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The longitudinal association between externalizing behavior and frontoamygdalar resting-state functional connectivity in late adolescence and young adulthood

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Background: Externalizing behavior has been attributed, in part, to decreased frontolimbic control over amygdala activation. However, little is known about developmental trajectories of frontoamygdalar functional connectivity and its relation to externalizing behavior. The present study addresses this gap by examining longitudinal associations between adolescent and adult externalizing behavior and amygdala–anterior cingulate cortex (ACC) and amygdala–orbitofrontal cortex (OFC) resting-state functional connectivity in a sample of 111 typically developing participants aged 11–23 at baseline. **Methods:** Participants completed two-to-four data waves spaced approximately two years apart, resulting in a total of 309 data points. At each data wave, externalizing behavior was measured using the Externalizing Behavior Broadband Scale from the Achenbach Youth/Adult Self-Report questionnaire. Resting-state fMRI preprocessing was performed using FSL. Amygdala functional connectivity was examined using AFNI. The longitudinal association between externalizing behavior and amygdala–ACC/OFC functional connectivity was examined using linear mixed effect models in R. **Results:** Externalizing behavior was associated with increased amygdala–ACC and amygdala–OFC resting-state functional connectivity across adolescence and young adulthood. For amygdala–ACC connectivity, externalizing behavior at baseline primarily drove this association, whereas for amygdala–OFC functional connectivity, change in externalizing behavior relative to baseline drove the main effect of externalizing behavior on amygdala–OFC functional connectivity. No evidence was found for differential developmental trajectories of frontoamygdalar connectivity for different levels of externalizing behavior (i.e., age-by-externalizing behavior interaction effect). **Conclusions:** Higher externalizing behavior is associated with increased resting-state attunement between the amygdala and ACC/OFC, perhaps indicating a generally more vigilant state for neural networks important for emotional processing and control. **Keywords:** Externalizing behavior; amygdala; functional connectivity; anterior cingulate cortex; orbitofrontal cortex.

Introduction

Externalizing problems, such as aggressive, rule-breaking, and oppositional behavior, have been shown to fluctuate over the course of development, but peak in late adolescence (15–19 years) and decrease thereafter (Petersen, Bates, Dodge, Lansford & Pettit, 2015). This peak in late adolescence may be unsurprising, given that this period includes important challenges, such as changing relationships with parents, the exploration of new roles, the experience of intimate partnerships, and identity formation (Eccles & Gootman, 2002). Nevertheless, acting-out behaviors that occur during this period can substantially alter life trajectories. Brain regions involved in executive functioning and higher-order emotional processing continue to mature into early adulthood (Giedd et al., 1999; Lebel & Beaulieu, 2011; Mills et al., 2016) and may play a role in the fluctuations in externalizing behaviors across the late adolescent and early adulthood period. Understanding the neural underpinnings of this behavior, which is closely related to the capacity for control or regulation, has the potential to suggest targets of intervention. Nevertheless, little is known about the longitudinal associations between externalizing behaviors and brain function in late adolescence and early adulthood.

In recent decades, several neuroimaging studies have explored the structural and functional correlates of externalizing behavior, focusing mostly on clinical cross-sectional samples (e.g., Marsh et al., 2011; Thijssen & Kiehl, 2017). As the brain undergoes protracted development (Giedd et al., 1999; Lebel & Beaulieu, 2011; Mills et al., 2016), the association between externalizing behavior and brain structure and function may differ over time and age, and may be different for clinical versus healthy populations. Cross-sectional studies are limited in the developmental information they can provide and may not be able to provide nuanced information on developmental neural trajectories underlying the development of externalizing behavior. In addition, as externalizing behaviors vary across a continuum, important information may remain obscured when all individuals showing subclinical and all individuals showing clinical levels of

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externalizing behaviors are treated uniformly and are contrasted using group designs.

The existing neuroimaging literature most consistently implicates the amygdalae, medial prefrontal cortex, and cingulate cortex in externalizing behavior (Siever, 2008). Of particular importance may be connectivity of frontoamygdalar circuitry comprised of the amygdalae and medial prefrontal structures such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC; Romero-Martínez et al., 2019). Direct inputs from the medial prefrontal cortex to the amygdala, a region implicated in salience and threat detection (Phelps & LeDoux, 2005), suggest that these frontal circuits are involved in top-down control of the amygdala (Banks, Eddy, Angstadt, Nathan, & Phan, 2007). The importance of this circuitry for externalizing behavior has been highlighted by studies comparing patients with psychiatric disorders characterized by high rates of externalizing behaviors, such as conduct disorder and psychopathy, versus control participants. For example, Ewbank et al. (2018) showed that amygdala–ACC functional connectivity in response to angry versus neutral faces may be altered in subgroups of externalizers. Moreover, in male youth, psychopathic traits were associated with reduced amygdala–OFC functional connectivity when making moral judgments (Marsh et al., 2011). Compared to healthy controls, youth with disruptive behavior disorders show decreased amygdala–ACC functional connectivity under conditions of high provocation (White et al., 2016), and in these youth, amygdala–ACC connectivity is inversely associated with retaliatory responses and aggressive behavior.

These findings of decreased functional connectivity during emotional or moral processing suggest decreased regulatory control of the prefrontal cortex over the amygdala in externalizing disorders (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). As indicated above, most studies examining frontoamygdalar connectivity have focused on clinical samples and examine task-based functional connectivity; less is known about the association between externalizing behavior in the general population and amygdala–ACC and amygdala–OFC functional connectivity in the brain at rest.

Resting-state activity describes the brain's neural activation in the absence of a task. Resting-state activity consumes a major portion of the body's energy (~20%), despite the brain being only 2% of the body's total mass (Fox & Raichle, 2007). Even at rest, brain regions form tightly connected networks. Imaging studies have identified a number of robust networks that are found across studies, suggesting the existence of universal pattern of intrinsic functional connections (e.g., Doria et al., 2010; Mowinckel, Espeseth & Westlye, 2012; Muetzel et al., 2016). Importantly, individual differences in resting-state functional connectivity have been consistently associated with psychopathology in general (e.g., Hoekzema et al., 2014; Veer et al., 2010), as well as externalizing behavior specifically (e.g., Cohn et al., 2015; Thijssen et al., 2017). The few studies that have examined associations between externalizing behaviors and frontoamygdalar resting-state functional connectivity suggest a different pattern than what is observed in task-based functional connectivity studies: In adolescence, conduct disorder has been associated with *increased* basolateral amygdala–ACC connectivity (Aghajani et al., 2017). Results regarding amygdala–OFC functional connectivity are inconsistent. In childhood, externalizing behavior has been associated with decreased amygdala–OFC functional connectivity (Park et al., 2018), whereas in adolescence, a positive association between externalizing behavior and amygdala–OFC functional connectivity was found (Saxbe et al., 2018). However, centromedial amygdala–OFC functional connectivity was decreased in individuals with conduct disorder and callous and unemotional traits, and in adults, trait anger has been associated with decreased amygdala–OFC functional connectivity (Fulwiler, King, & Zhang, 2012).

As a consequence of the relative infancy of our field, data collection for multiwave longitudinal studies has only recently been achieved, and longitudinal developmental investigations of associations between externalizing behavior and amygdala–ACC and amygdala–OFC functional connectivity have – to our knowledge – not yet been performed. However, longitudinal studies are essential for our understanding of the neural trajectories underlying the development of externalizing behavior. To address this gap and to contribute to this emerging literature, the present study examined the longitudinal relationship between self-reported externalizing behaviors and amygdala–ACC and amygdala–OFC functional connectivity in a typically developing sample of adolescents and young adults. Based on previous literature (Aghajani et al., 2017; Saxbe et al., 2018), we hypothesized increased resting-state functional connectivity in individuals with increasing externalizing behaviors. As this is the first study to examine developmental changes of amygdala–ACC and amygdala–OFC functional connectivity in relation to externalizing behavior, we have no directional hypotheses regarding differential longitudinal trajectories for individuals with higher versus lower externalizing behavior but expect that the trajectories will differ depending on level of externalizing behavior. Additionally, we explored whether associations between externalizing behavior and amygdala functional connectivity differed for males and females. Moreover, as relatively few studies have reported age-related changes in functional connectivity over adolescence and young adulthood, we also report developmental changes in amygdala–ACC and amygdala–OFC functional connectivity.

Methods

Participants

The present study uses data from a study focused on the normative development of 197 individuals aged 9 to 23 collected at the University of Minnesota (e.g., Almy, Kuskowski, Malone, Myers, & Luciana, 2018; Urošević, Collins, Muetzel, Lim, & Luciana, 2012). Participants were recruited between 2004 and 2006 from a community database of research volunteers maintained by the Institute of Child Development at the University of Minnesota, by postcard mailings to nonacademic employees of the University, and by flyers posted throughout the university campus. Potential participants were excluded if they had been diagnosed with a psychological or neurological disorder, had chronic physical illnesses, were born preterm or had other birth complications, were non-native English speakers, abused psychoactive substances, had uncorrected vision or hearing difficulties, were non-right handed, or if they had contraindications to MRI scanning. The protocol was approved by the Medical/Biological Committee of the University of Minnesota's Institutional Review Board. For this study, five waves of data were collected approximately two years apart. Although resting-state functional MRI (rsfMRI) was not part of the MRI protocol at baseline, at the second visit, a resting-state acquisition was added to the MRI protocol. Participants were 11 to 25 years old at time 2, from now on referred to as rest baseline. Of the 197 baseline participants, 163 participants had at least one resting-state fMRI scan available beginning at the second assessment wave. Of these 163 participants, we only included the 122 (64 female) participants who had resting-state fMRI data from at least two time points. The 122 participants provided a total of 351 data points, of which 23 data points were excluded due to poor quality of the imaging data and an additional eight data points were excluded as no data on externalizing behavior were available. The exclusion of these data points led to the exclusion of 11 participants, who now no longer had longitudinal resting-state data available. Thus, the present sample included 111 participants with two or more good quality resting-state datasets as well as externalizing behavior data. Of these participants, 45 had data on 2 data waves, 45 on 3, and 21 on 4. In total, 309 data points were included in the analyses. Ninety-three of the 111 participants had good quality data available at rest baseline. At consecutive data waves 2, 3, and 4, data were available for 46, 92, and 78 of the 111 participants, respectively. The low attendance rate at resting-state data wave 2 (overall study wave 3) was due to a temporary gap in extramural funding that limited the number of individuals who could be tested.

Participants who were excluded did not differ from the included sample in externalizing behavior, sex, income, or ethnicity. Excluded individuals were older at rest baseline, $t(161) = -3.40$, $p = .001$.

Measures

Externalizing behavior. Externalizing behavior was measured using the Externalizing Behavior Broadband scale of the Achenbach Youth Self-Report for individuals younger than 18, and Adult Self-Report for individuals 18 years and older (Achenbach, 1991; Achenbach & Rescorla, 2003). The externalizing behavior scale is comprised of the Aggressive Behavior subscale and the Rule-Breaking (youth) or Delinquency (adult) subscale. Externalizing behavior raw scores were converted to the percentage of maximum attainable score to account for item-number differences between the youth and adult questionnaires (Olson, Hooper, Collins, & Luciana, 2007). See Table S1 for the number of participants with youth or adult questionnaire per data wave. Mean scores for each data wave can be found in Table 1. Figure S1 depicts the distribution of externalizing behavior scores over age.

Resting-state fMRI acquisition and preprocessing. Participants underwent a 6-min resting-state fMRI scan. Information about fMRI acquisition as well as preprocessing and quality control can be found in Appendix S1.

Analyses

Using the Harvard Oxford Subcortical Atlas within FSL, a bilateral amygdala mask was created including voxels with a probability of =>0.90 of belonging to the left or right amygdala. This mask was then registered to native EPI space. Using FSL, weighted average amygdalae time series were extracted from the preprocessed datasets. For the examination of functional connectivity with relevant regions of the prefrontal cortex, five ACC and OFC ROIs were created by averaging left and right seeds described by Kelly et al. (2009) for ACC and by Liu et al. (2015) for OFC (Figure 1). Voxels within a 3.5 mm sphere radius surrounding the coordinates were included in the masks. AFNI (Cox, 1996) was used to calculate amygdala–whole brain connectivity maps (3dTcorr1D) in standard space,

Table 1 Sample characteristics

	Rest baseline (n = 93)	T2 (n = 46)	T3 (n = 92)	T4 (n = 78)
Age range	11.62–24.93	13.36–29.98	15.84–29.42	18.04–32.28
Age	17.60 (3.76)	19.73 (3.23)	21.74 (3.88)	23.35 (3.36)
Female (n)	49 (51%)	30 (64%)	53 (55%)	43 (54%)
Family income (US dollars)	116,000 (84,931)	112,580 (87,644)	105,925 (65,837)	–
Ethnicity				
Caucasian (n)	84 (90.3%)	44 (95.7%)	83 (90.2%)	71(91.0%)
African American	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (1.3%)
Hispanic	1 (1.1%)	1 (2.2%)	2 (2.2%)	2 (2.6%)
Asian	2 (2.2%)	1 (2.2%)	2 (2.2%)	2 (2.6%)
Other	5 (5.4%)	0 (0.0%)	4 (4.3%)	2 (2.6%)
Externalizing behavior (% of total possible endorsement)	10.63 (8.26)	11.71 (9.27)	11.79 (9.31)	12.21 (10.51)
Externalizing behavior (%) range	0.00–45.71	0.00–32.81	0.00–56.25	0.00–45.71
Externalizing behavior T score	46.46 (8.71)	47.35 (9.29)	47.82 (9.00)	47.63 (9.87)
Externalizing behavior T score range	29–71	29–65	30–76	30–71
Clinical or subclinical externalizing behavior (n)	5 (5.4%)	7 (15.2%)	9 (10.9%)	9 (11.6%)

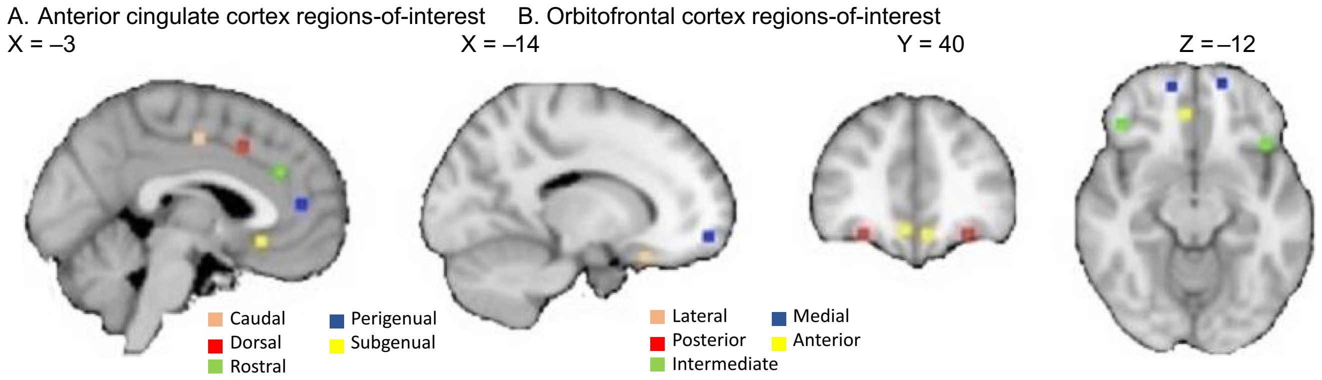


Figure 1 Anterior cingulate and orbitofrontal cortex regions of interest [Colour figure can be viewed at wileyonlinelibrary.com]

perform Fisher R to Z transformations, and consequently extract amygdala–ROI connectivity values. Several of the connectivity measures contained outliers ($z > 3$). Outliers (0–3 per outcome variable, see Table S4) were winsorized to match the highest nonoutlier value. Resting-state fMRI functional connectivity values from the baseline data wave were residualized for the scanner upgrade that occurred mid data collection. The psych package was used to calculate two-way mixed intraclass correlations (ICC) for the longitudinal connectivity measures and the measure of externalizing behavior. We report both ICC(3,1) as ICC(3,k) coefficients to allow comparison with other studies (Koo & Li, 2016). As measurements of functional connectivity and externalizing behavior are used separately (instead of the mean value of functional connectivity), ICC(3,1) is more appropriate for the current study.

The lme4 package in R was used to conduct linear mixed effect analyses (Bates, Maechler, Bolker, & Walker, 2014). First, we examined the changes in externalizing behavior over age. In initial analyses, linear and quadratic age effects were modeled. Models with a random intercept, random slope, and both random intercept and slope were tested. Best fitting models (based on Akaike's information criteria (AIC) and Bayesian information criteria (BIC)) were retained and remodeled with an autoregressive error structure. If the autoregressive model had lower AIC/BIC than the default independent error structure model, this model was used as a final model. This same strategy was used to examine the baseline model of the functional connectivity data (see Table S5 for model fit parameters). In order to assess developmental trajectories of functional connectivity, this baseline model was used controlling for sex and framewise displacement. We also tested age-by-sex interaction effects, but these did not increase model fit.

In order to examine the association between externalizing behavior and functional connectivity, the effect of externalizing behavior was added to the baseline model, controlling for age, sex, and average framewise displacement. To assess whether externalizing behavior was associated with differential developmental trajectories of frontoamygdala functional connectivity, and to assess sex differences in the association between externalizing behavior and frontoamygdala functional connectivity, models with age-by-externalizing and sex-by-externalizing behavior interactions effects were also tested. Significant externalizing effects were followed up by analyses examining whether the effect of externalizing behavior can be explained by between-subject differences in level of externalizing behavior at rest baseline or by within-subject change in externalizing behavior over time. It is important to note that change over time does not equal change over age given the study's cohort sequential design as well as individual difference factors. Different individuals can show fluctuations in externalizing behaviors over time, that on the group level, do not provide evidence of change over age. For example, individual 1 shows an increase in externalizing behavior between age 14 and age 17 and remains at the higher level at subsequent time points. Individual 2 shows a peak in externalizing behavior at age 15 and decreases thereafter. These individuals *do* show change over time, and both types of change may be supported by corresponding alterations in functional connectivity. However, on the group level, there may be *no* clear association between externalizing behavior and age. Thus, even in the absence of age-related changes in externalizing behavior, it may be relevant to assess whether within-person changes in externalizing behavior are associated with co-occurring changes in functional connectivity.

The afex package was used to compute statistical significance. Correction for multiple comparisons was performed using a Bonferroni correction procedure adjusted for correlated variables (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm; Perneger, 1998; Sankoh, Huque, & Dubey, 1997). For the ACC ROIs, the average intercorrelation was $r = .46$, resulting in an α of .028 (2-sided adjusted). For the OFC ROIs, the average intercorrelation was $r = .38$, resulting in an α of .025 (2-sided adjusted). Correlations between the different ROIs can be found in Table S6.

All R scripts used for this manuscript can be found on: https://github.com/sthijssen/Externalizing_amygdalaFCProject.

Results

Participant characteristics can be found in Table 1. There were no significant age differences between males and females (all p's > .372), nor were there significant sex differences in externalizing behavior (all p's > .210). Correlations between externalizing behavior, age, sex and framewise displacement can be found in Table S7. There was no significant linear or quadratic longitudinal relation between age and externalizing behavior, $p = .67$ (Figure S1). The ICC (3,1) for the different connectivity measures ranged from 0.10–0.25; for ICC(3,k), the range was 0.31–0.58 (see Table S8). The reliability of externalizing behavior was moderate, ICC(3,1) = .65 (ICC(3,k) = .88).

Before reporting the results regarding the association between externalizing behavior and amygdala–ACC and amygdala–OFC functional connectivity, we will first report age-related changes in functional connectivity.

Age-related changes in functional connectivity

After controlling for sex, and average framewise displacement, age was associated with increased

Table 2 Association between externalizing behavior and amygdala–ACC functional connectivity

	Caudal			Dorsal			Rostral			Perigenual			Subgenual		
	β	*t*	*p*	β	t	*p*	β	t	*p*	β	t	*p*	β	t	*p*
Intercept	0.00	4.29	<.001	0.00	−0.77	.502	0.00	−2.89	.003	0.00	−0.67	.502	0.00	1.10	.271
Externalizing behavior	0.13	2.40	.017[a]	0.14	2.38	.018[a]	0.11	1.71	.063	0.22	3.62	<.001[a]	0.02	0.39	.701
Age	0.34	6.13	<.001[a]	0.14	2.37	.019[a]	−0.02	−0.28	.662	0.03	0.58	.562	0.10	1.69	.092
Sex (female)	−0.04	−0.66	.507	0.09	1.42	.160	0.10	1.40	.120	0.01	0.11	.916	0.09	1.42	.159
Framewise Displacement	−0.01	−0.20	.846	0.10	1.83	.069	0.12	2.20	.032	0.07	1.27	.207	−0.00	−0.05	.959

[a] Survives correction for multiple testing.

amygdala–caudal ($\beta = 0.33$, $p < .00$) and amygdala–dorsal ($\beta = 0.13$, $p = .028$) ACC functional connectivity (but not with amygdala–rostral ($\beta = 0.03$, $p = .573$), amygdala–perigenual ($\beta = 0.02$, $p = .733$), and amygdala–subgenual ($\beta = 0.10$, $p = .097$) ACC functional connectivity, Figure S2a). For amygdala–lateral ($\beta = 0.20$, $p < .001$), amygdala–intermediate ($\beta = 0.24$, $p < .001$), and amygdala–anterior ($\beta = 0.17$, $p = .003$) OFC functional connectivity, but not for amygdala–posterior OFC functional connectivity ($\beta = 0.05$, $p = .416$), a linear increase over age was found (Figure S2b). The association between age and amygdala–medial OFC functional connectivity was significant and in the same direction, but did not survive correction for multiple testing ($\beta = 0.13$, $p = .029$).

Association between externalizing behavior and amygdala–anterior cingulate cortex functional connectivity

Results for the amygdala–ACC linear mixed effects models can be found in Table 2 and are depicted in Figure 2A. For amygdala–caudal, amygdala–dorsal, and amygdala–perigenual ACC functional connectivity, a significant positive effect of externalizing behavior was found, $\beta = 0.13$, $p = .017$, $\beta = 0.14$, $p = .018$, and $\beta = 0.22$, $p < .001$, for amygdala–caudal, amygdala–dorsal, and amygdala–perigenual ACC functional connectivity, respectively. All significant effects survived correction for multiple testing. For amygdala–rostral ACC functional connectivity, a nonsignificant effect in the same direction was found, $\beta = 0.10$, $p = .063$. For all structures, regardless of time point, higher levels of externalizing behavior were related to increased functional connectivity in accord with the study's hypothesis.

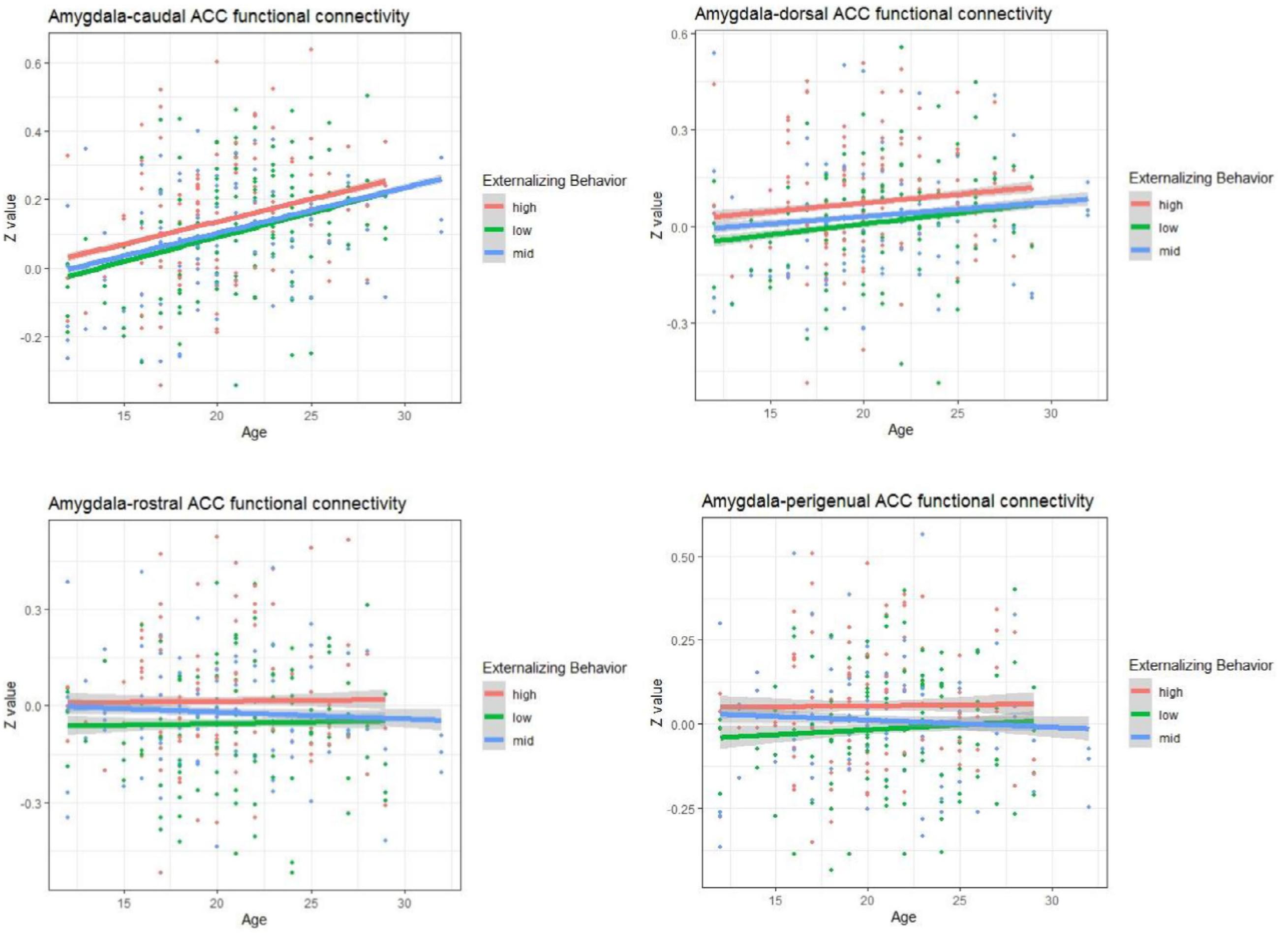
Models with age × externalizing behavior did not show evidence of better fit than models with a main effect of externalizing behavior only. Therefore, no evidence was found for differential age-related trajectories of amygdala–ACC functional connectivity depending on level of externalizing behavior. Models with sex × externalizing behavior effects also did not show evidence of better fit than models with a main effect of externalizing behavior only; however, for amygdala–dorsal ACC a significant sex × externalizing behavior effect was found, $\beta = 0.18$, $p = .014$. The increase in amygdala–dorsal ACC functional connectivity with increasing externalizing behavior was significant only for males ($\beta = 0.32$, $p < .001$, and $\beta = 0.04$, $p = .590$, for females; Figure S3).

For all ACC ROIs, the significant externalizing behavior effect could be explained by a significant positive association at rest baseline, $\beta = 0.12$, $p = .049$, $\beta = 0.18$, $p = .006$, and $\beta = 0.17$, $p = .016$, for amygdala–caudal, amygdala–dorsal, and amygdala–perigenual ACC functional connectivity, respectively. A significant effect of within-person change in externalizing behavior was found only for amygdala–perigenual ACC functional connectivity, $\beta = 0.19$, $p = .002$. For this region, higher between-subject baseline externalizing behavior predicted higher longitudinal amygdala–ACC functional connectivity, but also within-subject increases in externalizing behavior over time were related to increases in functional connectivity over time. For amygdala–caudal and amygdala–dorsal ACC functional connectivity, the change in externalizing behavior (relative to baseline externalizing behavior) was not significant, $\beta = 0.10$, $p = .07$, and $\beta = 0.06$, $p = .293$, for caudal and dorsal ACC, respectively. For these regions, only between-subject higher baseline levels of externalizing behavior were associated with increased amygdala functional connectivity.

Association between externalizing behavior and amygdala–orbitofrontal cortex functional connectivity

Results for the amygdala–OFC linear mixed effects models can be found in Table 3 and Figure 2B. Significant effects of externalizing behavior were found for the intermediate and posterior OFC, $\beta = .17$, $p = .006$, and $\beta = .13$, $p = .035$, respectively. For both outcome variables, higher levels of externalizing behavior were related to increased functional connectivity. Only the effect for amygdala–intermediate OFC functional connectivity survived correction for multiple testing. Models with age × externalizing or sex × externalizing behavior effects did not show evidence of better fit than models with a main effect of externalizing behavior only, nor were the interaction effects significant. Thus, no evidence was found for differential age-related trajectories based on externalizing behavior,

(A) Anterior cingulate cortex



(B) Orbitofrontal cortex

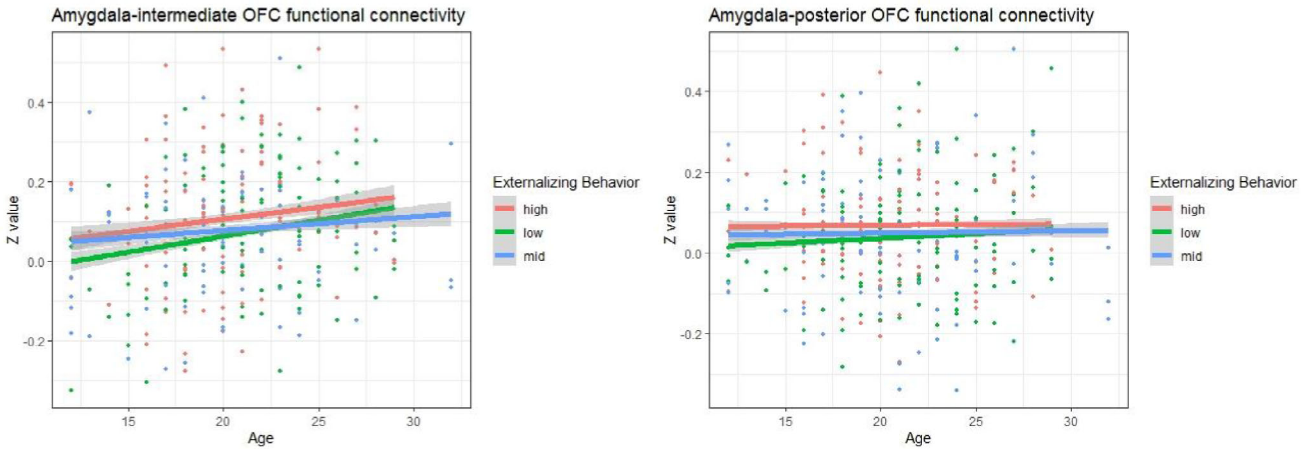


Figure 2 Longitudinal association between externalizing behavior and amygdala–ACC and amygdala–OFC functional connectivity over age. The figures display the association between amygdala–ACC/OFC functional connectivity and externalizing behavior over age. The *x*-axis shows age, whereas the different lines show different levels of externalizing behavior [Colour figure can be viewed at wileyonlinelibrary.com]

nor did the longitudinal association between externalizing behavior and OFC connectivity differ for boys and girls.

For amygdala–intermediate OFC functional connectivity, the effect of externalizing behavior was explained by both the level of externalizing behavior at rest baseline as well as the change in externalizing behavior over time, $\beta = .15$, $p = .036$, and $\beta = .13$, $p = .028$, respectively. For this region, higher between-subject baseline externalizing behavior predicted higher longitudinal amygdala functional connectivity, but also within-subject increases in externalizing behavior over time were related to increases in functional connectivity over time. For amygdala–posterior OFC functional connectivity, the effect of externalizing behavior was explained only by

Table 3 Association between externalizing behavior and amygdala–OFC functional connectivity

	Lateral			Posterior			Intermediate			Medial			Anterior		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
Intercept	0.00	3.78	<.001	0.00	2.20	.029	0.00	2.57	.011	0.00	2.37	.019	0.00	2.99	.003
Externalizing behavior	0.09	1.44	.151	0.13	2.12	.035	0.17	2.78	.006[a]	−0.06	−1.02	.310	0.07	1.13	.258
Age	0.20	3.46	<.001[a]	0.07	1.26	.210	0.26	4.40	<.001[a]	0.13	2.13	.034	0.20	3.37	.003[a]
Sex (female)	−0.06	−0.88	.380	0.03	0.50	.617	−0.07	−1.00	.319	−0.07	−1.15	.253	0.00	0.07	.942
Framewise Displacement	−0.11	−2.04	.043	−0.03	−0.51	.613	0.05	0.94	.347	−0.05	−0.82	.414	−0.03	−0.42	.679

[a] Survives correction for multiple testing.

within-subject change in externalizing behavior over time, β = .06, *p* = .363 for baseline, and β = .14, *p* = .020 for change in externalizing behavior, respectively.

Discussion

The present study examined the longitudinal association between externalizing behavior and amygdala–ACC and amygdala–OFC functional connectivity in adolescents and young adults in a healthy typically developing sample. Our results suggest limited age-related change in externalizing behavior across this time period, as well as stable or increasing frontoamygdalar functional connectivity over age. Importantly, increased levels of externalizing behavior were related to increased amygdala–ACC and amygdala–intermediate OFC functional connectivity. For amygdala–ACC functional connectivity, this association was explained mostly by between-subject differences in level of externalizing behavior at baseline, whereas for amygdala–OFC functional connectivity, the association between externalizing behavior and functional connectivity was driven by externalizing behavior at baseline as well as the with-subject temporal change in externalizing behavior relative to baseline. We did not find evidence for differential developmental trajectories of resting-state functional connectivity as a function of varying levels of externalizing behavior.

Although task-based fMRI studies generally report *decreased* functional connectivity in individuals scoring high on externalizing behaviors (Ewbank et al., 2018; Marsh et al., 2011), the few resting-state fMRI studies on the topic have reported *increased* functional connectivity in externalizing behavior in adolescence (Aghajani et al., 2017; Saxbe et al., 2018). Our results replicate and extend these resting-state fMRI findings, suggesting that at rest, higher externalizing behavior is related to increased positive functional connectivity between the amygdala and ACC as well as the OFC across adolescence and into young adulthood. Decreased frontoamygdalar functional connectivity during emotional or moral reasoning tasks in individuals scoring high on externalizing behavior is generally interpreted as decreased regulatory control over the emotionally reactive amygdala (Coccaro et al., 2007; Volman et al., 2016). At rest, higher externalizing behavior seems associated with increased attunement between the amygdala and ACC and OFC, perhaps suggesting a relatively more vigilant state for neural networks important for emotional processing and control.

In contrast with prior studies suggesting a peak in externalizing behavior in late adolescence, in our sample, no association between externalizing behavior and age was found. Despite the absence of an association between externalizing behavior and age, our results do suggest that change in externalizing behavior is associated with change in amygdala–OFC and amygdala–perigenual ACC functional connectivity. This finding may be surprising, as – especially in a developmental sample – maturational change in behavior is expected and believed to be the consequence of neural maturation. Nevertheless, the absence of a clear pattern of change over age does not mean that individuals did not vary in externalizing behavior over time. Regardless of age, externalizing behavior could change due to psychosocial factors, such as meeting a new delinquent friend (Brook, Brook, Rubenstone, Zhang & Saar, 2011), or in response to the divorce of parents (Nederhof, Belsky, Ormel & Oldehinkel, 2012) or loss of a loved one (Ionio, Camisasca, Milani, Miragoli & Di Blasio, 2018). Our results suggest that these and other age-independent changes in externalizing behavior co-occur with changes in amygdala–ACC and amygdala–OFC functional connectivity. The mechanisms that underlie these age-independent changes merit further investigation.

Significant associations between externalizing behavior and amygdala–OFC functional connectivity were found for the intermediate (and posterior) ROIs only. Compared to other OFC regions, the posterior OFC shows dense connections, as well as strong gray matter volume correlations with the amygdala (Liu et al., 2015; Zikopoulos, Höistad, John, & Barbas, 2017), and is suggested to play an important role in inhibiting amygdala activation. The intermediate OFC shows strongest gray matter volume correlations with the bilateral ACC, superior frontal gyrus and temporal pole, all regions previously implicated in social and emotional processing or inhibitory control (Hu, Ide, Zhang, & Li, 2016; Lavin et al., 2013; Olson, Plotzker, & Ezzyat, 2007). Traditionally, lateral regions of the OFC (such as the intermediate and posterior OFC) have been associated with processing negative emotions, while other findings suggest a medial–lateral dissociation in processing internal stimuli versus external stimuli (Wallis, 2012), and provide support for the involvement of lateral regions of the OFC in externalizing behavior.

Amygdala–OFC functional connectivity increased with age, which is itself an important developmental finding. Only for amygdala–caudal and amygdala–dorsal ACC functional connectivity significant increases over age were found. Whereas subgenual and perigenual ACC have been implicated in affective processes, the more posterior regions have historically been ascribed a more cognitive role (Stevens, Hurley, & Taber, 2014). Our results of developmental changes in more posterior but not anterior regions are in line with the notion that – compared to regions implicated in sensory and emotional processes – regions involved in cognition follow a more protracted developmental trajectory (Giedd et al., 1999; Gogtay et al., 2004). However, Van Duijvenvoorde et al. (2019) found no significant longitudinal associations between age and amygdala–ACC functional connectivity, and in a small cross-sectional study ($N = 58$), amygdala–ACC functional connectivity has been suggested to increase over adolescence and young adulthood for more ventral regions of the ACC only (Gabard-Durnam et al., 2014). Thus, the current literature on developmental trajectories of amygdala–ACC functional connectivity shows mixed results and warrants further examination.

Psychopathology, such as attention deficit hyperactivity disorder, has been associated with aberrant brain maturation in childhood (Shaw et al., 2007; Shaw et al., 2012). Despite evidence of increasing amygdala–OFC and amygdala–ACC functional connectivity with age as well as externalizing behavior, we did not find evidence of differential developmental trajectories of normative variation in externalizing behavior during adolescence and young adulthood in this nonclinical sample (i.e., no age-by-externalizing behavior interaction effects). These results are in line with Bos et al. (2018), who also reported longitudinal associations between externalizing behavior and structure of several brain regions but no interactions with age, and suggest that changes in externalizing behavior during adolescence and adulthood are uniformly correlated with changes in brain structure and function. Future studies examining developmental neural trajectories of externalizing behavior should include younger children and a broader range of externalizing behaviors to provide a more complete picture of the neural underpinnings of externalizing behavior and its expression over time.

To our knowledge, this is one of the first longitudinal studies on resting-state functional connectivity spanning more than 5 years. Besides providing insights on developmental changes in resting-state functional connectivity, longitudinal studies can be used to report on stability of functional connectivity measures. In our four-wave study with waves spaced 2 years apart, we report low stability (all ICC's < .50) of amygdala–ACC and amygdala–OFC functional connectivity. These ICCs are comparable to other studies in adolescents (Van Duijvenvoorde et al., 2019) and adults (for a meta-analysis, see Noble, Scheinost & Constable, 2019), which show lower stability for functional connectivity of subcortical structures compared to cortical structures and for resting-state fMRI compared to task-based fMRI. In a developmental sample, especially in an accelerated cohort design spanning several years, low stability does not necessarily mean poor consistency or low validity: Individuals are expected to mature over time, and given the age differences between participants at inclusion, some participants may show greater developmental change than others. Indeed, for several of the ACC and OFC regions, we found linear increases in amygdala functional connectivity over age.

Several limitations of the present study should be noted. The present study examined a typically developing sample with relatively few participants with externalizing behavior in the clinical range and included mostly White participants from middle to upper middle socioeconomic groups. As a consequence, results may not generalize to individuals with more frank clinical levels of externalizing behavior or individuals from different socioeconomic or racial backgrounds. Moreover, although large for this type of study, our sample size may not be optimized to detect age- or sex-by-externalizing behavior interactions over time. Finally, due to the age range of the participants, externalizing behavior was measured using two versions (adult vs. child) of the same questionnaire. We accounted for item-level differences between these questionnaires without losing important developmental differences associated with standardizing the scores (i.e., the average score for both adults and adolescents would become 0 and thus indistinguishable) by computing the percentage of maximum attainable score per version. This strategy yields expected associations among constructs. Finally, due to a shortfall in funding, relatively few participants were scanned at resting-state wave 2, which resulted in missing data at that time point.

In conclusion, our results suggest that individual differences in externalizing behavior are associated with variations in amygdala–ACC and amygdala–OFC functional connectivity during adolescence and young adulthood in a healthy sample and in the context of a longitudinal assessment. Whereas for amygdala–ACC functional connectivity the association with externalizing behavior was mostly explained by the level of externalizing behavior at baseline, the association between externalizing behavior and amygdala–OFC functional connectivity seems driven by within-subject (temporal) change in externalizing behavior over time. As a consequence, our results emphasize the differential role of networks involved in emotional processing and highlight the need to investigate changes in brain function and behavior using longitudinal data. Future studies including larger and more varied samples should shed further light on neurodevelopmental trajectories of externalizing behavior.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Resting-state fMRI acquisition and preprocessing.
Table S1. Distribution of youth versus adult questionnaire.
Table S2. Coefficients of externalizing behavior when controlling for extended scan length at T3 and T4.
Table S3. QC-FC correlations.
Table S4. Number of outliers per outcome variable.
Table S5. Model fit parameters.
Table S6. Correlations between ROIs.
Table S7. Correlations between independent variables.
Table S8. Intraclass correlations of amygdala-ACC and -OFC functional connectivity.
Figure S1. Individual trajectories of externalizing behavior (percentage of maximum attainable score).
Figure S2a. Developmental trajectories of amygdala-ACC functional connectivity.
Figure S2b. Developmental trajectories of amygdala-OFC functional connectivity.
Figure S3. Sex by externalizing interaction effect for amygdala-dorsal ACC functional connectivity.

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Key points

- Externalizing behavior has been associated with amygdala–anterior cingulate (ACC) and amygdala–orbitofrontal cortex (OFC) resting-state functional connectivity. It is currently unknown how this association develops over age.
- From age 11 to 32, externalizing behavior is consistently associated with increased amygdala–anterior cingulate (ACC) and amygdala–orbitofrontal cortex (OFC) functional connectivity.
- For amygdala–ACC connectivity, externalizing behavior at baseline primarily drove this association.
- For amygdala–OFC functional connectivity, change in externalizing behavior relative to baseline drove the longitudinal effect of externalizing behavior on amygdala–OFC functional connectivity.
- No evidence was found for differential developmental trajectories of frontoamygdalar connectivity for different levels of externalizing behavior (i.e., age-by-externalizing behavior interaction effect).

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