Development of white matter microstructure and intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex: associations with anxiety and depression

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Abstract

Background—Connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC) is compromised in multiple psychiatric disorders, many of which emerge during adolescence. To identify what extent the deviations in amygdala-vmPFC maturation contribute to the onset of psychiatric disorders, it is essential to characterize amygdala-vmPFC connectivity changes during typical development.

Methods—Using an accelerated cohort longitudinal design (1–3 time points, 10–25 years, N=246), we characterized developmental changes of amygdala-vmPFC subregion functional and structural connectivity using resting state fMRI and diffusion-weighted imaging.

Results—Functional connectivity between the centromedial amygdala and rostral anterior cingulate (rACC), anterior vmPFC, and subgenual cingulate significantly decreased from late childhood to early adulthood in males and females. Age associated decreases were also observed between the basolateral amygdala and rACC. Importantly, these findings were replicated in a separate cohort (10–22 years, N=327). Similarly, structural connectivity, as measured by quantitative anisotropy, significantly decreased with age in the same regions. Functional connectivity between the centromedial amygdala and rACC was associated with structural connectivity in these same regions during early adulthood (ages 22–25). Finally, a novel time-varying coefficient analysis showed that increased centromedial amygdala-rACC functional connectivity was associated with greater anxiety and depression symptoms during early adulthood,

while increased structural connectivity in centromedial amygdala-anterior vmPFC white matter was associated with greater anxiety/depression during late childhood.

Conclusions—Specific developmental periods of functional and structural connectivity between amygdala-prefrontal systems may contribute to the emergence of anxiety and depressive symptoms, and may play a critical role in the emergence of psychiatric disorders in adolescence.

Keywords

amygdala; ventromedial prefrontal cortex; resting state functional neuroimaging; development; diffusion spectrum imaging; anxiety; depression

Introduction

The transition from adolescence to adulthood is a unique period of development when enhancements in cognition support improved control of affective processes, which are supported by specialized brain maturation (1). This is also a time when the prevalence of psychiatric disorders increases (2), which may be due to deviations from typical neurodevelopmental trajectories. The amygdala and ventromedial prefrontal cortex (vmPFC) have been associated with multiple cognitive and emotional functions that continue to mature through adolescence (3–5), as well as with psychiatric disorders (6–8). Initial resting state (rsfMRI) and diffusion-weighted imaging (DWI) results show that amygdala-vmPFC connectivity and the uncinate fasciculus, a major white matter tract supporting amygdala-vmPFC connectivity, increases linearly from childhood to adulthood (9–11). However, how these typical developmental changes are related to clinically relevant traits (e.g., anxiety and depression) are not well understood. Moreover, the relationship between functional and structural connectivity of this circuitry proceeds through this period has not yet been probed, limiting our current understanding of possible mechanisms of specialization.

The amygdaloid complex is grouped into three distinct, cytoarcitectonically defined subregions: centromedial (CM), basolateral (BL), and superificial (12;13). Because a large body of literature exists on the differing functions of the CM and BL amygdala, but not the superficial region (14–16), this paper focuses on the CM and BL subregions. These two subregions have distinct morphology, neuronal firing patterns, and structural and functional connectivity patterns (17–19). Furthermore, the manner in which information is sent to the two regions differs: the BL amygdala receives sensory information, while the CM amygdala is the major output station of the entire amygdala (17;20;21). These regions also support distinct functions, with the CM amygdala involved in enhancing attentional allocation and determining the salience of input and the BL amygdala involved in assessing the emotional content of sensory information (14–16). The differing characteristics of the CM and BL amygdala suggest that they may also follow distinct developmental trajectories that differentially contribute to the emergence of psychiatric disorders.

Distinct, cytoarcitectonic subregions of the vmPFC (22) have also been delineated, including the subgenual cingulate, rostral anterior cingulate (rACC), medial orbitofrontal cortex, and anterior vmPFC. Corresponding functional distinctions of the vmPFC have also been identified (23). The medial orbitofrontal regions (ventral BA 11) have been associated with

stimulus value assignment (24–27) and goal-directed decision-making (28–32) rACC (caudal BA 24) and anterior vmPFC (dorsal BA 11 & rostral-most portion of BA 32) are often associated with the cognitive control of emotion (33;34). The subgenual cingulate (BA 25) has been associated with depression (35). How functional and structural connectivity between amygdala and vmPFC subregions mature into adulthood has not been examined in detail.

rsfMRI and DWI studies find strong associations between amygdala-vmPFC connectivity and a range of psychiatric disorders, including psychosis, mood and anxiety disorders (36–47). However, even within a single disorder, results are conflicting, some reporting hypo-connectivity while others find hyper-connectivity(8;40;48;49). Discrepancy in amygdala-vmPFC connectivity findings may be due to differences in age ranges examined (50;51), not addressing developmental effects (52;53), and the specific amygdala and vmPFC subregions examined.

Though initial, cross-sectional studies have examined age-associated changes in amygdala subregion functional connectivity (50;54), this is the first longitudinal study to assess developmental changes in amygdala-vmPFC subregion functional connectivity, replicate the findings in a independent, cross-sectional sample, and simultaneously examine development of amygdala-vmPFC functional and structrual connectivity. Thus, we aimed to further probe changes through adolescence in amygdala-vmPFC connectivity by characterizing 1) connectivity between *subregions* and 2) concurrent relationships in functional and structural connectivity. Based on previous developmental studies (9–11;54;55), we hypothesized that amygdala-vmPFC subregion functional and structural connectivity would increase through adulthood. We hypothesized that the strongest age-related changes would be found between BL amygdala and other vmPFC regions, since the BL amygdala has the strongest bilateral structural connections with the vmPFC (17). We also hypothesized that relationship between amygdala-vmPFC structural and functional connectivity would increase in adulthood, similar to studies probing other brain systems (56–58). Finally, we examined two exploratory aims related to amygdala-vmPFC connectivity: 3) to what extent functional connectivity between amygdala-vmPFC subregions predicts changes in structural connectivity (or vice-versa) and 4) identification of developmentally specific associations with individual differences in anxiety and depression. Due to the close associations and common comorbidity between anxiety and depressive disorders(59;60), we chose to combine these symptoms.

Methods

Participants

Neuroimaging and behavioral testing was collected on 157 participants (10–22 years) as part of a longitudinal study (three 15 month follow-ups) and 89 participants (20–25 years) from a complimentary cross-sectional study. Participants and their first-degree relatives did not have a psychiatric disorder determined by phone screen and a clinical questionnaire (52;53). Data was available for 246 participants (121 female), with follow-up data for two (N=117, 62 female) or three (N=90, 48 female) visits, with a total of 453 scans. Replication was

performed on 327 participants (10–22 years) from the Philadelphia Neurodevelopmental Cohort (PNC, 61), details in Supplemental Materials.

Anxiety and Depression Scores

Anxiety and depression scores were measured using the Youth or Adult Self-Report (62;63), details in Supplemental Materials.

MR Data Acquisition

Data were acquired using a Siemens 3 Tesla Tim Trio at the University of Pittsburgh Medical Center Magnetic Resonance Research Center using a 12-channel phase array head coil. We collected five minutes of resting-state data with eyes closed while awake. Functional images were acquired using an echo-planar sequence sensitive to BOLD contrast (T_2*). rsfMRI parameters were: TR/TE=1500/29 ms, flip angle=70°, voxel size=3.125×3.125mm in-plane, 29 contiguous 4-mm axial slices, 200 TRs. DWI were acquired using a single-shell scheme. A total of 60 diffusion gradient directions were acquired (TR=6.4s, TE=0.89s, FOV=255×255mm, slice thickness=2.5 mm, b-value=850 s/mm^2). One non-diffusion sensitized volume (b0 image) was also acquired (b-value=0/s/mm^2). A magnetization-prepared rapid gradient-echo sequence (MPRAGE) was acquired to measure brain structure and for alignment of the rsfMRI images. MPRAGE parameters were: TR/TE1570/3.4ms, flip angle=8°, TI=800 ms, voxel size:0.78125 × 0.78125 × 1 mm, 200 TRs.

rsfMRI Preprocessing

Functional images were processed using Analysis of Functional NeuroImages (AFNI) software package(64). Like recent publications (65;66), we used a rigorous rsfMRI processing pipeline to account for head motion and used several processing pipeline (Supplemental Materials).

Regions of Interest

For each subject, we obtained subregion ROIs for the BL and CM amygdala using stereotaxic, probabilistic maps of cytoarchitectonic boundaries (12, Figure 1A). ROIs for subregions of vmPFC were determined using the Mackey vmPFC atlas, available in AFNI(22). Details on subregion ROIs and the rsfMRI first level statistical analyses are in the Supplemental Materials.

DWI Preprocessing

For DWI scans, non-brain regions were removed using FSL's brain extraction tool from the FMRIB Software Library(68). We used FSL's EDDY tool to correct images for eddy current distortion and movement(69), which exhibits superior performance to "eddy_correct" (70). DWI data was then imported into DSI studio (http://dsi-studio.labsolver.org,12/07/2016) and reconstructed using Q-space diffeomorphic reconstruction method (QSDR,71). The QSDR method obtains the spatial mapping function of quantitative anisotropy values (QA) from individual subject diffusion space to the FMRIB 1-mm fractional anisotropy atlas template.

Details on DWI preprocessing and fiber tracking are reported in the Supplemental Materials.,

Second Level Statistical Analyses

Developmental changes—Data was analyzed using a mixed-effects regression with *lme4* in R (72). We used a natural spline model, which fits piecewise polynomials at specified knots (ages). Details can be found in Supplemental Materials. For both the rsfMRI and DSI analyses, we included an overall measure of motion (mean motion displacement) as a nuisance covariate. We repeated analyses examining the four amygdala-vmPFC rsfMRI connectivity pairs that exhibited development changes in a normative subset of the PNC. Specificity of amygdala-vmPFC developmental effects was examined with exploratory, voxelwise analyses (Supplemental Materials).

Maturation Timing—For amygdala-vmPFC connectivity pairs showing significant developmental effects, we examined rates of change during development, using the first derivative from the spline model identified in the age-related changes analyses (9). Details are reported in the Supplementary Materials.

Structure-Function Relationships—For amygdala-vmPFC connectivity pairs that showed a significant developmental effects, we used mixed-effects regression to examine the extent to which rsfMRI and QA measures were significantly associated with one another at different points in development. The corresponding rsfMRI variable and age were added as predictors with QA as the dependent variable, to test whether one measure predicted the other, regardless of age. We added an interaction term to the model (age*predictor variable) to determine whether there were different relationships between structure and function at different ages. Significant interaction results were followed up using the Johnson-Neyman technique, a statistical procedure that obtains parameters estimates and points of significance from the interaction between two continuous variables (73–75).

We conducted exploratory analyses to determine if structural connectivity at the initial visit predicted functional connectivity at subsequent visits (and vice versa). Details are reported in Supplemental Materials.

Relationships with Individual Differences in Anxiety and Depression—To test whether developmental brain changes were associated with individual differences in anxiety and depression, we applied a time-varying effect model (TVEM) using SAS TVEM Macro (v3.1.0, 76). TVEM is an extension of the general linear model; however, in a TVEM, the relationship between amygdala-vmPFC connectivity and anxiety and depression is treated as a dynamic function (non-parametric) that exerts effects at different stages of development. Details are reported in the Supplemental Materials.

Results

Development of amygdala-vmPFC rsfMRI connectivity

Developmental effects were observed for functional connectivity between four amygdala and vmPFC subregions (Figure 2). We observed age-related *decreases* in connectivity

strength between the right CM amygdala and the following vmPFC subregions: right subgenual ACC (χ^2=16.4, p=0.0003, p_{holm}=0.008, age range of maturation: 14.3–20.4 years), right rACC (χ^2=22.4, p=0.00001, p_{holm}=0.0004, range:12.4–21 years), right anterior vmPFC (χ^2=19.6, p=0.00005, p_{holm}=0.002, range:10–19 years). We also observed significant age-related *decreases* in functional connectivity between the right BL amygdala and the right rACC (χ^2=13.1, p=0.001, p_{holm}=0.04, range: 10.1–18.6 years). By adulthood, the strength of connectivity in these amygdala-vmPFC subregions approached zero (average Fisher's Z range: 0.03–0.09). Results remained significant when we implemented different processing steps: 1) including global signal regression, a controversial method (77;78), 2) no spatial smoothing, 3) smoothing within the amygdala subregions only, and 3) when a 10-mm spherical ROI time series was extracted from the center of mass of each subregion (S2 Table). In the PNC, we replicated our results in all of the amygdala-vmPFC pairs (all p_{holm}<.05, S3 Table, S3 Figure). CM amygdala-vmPFC developmental decreases remained statistically significant in voxelwise analyses (S5 Table). In both cohorts, there were no significant interactions between sex and age, nor were there any main effects of sex in any amygdala-vmPFC connectivity pairs. These results provide strong evidence of age-related ***decreases*** in functional connectivity between the right CM and BL amygdala and specific vmPFC subregions (subgenual cingulate, rACC, anterior vmPFC) between the ages of 10–25 years.

Development of amygdala-vmPFC white matter tracts

We tested parallel developmental trajectories in amygdala-vmPFC structural connectivity. Corresponding developmental decreases in QA were also observed in amygdala and vmPFC subregions (Figure 3). There were age-related *decreases* in QA between the right CM amygdala and the right subgenual ACC (χ^2=9.8, p= 0.007, p_{holm}= 0.01, range: 15.2–21.1 years), right rACC (χ^2=12.5, p=0.001, p_{holm}= 0.003, range: 10.1–18.9 years), right anterior vmPFC (χ^2=7.1, p=0.02, p_{holm}= 0.03, range: 10.1–18.0 years). We also observed significant age-related *decreases* in QA between the right BL amygdala and the right rACC(χ^2=20.6, p=0.00005, p_{holm}= 0.001, range: 10.1–19.7 years). There was a significant overall main effect of sex for all connectivity pairs examined (p_{holm} 6.0e–6), with males exhibiting significantly higher QA. Results remained statistically significant when additional motion parameters were added as covariates to the model (Supplemental Materials).

Development of amygdala-vmPFC structure-function relationships

Functional connectivity between the right CM amygdala and rACC predicted QA differentially between these same regions at various stages in development (χ^2=8.5, p=0.003, p_{holm}=0.01). From 10–15 years old, increased functional connectivity between the right CM amygdala-rACC was associated with decreased QA in the same region (simple slope at 10 years: t=−2.8 p=0.005, simple slope at 15.35 years: t=−1.97, p=0.05); however, in adulthood, increased right CM amygdala-rACC functional connectivity was associated with increased right CM amygdala-rACC QA (age 22.42–25.94, simple slope at 22.42 years: t=1.97, p=0.05 simple slope at 25.94 years: t=2.27, p=0.02, Figure 3A). A similar trend was observed between CM amygdala-anterior vmPFC functional connectivity and QA (χ^2=4.9, p=0.02, p_{holm}=0.06, Supplemental Materials). Thus, increased functional and structural connectivity between the CM amygdala-anterior vmPFC and CM amygdala-rACC show a

negative relationship during late childhood and become positively correlated with each other in adulthood.

Time-varying relationship between amygdala-vmPFC connectivity and individual differences in anxiety & depression

Increased right CM amygdala-rACC functional connectivity was significantly associated with greater anxiety and depression scores during early adulthood for (23.2–25.9 years, Figure 4A). This relationship also remained present when analyses were conducted on the data when global signal was regressed and when data was extracted using a 10-mm spherical ROI to identify the CM amygdala (S2 Table). High CM amygdala-anterior vmPFC QA was associated with higher anxiety and depression scores during late childhood (10–11.7 years, Figure 4B). Details on establishing model fits are in the Supplemental Materials.

In summary, higher functional connectivity in CM amygdala-rACC was associated with increased anxiety and depression in adulthood, but not childhood. For structural connectivity, increased amygdala-anterior vmPFC QA was associated with higher anxiety and depression in late childhood, not adulthood.

Discussion

We examined developmental changes in structural and functional subregion connectivity between the amygdala and vmPFC. We found and replicated decreases in connectivity between the CM amygdala and rostral anterior cingulate (rACC), anterior vmPFC, and subgenual cingulate, and the BL amygdala and rACC, from late childhood through adulthood. Structural and functional connectivity between CM amygdala and rACC was positively coupled during adulthood, following a period of re-organization during adolescence. Finally, increased CM amygdala-rACC functional connectivity was associated with greater anxiety and depression in adulthood, while increased CM amygdala-anterior vmPFC structural connectivity was associated with greater anxiety and depression in childhood. Our results provide a novel view of developmental functional and structural connectivity within a neural circuit that has been implicated in a wide array of cognitive and emotional processes (79–82) and psychiatric disorders (18;36–38;44–46;83).

Developmental rsfMRI connectivity changes in the CM Amygdala-vmPFC subregions

The majority of significant developmental effects were found in connectivity between the CM amygdala and vmPFC subregions, but not the BL amygdala. The CM amygdala receives information from all other nuclei of the amygdala, including the BL amygdala (17). Thus, as the "output station", CM amygdala is crucial for driving the behavioral responses to environmental stimuli (84–86). Furthermore, the primary functional role of the CM amygdala is to determine what is salient in one's environment and to mediate fear/anxiety responses (79). Attentional allocation to what is considered salient changes during adolescence (87;88); connectivity between the CM amygdala and vmPFC may underlie this change. vmPFC subregions that showed decreased connectivity with the CM amygdala across development were regions largely implicated in depression (subgenual cingulate, 35) and the cognitive control of emotion (rACC, anterior vmPFC (89–91). These developmental

decreases in rsfMRI connectivity from late childhood to adulthood may be due to a shift in networks being used, with the vmPFC creating stronger cortical connections with other prefrontal regions involved in the control of emotional information (i.e., ventrolateral prefrontal cortex, 92) while decreasing engagement with amygdala. Finally, projections from the vmPFC to inhibitory GABAergic neurons in the amygdala are responsible for the regulation of responses to emotional stimuli (93;94), pointing to a potential mechanism underlying this change. Evidence from rodent models show that significant dendritic remodeling (both pruning and increased branching) occurs in the amygdala and vmPFC during adolescence, providing support for dynamic processes taking place during adolescence in this neural circuit (95;96).

Our findings of *decreased* connectivity between the amygdala and vmPFC subregions from late childhood into adulthood are in agreement previous reported subcortical-cortical connectivity *decreases* into adulthood (97–100). However, our results are in contrast to two studies: one that found increases in amygdala-vmPFC connectivity with increasing age (54) and another that compared amygdala connectivity of children to amygdala connectivity of adults and found increases in adult amygdala-vmPFC connectivity (55). Several important differences between our study and these studies (54; 55) may underlie these differences. The age range for Gabard-Durnam et al. (54) included younger participants starting at 4 years of age, while Qin et al. (55) compared two samples: youth 7–9 years old vs. adults. Our youngest participants were 10 years old. Dual systems models of development propose that there is a peak in affective processing during adolescence (101). Thus, amygdala/vmPFC connectivity may have a peak in connectivity in adolescence. The cross-sectional data in both studies may have predominantly reflected possible childhood increases, undermining the ability to assess decreases through adolescence. Our longitudinal study also had a greater number of subjects (246 vs. 58 for (54) and 48 for (55)) and may have been better powered to detect these decreases. We also implemented recent approaches to control for the known age effects of motion on rsfMRI (77;102;103), including wavelet despiking and simultaneous bandpass/nuissance regression (77;104;105), and used greater restrictions for head movement (< 0.5 mm and/or 5 DVARS vs. 2.5 mm or 2° of motion in (54) and no scrubbing in (55)). Moreover, given this discrepancy in results we subjected our data to several processing pipeline streams and parcellations and our findings remained significant. Our evidence supports that this is a robust finding, given that amygdala-vmPFC developmental decreases remain significant at the voxelwise level. Finally, we replicated the amygdala-vmPFC subregion functional connectivity decreases in an independent sample. Thus, we are confident there are decreases in amygdala-vmPFC functional connectivity between the ages of 10–25 years.

In our exploratory, voxelwise analyses, several other significant age associated clusters emerged. In addition to the CM amygdala-vmPFC developmental decreases, there were also significant developmental decreases between the CM amygdala and the following regions: putamen, caudate, ventrolateral prefrontal cortex, insula, and precuneus. Future, in-depth examination of these developmental connectivity patterns is necessary.

Age-associated white matter changes in CM Amygdala-vmPFC subregions

We found age-related white matter changes between concomitant amygdala-vmPFC regions. Our results are comparable with existing studies, which identify protracted development of the uncinate fasciculus using tensor-based DWI methods(9–11). Developmental decreases in QA may appear surprising, given that these other studies assessing diffusion with the tensor model found developmental increases in fractional anisotropy. However, these same studies typically report developmental decreases in diffusion along the parallel axis, axial diffusivity, during adolescence(9–11), which may be a more similar, though less robust, measure to QA. Thus, decreases in QA may reflect a developmental refinement in connectivity between amygdala and vmPFC subregions. Recent studies indicated dynamic changes in connectivity during learning (106), which may be akin to specialization in development.

Shift in CM Amygdala-rACC functional-structural relationships during development

We were interested in developmental relationships between functional and structural connectivity. We found that into adolescence greater functional connectivity was associated with relative decreases in structural connectivity, which by adulthood were positively correlated. We speculate that this could reflect a process of specialization, as brain processes such as myelination and synaptic pruning support greater affinity between functional and structural connectivity (56–58). Future studies examining timing of functional and structural connectivity in relationship with development of behaviors relevant to this neural circuit (e.g., cognitive control of emotion), would further clarify this result.

Our results failed to show that, across development, amygdala-vmPFC functional connectivity at the initial visit predicted amygdala-vmPFC structural trajectories (and vice versa). One potential conclusion is that functional and structural connectivity are parallel processes, both changing during adolescence and into adulthood, but connectivity at one time point does not predict future changes in another type of connectivity. Alternatively, the sample design we utilized in this study (hybrid longitudinal, 1–3 visits) may not be ideal for testing this hypothesis. To accurately assess whether the development of structural connectivity needs to be in place before functional connectivity is established (or vice versa), it is ideal to follow a sample of same-aged youth with greater than 3 visits.

Relationships with anxiety and depression at distinct points in development

This was the first study, to our knowledge, to use a novel time-varying analytic approach to characterize how connectivity measures are related to individual differences in anxiety and depression at different stages of development, from late childhood through adulthood. Higher functional connectivity between the CM amygdala and rACC in young adulthood (22–24 years) was associated with higher anxiety and depression scores. These findings suggest that a lack of developmental decrease in neural connectivity between CM amygdala and rACC associated with increases in anxiety and depression traits. In support of these findings, task-based neuroimaging studies of emotional face processing show a shift from positive to negative connectivity in amygdala fronto-limbic circuits during typical development (109); young adults with anxiety fail to show this change, suggesting that an altered pattern of age-associated changes in amygdala connectivity is associated with

increased anxiety(110). Intriguingly, higher amygdala-vmPFC connectivity has been associated with anxiety in typically developing 7–9 years olds (50); however, the effects were strongest in the BL amygdala, not the CM amygdala. Perhaps increased functional connectivity between the BL amygdala and vmPFC identifies young children at risk for anxiety and depression, while increased CM amygdala-vmPFC functional connectivity is related to these symptoms as an adult. Future studies are necessary to examine the dynamic relationship of amygdala-vmPFC functional connectivity and individual differences in anxiety and depression across wide age ranges, to explore how unique biomarkers may be important for a particular developmental stage.

One potential mechanism underlying the relationship between amygdala-vmPFC functional connectivity and anxiety and depression symptoms is dysregulation in one's ability to respond to negative stimuli. This is supported by evidence that the CM amygdala is crucial for processing of fear and anxiety(79), the subgenual cingulate is associated with depression(35) and the rACC is important in control of emotional processing (80;89–91). However, studies that did not examine amygdala-vmPFC subregions find decreased connectivity in **adults** with anxiety disorders and depression (8;111), while others find amygdala-vmPFC hyper-connectivity in anxiety, but amygdala-vmPFC hypo-connectivity in depression (112). Importantly, we found this relationship within a normative population, underscoring the importance of studying anxiety and depression as a dimensional constructs (113;114) as indicated in RDoC approaches (115;116). This report provides a strong foundation for future clinical studies to build upon, particularly in regards to examining the role that the development of fronto-limbic functional and structural connectivity contributes to the onset of psychiatric disorders.

It is intriguing that CM amygdala-anterior vmPFC structural connectivity predicts anxiety and depression in childhood, while CM amygdala-rACC functional connectivity predicts anxiety and depression in adulthood. Anxiety and depression symptoms increase steadily through adolescence and reach a plateau at the transition to adulthood(117;118). Perhaps delayed amygdala-vmPFC white matter maturation contributes to increased anxiety and depression symptoms observed during adolescence, while typical maturation of amygdala-vmPFC functional connectivity is what leads to plateauing of anxiety and depression symptoms in adulthood. This provocative idea presents the possibility that biological factors exert differential influences on behavior at distinct points in development. Though our results are intriguing, use of TVEM modeling to address psychological phenomena is relatively new. To our knowledge, this is the first application of TVEM to neuroimaging and clinical measures. Thus, more in-depth follow up is warranted to determine to what extent these relationships are replicated in typically developing and clinical samples. Taken together, these results provide preliminary evidence of developmentally sensitive neural markers associated with anxiety and depression at different points in development. These results could inform future studies characterizing developmental windows of vulnerabilities and resilience to anxiety and depression and markers of efficacy of evidence-based interventions to alter neural trajectories.

Conclusion & Future Directions

Our results provide evidence for dampening of amygdala-prefrontal emotional control regions through adolescence, particularly in CM amygdala and rACC, paralleling known decreases in the influence of affect on behavior into adulthood. Developmental enhancements in the coupling of functional and structural connectivity suggest specialization of this circuitry. Associations between earlier structural and later functional connectivity with dimensions of anxiety and depression suggest possible windows of vulnerability to inform risk and treatment efficacy. Future studies are needed to probe disease specificity and markers of general risk factors across psychopathology. Finally, this study sets the foundation for a normative template of amygdala-vmPFC to better assess abnormal trajectories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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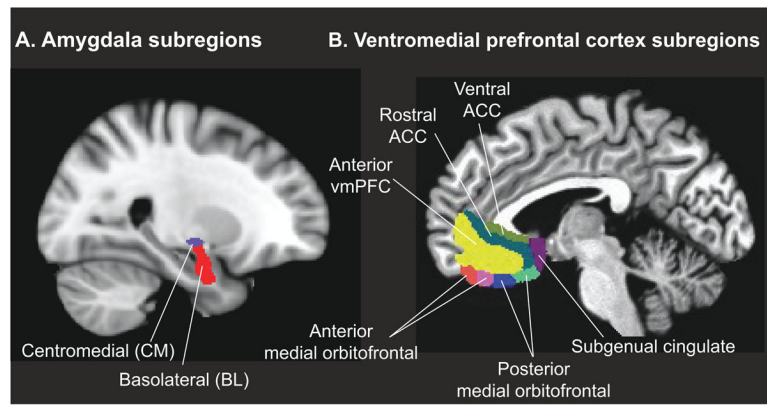
Figure 1.
A). Amygdala subregions examined in this study, taken from FSL's Juelich histological atlas (Eikhoff et al., 2007) B). Ventromedial prefrontal subregions examined in this study, taken from Petrides & Mackey (2014).
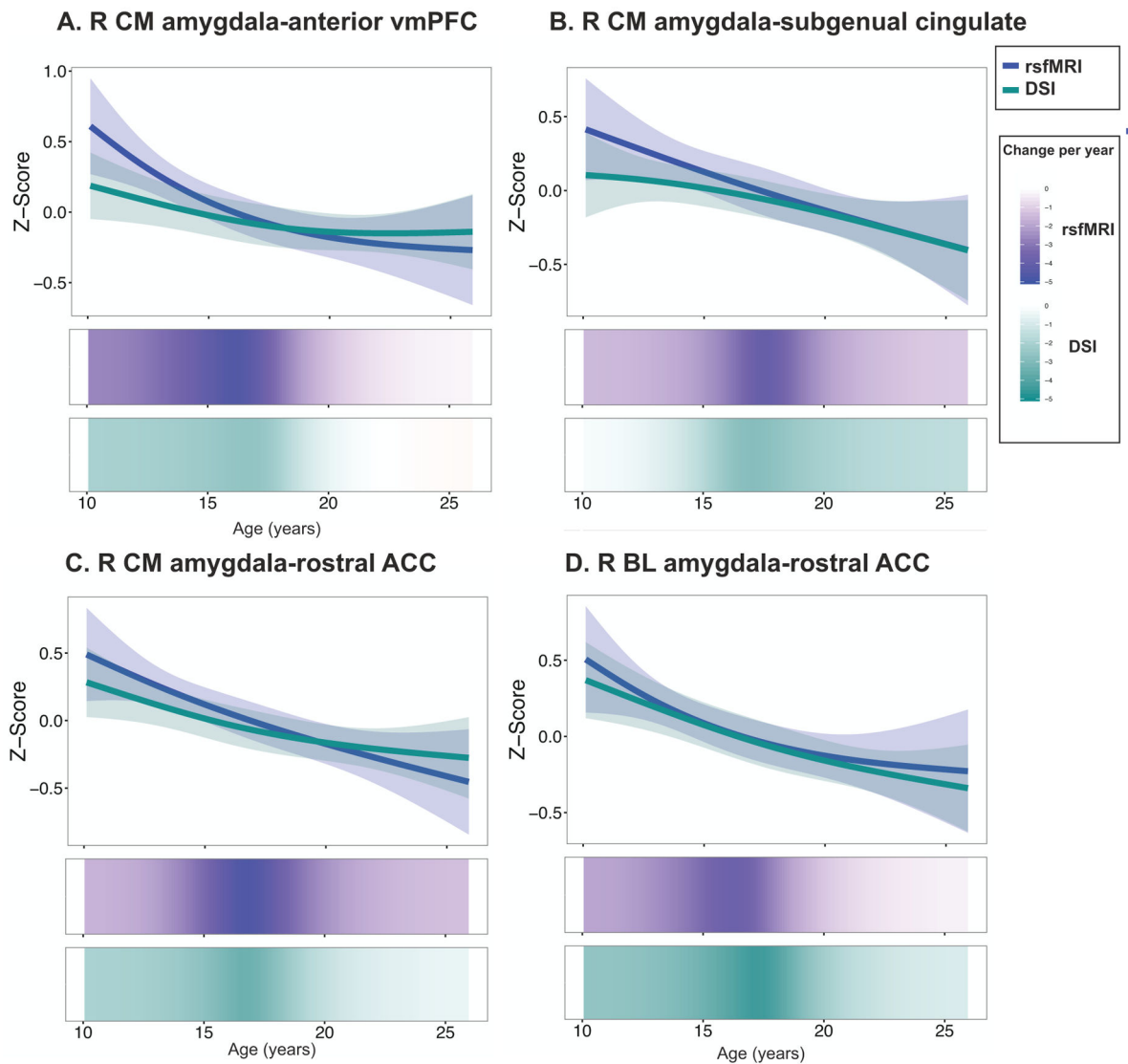
Figure 2.
Significant age-associated changes in functional and structural connectivity of amygdala-vmPFC subregions and corresponding maturation rates. Z-scores of all measures were created and then an age-related fit line was calculated for rsfMRI (blue) and DSI (dark cyan) amygdala-vmPFC pairs: A) right centromedial (CM) amygdala-anterior ventromedial prefrontal cortex (vmPFC); B) right CM amygdala-subgenual cingulate; C) right CM amygdala-rostral anterior cingulate (rACC); and D) right basolateral (BL) amygdala-rACC. Beneath each plot, maturation rates for the respective measure are plotted. When the change rates were > 2.5 SD away from the null distribution, we considered this to be a period at which significant maturation was occurring.
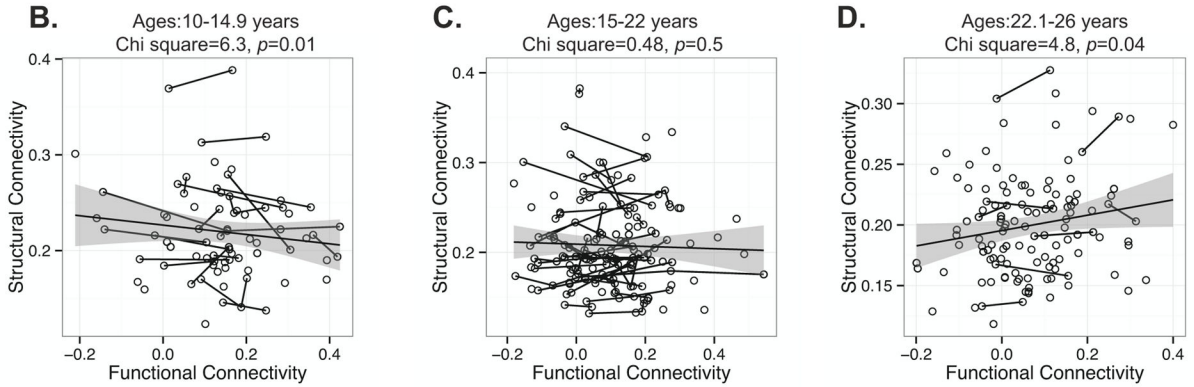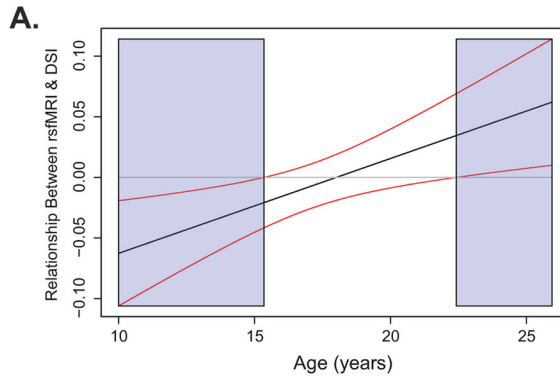
Figure 3.
A) For connectivity between the right centromedial (CM) amygdala and rostral anterior cingulate (rACC), in late childhood higher rsfMRI is associated with decreased QA, while in adulthood, higher rsfMRI positively coupled with QA. Black lines represent the relationship between rsfMRI and DSI at each age and the red lines are the 95% confidence intervals. Transparent blue boxes represent periods of development in which there was a significant relationship between rsfMRI and DSI. B) Plots of relationships between functional and structural connectivity in the right CM amygdala and rACC in B) late childhood through mid-adolescence (10–14.9 years), C) mid-adolescence to early adulthood (15.0–22 years), and D) adulthood(22.1–26 years).
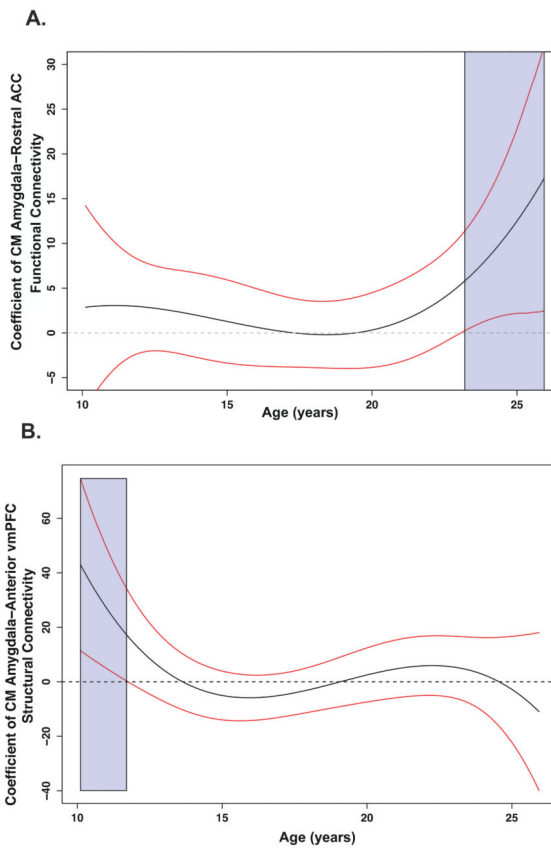
Figure 4.
Effects of A) CM amygdala-rostral ACC functional connectivity and B) CM amygdala-anterior vmPFC structural connectivity on anxiety and depression across development. Black lines represent the relationship between the connectivity measure and anxiety/depression at each age and the red lines are the 95% confidence intervals. Transparent blue boxes represent periods of development in which there was a significant relationship between the connectivity pair and anxiety and depression.