ANALYSIS

Maturation of frontoamygdala functional connectivity

Big (generalized) additive (mixed) models (BAMs) were used to test associations between age and functional connectivity (mgcvbam, R version 4.0.3 via RStudio version 2022.12.0).²¹⁹ BAMs are similar to generalized additive (mixed) models (GAM/Ms), which include smooth functions (“splines”) that are sensitive to linear and non-linear effects, with the added benefit of improved computational efficiency. Random intercepts and slopes were estimated for each participant to determine the longitudinal trajectory of each individual’s connectivity over time (i.e., repeated visits). ‘Age’ was included as a smoothed term to capture non-linear development of connections, which may represent a better fit than traditional linear models used to fit adolescent developmental change over time.²²⁰ Our models implemented thin plate regression splines with three knots (maximum degrees of freedom for the smoothed term was $k=1=2$).^{221,222} We fit independent models for each of the six prefrontal regions that included a factor-smooth interaction term between age and amygdala nuclei, which allowed us to fit separate developmental splines modeling prefrontal connectivity development for each of the amygdala nuclei. To maximize the amount of fMRI data used per participant in the sample, we included both resting-state and background connectivity data as the dependent variable in our models, thereby fitting age smooths that characterize the overall development of resting and background (“intrinsic”) functional connectivity. Given that our measure of intrinsic functional connectivity collapsed across resting-state and background connectivity scans, we included a ‘context’ factor to control for differences associated with a specific scan context. Because we did not have any specific hypotheses regarding laterality, models included ‘laterality’ (ipsilateral/contralateral) and ‘PFC ROI side’ (right/left) as covariates to include all four connections for any given frontoamygdala ROI pair (L-L, L-R, R-L, R-R), consistent with a previous approach we have employed when examining adolescent functional connectivity development.^{191,223}

We applied Bonferroni corrections to control for multiple comparisons across statistical models, which is typically necessary when conducting multiple independent statistical tests, each with its own error rate, thereby inflating the family-wise error rate. To test frontoamygdala functional connectivity age effects, we ran six separate models, one for each PFC ROI, with all five amygdala nuclei modeled simultaneously in each model using a within-model factor. Since all age effects are estimated simultaneously as part of a unified generalized additive mixed model (GAMM) across nuclei, terms are not treated as independent tests but rather as interrelated components of a single model fit. The structure of regression and multilevel models mitigates concerns about multiple comparisons by accounting for shared variance and applying shrinkage, reducing false positives.²²⁴ As such, we ran six independent GAMMs—one for each PFC ROI—and therefore applied a Bonferroni threshold of $p < .008$ (.05/6).

Each PFC subregion was tested separately for its age-related changes in functional connectivity across amygdala nuclei as such:

$$\text{bam}(FC \sim s(\text{age}, k = 3, fx = T, by = \text{amygdala}_{\text{ROI}}) + \text{amygdala}_{\text{ROI}} + \text{laterality} + \text{ROI}_{\text{side}} + \text{context} \\ + \text{random} = \text{list}(id = 1 + \text{visit}))$$

‘FC’ above refers to functional connectivity. ‘REML’ and ‘discrete’ both set to ‘TRUE’ when running these models. Absolute values of standardized (z-scored) residuals from the initial model that were ≥ 2 were removed prior to the final analysis for a given frontoamygdala connection to remove the influence of outliers.

We additionally sought to determine whether separating age effects by amygdala nuclei improved model fits. That is, for each PFC ROI, we compared models with and without the ‘by = amygdala_{ROI}’ term in the above model using Akaike Information Criteria (AICs) to identify whether separating age effects by amygdala nucleus improved model fits (with lower AICs indicating better model fit).

Sensitivity analyses for age-related connections

We performed sensitivity analyses that controlled for sex, the PFC ROI and amygdala nucleus' tSNR, the PFC and amygdala nucleus' ROI size (number of voxels), and motion (percent of censored TRs at the cutoff of FD > 0.3mm) in four separate models for each significant age-related fronto-amamygdala connection to confirm that these potential confounds were not underlying observed age effects.

In addition to these sensitivity analyses, we also tested for interactions to examine whether there were sex-related differences in the maturation of fronto-amamygdala functional circuitry across adolescence and into early adulthood given previous evidence suggesting potential developmental sex differences in amygdala subregional functional connectivity.²⁷ To accomplish this, we modeled 'sex' as an ordered factor and used the factor-smooth ("by" term) to separately test each fronto-amamygdala connection significantly associated with age. In cases where we observed a significant ($p < .05$) age-by-sex interaction, we conducted follow-up analyses within each sex to identify whether age-related effects were specific to males or females.

We additionally examined the (main and moderating) effects of sex (assigned at birth) on the relationship between age-related fronto-amamygdala functional connectivity and our behavioral measures of interest. For each fronto-amamygdala connection significantly associated with age following multiple comparison corrections, we retested our brain-behavior associations with a sex-by-behavior term, again controlling for non-linear age effects as before. If we observed a significant ($p < .05$) sex-by-behavior interaction effect for a given fronto-amamygdala connection and behavioral measure, suggesting sex differences, we subsequently performed post-hoc analyses that tested this relationship separately in males and females. As these tests were not central to our primary study aims, we report uncorrected p -values for these analyses.

Brain-behavior relationships

To identify whether there were associations between fronto-amamygdala functional connectivity and affective measures (i.e., internalizing/externalizing behaviors and emotion regulation) or cognitive measures (i.e., MGS accuracy, latency, accuracy variability, and latency variability) in the connectivity pairs where we observed age-related changes, we tested linear relationships within a BAM framework, examining one PFC region and one amygdala nucleus at a time. This enabled us to capture and covary for non-linear functional connectivity age effects while modeling linear associations with facets of affect and cognition. As such, our brain-behavior models took the following form:

$$\text{bam}(FC \sim s(\text{age}, k = 3, fx = T) + \text{behavior} + \text{laterality} + ROI_{\text{side}} + \text{context} + \text{random} = \text{list}(id = 1 + \text{visit}))$$

The behavioral variables of interest ('behavior') above were tested in seven separate models—one for each 'behavior' measure (internalizing, externalizing, emotion regulation, MGS accuracy, MGS latency, MGS accuracy variability, MGS latency variability)—for each of the eight significant age-related connections. For brain-behavior analyses, we restricted analyses to connections that showed developmental change, to test how variability in connectivity strengths within these connections relate to individual differences in behavior. As each connection represented a separate hypothesis regarding brain-behavior relationships, we applied a Bonferroni correction across the 8 connections we identified as having age-related change in connectivity strength, i.e., $p < .006$ (.05/8).

Psychological domain decoding analyses

Finally, we generated whole-brain amygdala nuclei-seeded connectivity maps for adult participants (ages 18–32) from rsfMRI data and applied a psychological domain decoding analysis to determine potential associations with meta-analytic phenotypes related to each amygdala nucleus' cortical circuitry. We only included adults in these analyses to capture relatively stable main effects of connectivity and to identify potential functions that may be associated with relatively stable (adult) fronto-amamygdala circuitry. Specifically, for every participant, we conducted whole-brain voxel-wise RSFC analyses with each amygdala nucleus as a seed region. Individual participant brain connectivity maps for each amygdala nucleus were then group-averaged using AFNI's '3dMean' to produce a single group average brain connectivity map. Neurosynth²²⁵ version 0.7 was used to create meta-analytic maps for psychological terms to capture spatial topography associated with a wide range of psychological constructs. Based on previous work,²²⁶ we obtained meta-analytic activation maps for 124 cognitive terms that overlapped in the Neurosynth database and the Cognitive Atlas.²²⁷ Maps were obtained using the Neuroimaging Meta-Analysis Research Environment (NiMARE).²²⁸ Term-specific maps were computed in volumetric space using multilevel kernel density Chi-square analysis, mapped to the fslr surface, and parcellated with the HCP-MMP parcellation. Values in term-specific maps are association test z-scores quantifying the extent to which activation in a cortical region occurred more consistently in prior fMRI studies that mentioned a given term compared to studies that did not.

Given our interest in fronto-amamygdala neurodevelopment, we incorporated an additional exploratory analysis where we reanalyzed our psychological domain decoding analysis based on age-specific connectivity maps. To accomplish this, we ran a 3dLME model, which included fixed effects for age at scan (mean-centered at 20 years for modeling to reduce multicollinearity and improve model convergence, estimation, and interpretation), sex assigned at birth (factor: M, F), hemisphere (factor: left, right; every participant's scan visit consisted of two whole-brain connectivity maps, one for each amygdala seed region per

hemisphere), visit (categorical, to control for session-specific effects), and two- and three-way interactions among age, sex, and hemisphere. Subject-specific intercepts were included as a random effect to account for within-subject effects across repeated visits. General linear tests (GLTs) were used to extract model-predicted connectivity maps in one-year intervals at each age from 10 to 32. The resulting connectivity maps were used as the basis for age-specific psychological domain decoding to identify how potential psychological associations of each amygdala seed region's functional connectivity pattern changed throughout development.