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Structural connectivity between rostral anterior cingulate cortex and amygdala predicts first onset of depressive disorders in adolescence

Short Title: rACC and amygdala connectivity predicts depression.

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Abstract

Objective: Adolescent-onset depressive disorders (DD) are associated with deficits in the regulation of negative affect across modalities (self-report, behavioral paradigms, and neuroimaging), which may manifest prior to first-onset DD. Whether the neurocircuitry governing emotional regulation predates DD is unclear. This study tested whether a critical pathway for emotion regulation (rostral anterior cingulate cortex (rACC)-amygdala structural connectivity) predicts first onset DD in adolescent females.

Methods: Diffusion tensor imaging (DTI) data were acquired on adolescent females (N=212) without a history of DD and the cohort was re-assessed for first onset DD over the next 27 months.

Results: 26 girls developed first onsets of DD in the 27 months after imaging. Multivariate logistic regression showed that lower weighted average fractional anisotropy of uncinate fasciculus tracts between rACC and amygdala prospectively predicted first onset of DD (adjusted odds ratio = .44, p = .005), above and beyond established risk factors including baseline depression symptom severity, history of anxiety disorders, parental history of depression, parental education, and age.

Conclusions: This study provides evidence for the first time showing that aberrant structural connectivity between rACC and amygdala prospectively predates first onset of DD in adolescent females. These results highlight the importance of a well-established neural circuit implicated in the regulation of negative affect as a likely etiological factor and a promising target for intervention and prevention of DD.

Introduction

Depressive disorders (DD) are a leading cause of disability worldwide (1), constituting a significant public health problem. First incidence of DD increases sharply after age 14, with females twice as likely to develop DD as males (2). Hence, mid-adolescent females represent an optimal demographic stratum to investigate risk factors for development of depression because this may be the stratum in which to target prevention and treatment efforts to pre-empt life-long sequelae of depression (1, 3). An examination of neurobiological mechanisms of DD can provide clues for development of psychopharmacological and psychological interventions (4).

There is converging evidence from affective neuroscience and psychopathology research that depression is linked to disturbance in neural circuits subserving the processing and regulation of negative affect (5, 6). Emotion regulation refers to processes by which we implicitly or explicitly control the type of emotions, their onset, intensity, duration as well as how we experience and express them (7). Depression is characterized by an increase in self-reported negative mood, reduced reactivity to negatively (and positively) valenced stimuli in lab contexts, and instability of negative affective states in daily life (8). Indeed, depression involves increased rumination and avoidance, decreased reappraisal and acceptance (9, 10), as well as ineffective cognitive control strategies when regulating negative affect (11). Adolescence is also characterized by less differentiation of negative emotions (12), more frequent and intense emotions (13, 14), and decreased self-reported regulation of negative emotions (15). These deficits in emotion regulation are a major risk factor for developing depression in adolescents (16). To understand exactly how processing and regulation of negative affect are associated with the development of depression in adolescence, it is important to examine the neural mechanisms that support these functions.

Emotion processing and regulation occurs via a complex network of prefrontal and limbic regions, with the ventral and rostral aspects of anterior cingulate cortex (rACC) playing a key role due to their anatomical connectivity with limbic regions, specifically the amygdala (17-19). In fact, it is well-documented in tracer and cytoarchitectural studies that among prefrontal cortical regions rACC has

extensive and direct anatomical connections with the amygdala (20-22). Furthermore structural integrity of the uncinate fasciculus (UF), a major tract connecting the ventral medial parts of the prefrontal cortex, including the rACC, with the amygdala is associated with processing of emotional expressions (23) and is often reduced in adults and adolescents with depression compared to healthy controls (24-26). Overall, these findings raise the question whether rACC-amygdala structural connectivity deficits play a role in the etiopathogenesis of DD, or are simply correlates or consequences of depression, long term exposure to antidepressants, and/or clinical risk factors (e.g., family history, and prior anxiety disorder). To our knowledge, no study so far has investigated whether rACC-amygdala structural connectivity can prospectively predict first onset of DD, thus allowing us to understand whether it serves as a vulnerability or consequence of depression.

In the present study, we used Diffusion Tensor Imaging (DTI) to measure the structural connectivity between rACC and amygdala in a community sample of adolescent girls without a history of DD who were followed prospectively for 27 months. We hypothesized that lower weighted average Fractional Anisotropy (FA) between rACC and the amygdala would predict subsequent first onset of DD, even after controlling for known risk factors including parental history of depression, adolescents' history of anxiety disorders, and baseline depression symptom severity. This study provides a critical test of the role of structural connectivity between two major regions involved in emotion regulation in the development of adolescent depression, furnishing new knowledge to update and refine current models of depression risk. Furthermore, knowledge of connectivity-related risk factors holds promise for the development of emotion regulation-focused preventive strategies as well as pharmacological targets for this age group.

Methods

Participants

The current study used a subset of participants in the Adolescent Development of Emotions and Personality Traits (ADEPT) project. In ADEPT, 550 female participants aged 13.5-15.5 in Suffolk

52 County, NY completed five assessment waves administered at nine-month intervals, over 3 years.
53 Approval from the Institutional Review Board at Stony Brook University was obtained, and participants'
54 legal guardians provided written informed consent. Participants were recruited through commercial
55 mailing lists, fliers, referral from schools, and online classified advertisements.

56 At the first wave, exclusion criteria were lifetime history of dysthymia, major depressive episode,
57 or intellectual disability. Eligibility for the protocol was determined by a structured diagnostic interview,
58 the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-
59 PL) for School-Age Children, Present and Lifetime Version (27). At the second wave, all participants
60 were invited for the neuroimaging component: 261 met criteria and agreed to participate for DTI.
61 Participants were removed for further data analyses if they had developed DD by the time of MRI or did
62 not complete further follow-up assessment waves (N = 11). Participants' data were further removed from
63 analyses if the imaging data failed cortical and sub-cortical segmentation or artifacts in the T1 weighted
64 structural images (N = 28), or due to low quality of their DTI-derived measures (N = 3). The final DTI
65 sample size was 212 participants. Five participants had a history of antidepressants at the first wave of
66 assessment, with one of them developing clinical depression in the follow up assessments. Data from
67 these MRI participants have been previously published (28-30). Most participants were Non-Hispanic
68 White (*N*=209, 80.0%) and had a parent with bachelor's degree or higher (*N*=164, 63.0%).

69

70 *Clinical measures*

71 Adolescents' lifetime history of anxiety disorders and DDs (Major Depressive Disorder and
72 Dysthymic Disorder) was assessed using the K-SADS-PL (27) at the initial assessment. Also, history of
73 DDs in the participating biological parent was assessed using the Structured Clinical Interview for DSM-
74 IV (SCID-IV) (31). Adolescents' depression symptom severity during the two weeks prior to the imaging
75 session was assessed using the general depression scale of the Inventory of Depression and Anxiety

Symptoms (IDAS-II) (32). DD first-onsets were assessed using the K-SADS-PL at the time of the neuroimaging session as well as in three follow-up waves at 9, 18, and 27 months after the neuroimaging session. Participants were assigned to the DD group if they met criteria for DD on K-SADS-PL at any of the waves following but not including the neuroimaging assessment. Given that the pubertal development stage may deviate from the chronological age, in a separate set of analyses, we controlled for pubertal development instead of age (**Supplementary materials**). The PDS is a self-report measure including five items assessing different aspects of maturity: height, body hair, skin changes, breast development, and menarche. The first four items are assessed on a four-point Likert scale ranging from 1 (not yet started) to 4 (seems complete), and the last one was assessed dichotomously (yes or no). The PDS score was computed as the sum of the item responses and standardized before entering the logistic regression analysis.

Image acquisition

Participants received an MRI on a Siemens TrioTim with a 12-channel SENSE head coil at Stony Brook University. Diffusion scans used a single-shot echo planar imaging (EPI) sequence with the following parameters: TR = 8300 ms, TE = 95 ms, Flip Angle 90 degrees, orientation = transversal, 3D FOV = 240 x 240 x 250 mm^3, voxel dimensions 2.5 mm^3, acquisition matrix = 96 x 96, b value = 1000 s/mm^2, and 64 collinear directions with 2 non-weighted images. DTI scan time was approximately 9.5 minutes. T1-weighted MPRAGE anatomical images were acquired in the same session with the following parameters: TR = 1900 ms, TE = 2.53 ms, Flip Angle = 9 degrees, FOV = 250 mm^2, voxel dimensions = 1mm^3 isotropic, IPAT factor 2, slice oversampling = 18.2%, and bandwidth = 170 Hz/Px. Anatomical scan time was approximately 4.5 minutes.

Image preprocessing

DTI images were processed through a pipeline of quality assurance tests for common artifacts, including ghost, ring, slice-wise intensity, venetian blind, and gradient-wise motion artifacts (33). An eddy current correction routine within FSL (Functional MRI of the Brain Software Library, http://www.fmrib.ox.ac.uk/fsl/) was used to correct distortion produced by gradient coils and head motion in the images. Non-brain tissue was isolated and removed from images using FSL's Brain Extraction Tool (BET). Fractional anisotropy (FA) was estimated using Camino (http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php), which computes the least-squares-fit diffusion tensor using non-linear optimization with a Levenburg-Marquardt algorithm constrained to be positive by fitting its Cholesky decomposition (34, 35).

Region of Interest (ROI) Definition

To define amygdala and rACC ROIs for the DTI analysis, non-uniformity in intensities in each participant's T1 anatomical images were corrected and non-brain regions were cropped using the Atropos and the Bias Field Corrector in Advanced Normalization Tools (ANTS; http://www.picsl.upenn.edu/ANTS/). T1 anatomical images were processed using the cortical reconstruction pipeline from Freesurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). Freesurfer surface models were inspected by trained technicians following a systematic quality control process shown to improve reliability of Freesurfer-derived outputs (36). The Freesurfer cortical and subcortical parcellation tools (37) were used to define the rACC and the amygdala in native space.

Tractography analysis

Probability tractography was generated using FMRIB's Diffusion Toolbox (FDT) (38). This algorithm calculates probabilistic streamlines by repeatedly sampling the principal diffusion direction in each voxel. This method generates the probability of connections from the seed to the target. The

algorithm was run using a curvature threshold set to .2 mm, the maximum number of steps per sample to 2000, length of each step to .5 mm and 5000 samples. Within the defined tracts, the sum of the voxel-based FA multiplied by the number of tracts at each voxel and then divided by the sum of the total number tracts to yield the weighted average of FA within the defined tracts. The bilateral seeds and targets of rACC and amygdala were chosen *a priori* based on the literature (outlined above). Tractography was visually inspected for quality control purposes (see **Supplementary materials**). A sample subject's tractography was shown in **Figure 1**.

Statistical analyses

Statistical analyses of DTI-derived variables were conducted using R (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) and SPSS (Version 22.0, IBM Corp., Armonk, NY). First, we conducted a t-test comparing weighted average of rACC-amygdala FA for groups which did and did not develop first onset of DD. Next, our main analysis was a multivariate logistic regression conducted to examine whether the weighted average of rACC-amygdala FA predicted onset of DD over 27 months following DTI, over and above several covariates and established risk factors. These psychosocial risk factors included age at DTI, parental education (coded as 0 = no, 1= one, and 2 = both parents attended college), parental history of DD, lifetime history of anxiety disorders, and level of depression symptoms at DTI (39, 40). Given that the pubertal development stage may deviate from the chronological age, in a separate set of analyses, we controlled for pubertal development instead of age (results reported in **Supplementary materials**). All predictors were standardized (converted to z-scores) before entering the regression analyses. Receiver operating characteristic curve (ROC) analyses were applied to evaluate the area under the curve (AUC). To test the robustness, we conducted the same logistic regression analysis using radial diffusivity (RD) and mean diffusivity (MD) in replacement of FA, respectively (results reported in **Supplementary materials**).

Results

At the time of neuroimaging session, the average age of participants was 15.29 (SD = .64) years and average depression severity measured using IDAS was 31.34 (SD = 10.60). Over the 27-month follow-up, 26 out of 212 adolescents (12.3%) who underwent DTI, developed a first onset of DD, including 15 with MDD, 4 with dysthymic disorder and 7 with both. At the time of neuroimaging, participants who were later diagnosed with DD had higher depression severity (Cohen's d = .66, t = 3.27, p = .001), but were not different in lifetime history of anxiety disorders ($\chi^2(1)$ = .13, p = .722) and parental history of depressive disorders ($\chi^2(1)$ = .26, p = .608) compared to participants who remained non-depressed (**Table 1**).

DTI and Depression

Adolescents who subsequently developed a first onset DD showed lower rACC-amygdala FA (averaged across the two hemispheres, Cohen's d = .66, t = 3.02, p = .005)(**Table 1**), an effect that was consistent for both hemispheres separately (Left: Cohen's d = .45, t = 1.97, p = .050. Right: Cohen's d = .75, t = 2.50, p = .013). Next, we conducted a multivariate logistic regression analysis to test whether rACC-amygdala FA prospectively predicted DD onset, above and beyond the effects of other risk factors. The model included age at DTI, parental education, lifetime history of anxiety disorders, parental history of depression, baseline depression severity, and rACC-amygdala FA values (averaged across two hemispheres). The correlations between the rACC-amgydala FA variable and the covariate risk factors are shown in **Table 2**. Baseline depression severity and rACC-amygdala FA independently predicted first onset DD over 27 months (**Table 3**). The scatter plots with LOESS fitting for baseline depression severity and rACC-amygdala FA predicting first onset DD are shown in **Figure 2**. Using the rACC-amygdala FA from each hemisphere separately in a single multivariate logistic regression yielded similar effects, with

both being significant (odds ratio = .65 and .54, with p = .049 and p = .011 for left and right rACC-amygdala FA, respectively). A follow-up ROC analysis showed that using baseline depression severity and rACC-amygdala FA to predict onsets of DD yielded an AUC of .75 (**Figure 3**).

All results remained significant when replacing the age at DTI with pubertal development stage (**Supplementary Table 1**). The predictive of FA above and beyond the risk factors remained significant even after excluding participants who had relatively high baseline depression (IDAS depression > 3) (Wald = 6.13, p = .013), or after excluding the participants who had a history of antidepressants at the initial wave of assessments (Wald = 7.67, p = .006). Furthermore, the prediction finding replicated when using radial diffusivity (RD) and mean diffusivity (MD) instead of FA (**Supplementary Table 2 and 3**). Overall, rACC-amygdala FA independently predicted first onset DD over 27 months, with similar results evident across both hemispheres.

Discussion

In the current study, we found that reduced white matter integrity, measured as the average weighted FA in the tracts between the rACC and the amygdala prospectively predicted first onset of DD in a sample of community-dwelling adolescent females without a prior history of depression. This effect was independent of well-established clinical risk factors, including baseline depression severity, past history of anxiety disorders, and parental history of depression. In addition, the finding that the connectivity measured using FA, MD, and RD were all significant in predicting future depression onset suggest that multiple aspects of the white matter integrity may be compromised in adolescent depression (41). Given that the rACC-amygdala is a critical circuit for emotion regulation, the current findings highlight rACC-amygdala connectivity as a potential neurobiological mechanism in the impaired emotion regulation that contributes to the development of DD in adolescence.

Structurally, there are direct projections from the rostral-ventral ACC portions, including subgenual ACC, to the amygdala (42). Functionally, these rACC projections may play a role in inhibiting amygdala activity as evidenced by studies showing that lesions in areas corresponding to rostral-ventral ACC in animals result in reduced inhibition of amygdala (43), while stimulation of rodent medial prefrontal cortex, including regions corresponding to the human rACC, has been shown to dampen amygdala output (44). In line with the animal literature, studies show that increased rACC activity is associated with reduced amygdala activity during emotion regulation in humans (19). Given that the central amygdala has widespread connectivity with the hypothalamus, bed nucleus of stria terminalis, and brain stem regions (45), impaired inhibition of the amygdala may lead to the dysregulated emotional and vegetative functions seen in depression. Interestingly, late childhood and adolescence is the period when positive functional connectivity switches to inverse functional connectivity between rACC/vmPFC and amygdala while processing emotional stimuli (46), suggesting that it may play a key role in the increased incidence of depression in this time period.

Our findings are in line with a previous study with the same cohort which used a well-established data-driven approach derived from connectome analyses (47-52) to show that resting state functional connectivity in a network consisting of amygdala, striatum and prefrontal cortex predicted future depression symptoms, with ACC and ventromedial prefrontal cortex connectivity contributing most to the variance in depression symptoms (29). In the current study we took an ROI-based approach to hone in on the structural connectivity of rACC and amygdala, two regions that are critical for emotion regulation, to show that connectivity alterations are a risk factor rather than result of DDs. The important difference between the previous resting state functional connectivity study and the current one is that while the resting state study supported that ACC/vmPFC based connectivity is associated with depression symptom severity, it did not point to the specific connectivity between amygdala and ACC/vmPFC as a particular risk factor for future onset of depressive disorders. Furthermore, another task-based functional MRI study in the same cohort has shown that reduced orbital frontal cortical activity in response to monetary loss is

220 related to the depression severity (28). However, due to a focus on reward/loss processing this study
221 exclusively examined orbitofrontal and striatal regions. Keeping in mind that loss evokes negative
222 emotions, our present results warrant further investigation of how regulation of loss may recruit the
223 rACC-amygdala circuitry and its worse recruitment may relate to future depression symptoms. Overall,
224 evidence from the series functional and structural studies in the present cohort point to the importance of
225 amygdala and the rostral and ventral PFC and ACC circuit as playing a key role in adolescent depression.
226 It is noteworthy that the predictive power of the rACC-amygdala connectivity in the present study is for
227 actual DD onset and that it is independent from that of baseline depression symptom severity as well as
228 other clinical risk factors such as parental history of depression and past history of anxiety.

229 While this study benefits from inclusion of community-dwelling adolescent girls with initially no
230 prior history of DD, it also has several limitations. First, the number of participants who developed DD
231 was relatively small, limiting the precision of effect size estimation. Also, our sample had a narrow age
232 range, and excluded males, indicating the need for future research examining whether these findings
233 generalize to other demographic populations. Besides the reason that adolescent females represent the
234 demographic stratum with the highest risk, the present study focuses on females to avoid confounding due
235 to sex differences, given that epidemiology and etiology research has suggested that female and male
236 depression may involve different mechanisms (53, 54). Future research is needed to examine whether the
237 structural connectivity between amygdala and rACC is a common risk factor for both females and males
238 or a unique risk factor for females only. Finally, while our sample is representative of the community
239 where the data were acquired, the sample was primarily Caucasian and was from families with a
240 relatively high mean education level. Future research is needed to examine the generalizability of the
241 current finding to more diverse demographic populations.

242 Adolescence is a period characterized by deficits in processing and regulation of negative affect
243 (55), changes in the structural connectivity of the rACC with the amygdala (56), and an increasing
244 incidence of depression (2). Here we demonstrated that reduced rACC-amygdala white matter integrity

245 precedes the first onset of depression, providing critical evidence for weaker rACC-amygdala coupling as
246 a risk factor for first onset of depression. Furthermore, these findings provide biological support for the
247 theory that emotion dysregulation is a risk factor for the development of depression (57), especially in
248 adolescence (55). Overall, these findings suggest the value of preventive programs and interventions that
249 target emotion processing and regulation.

Tables and Figures

Table 1. Baseline characteristics of adolescents who experienced first onset depression compared to those who did not over 27 months following DTI

	No lifetime DD through 27 months (N = 186)		**First onset of DD in the next 27 months (N = 26)**			
	Mean	**SD**	**mean**	**SD**	**Effect size (Cohen's d)**	**p**
Age at DTI	15.29	.64	15.29	.69	.00	.980
Parental education	1.59	.63	1.58	.50	.02	.899
Baseline depression severity	30.47	10.24	37.57	11.26	.66	.001
Bilateral mean of rACC-amygdala FA	.37	.03	.35	.03	.67	.005
	N	**%**	**N**	**%**	**Odds ratio**	**p**
Lifetime anxiety disorder	49	26.3	6	23.1	.84	.722
Parental history of depressive disorder	67	37.1	11	42.3	1.24	.608

Table 2. Bivariate correlations between the rACC-amygdala connectivity and other risk factors

	Age at DTI	Parental Education	Lifetime history of anxiety disorders	Parental history of depressive disorders	Baseline depression severity
rACC-amygdala FA (bilateral mean)					
Pearson's r	-.02	-.03	.02	.09	-.04
p value	.745	.64	.788	.205	.59

Table 3. Multivariate Logistic Regression Predicting First Onset Depression Dx over 27 Months of Follow-Up with all risk factors simultaneously

	Wald	p	Adjusted odds ratio	95% CI
(Intercept)	72.85	< .001	.10	
Age at DTI	.25	.617	.89	[.56, 1.41]
Parental Education	.27	.603	.88	[.55, 1.41]
Lifetime history of anxiety disorders	.19	.661	.90	[.57, 1.43]
Parental history of depressive disorders	.05	.817	1.05	[.67, 1.65]
Baseline depression severity	8.65	.003	1.84	[1.23, 2.76]
rACC-amygdala FA (bilateral mean)	7.98	.005	.44	[.25, .78]

Note: values from all variables were standardized prior to analyses to improve interpretability.

Figure 1.

rACC-Amygdala Tractography From A Sample Subject. Probabilistic tracts (green) generated between the rACC (seed in yellow) and amygdala (target in purple).

Figure 2.

Scatter Plots of Baseline Depression severity and Bilateral Mean of rACC-Amygdala FA Predicting First Onset Depression Over the Next 27 Months. The association between a predictor and outcome was depicted by LOESS (local regression) curve in blue with 95% confidence interval around it in grey.

Figure 3

ROC analyses results. To show the combined predictive power of rACC-amygdala FA and the baseline depression severity, area under curve (AUC) were computed.

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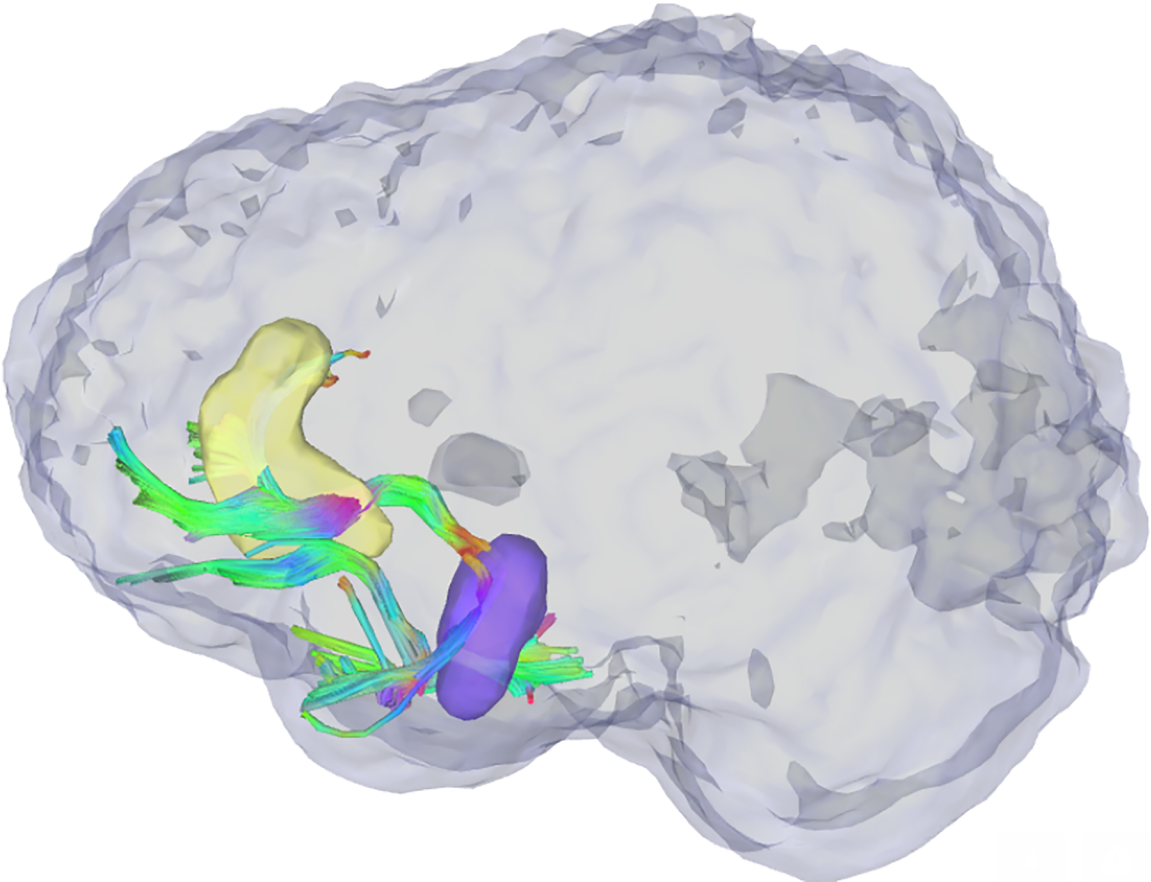
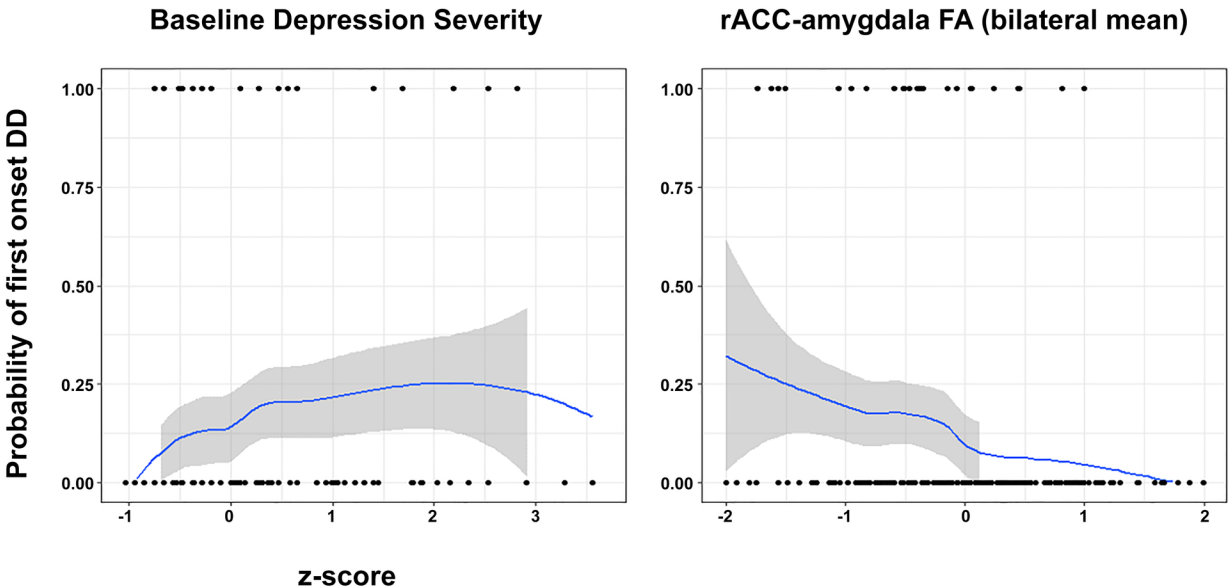
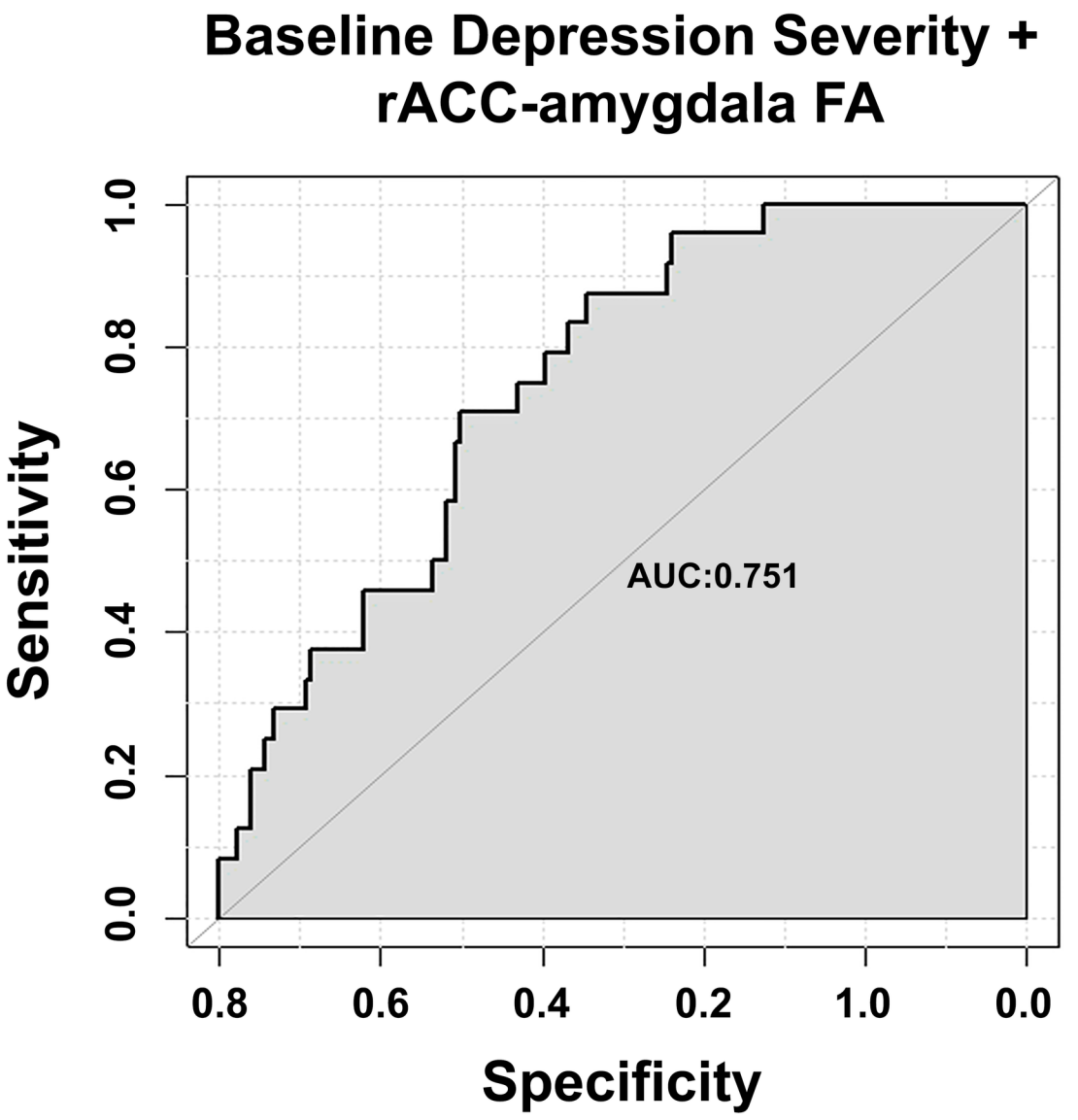



Baseline Depression Severity
rACC-amygdala FA (bilateral mean)
Probability of first onset DD
1.00
0.75
0.50
0.25
0.00
-1
0
1
2
3
-2
z-score


Baseline Depression Severity +
rACC-amygdala FA
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
AUC:0.751
0.8
0.6
0.4
0.2
1.0
0.0
Specificity