Title: Anxiety may alter the role of fronto-striatal circuitry in adolescent risky decision-making

Running Title: Neural bases of anxiety and risk-taking in adolescents

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Abstract: (234/250 words)

Background: Anxiety disorders often emerge in adolescence and are associated with risk aversion. Risk aversion is at odds with the typical adolescent propensity for heightened sensation-seeking and can interfere with learning and contribute to further anxiety development.

Methods: We investigated the neural and behavioral correlates of risk avoidance in 137 diverse early adolescents ($M_{\text{Age}}=11.3$, $SD_{\text{Age}}=1.41$; 61 girls) during a decision-making task involving risk-taking and cognitive control during fMRI. Voluntary cautious choice was compared to successful response inhibition to isolate the neural systems underlying risk avoidance and identify their relation to risk-taking and anxiety in adolescents. **Results:** Risk-taking frequency was not related to anxiety severity; however, higher anxious youth spent relatively longer making voluntary cautious choices than inhibiting when instructed. All youth showed widespread neural activation in decision-making and salience network regions when making cautious choices. Greater recruitment of the left inferior frontal gyrus during cautious choice was associated with greater risk-taking in high anxious youth and greater risk avoidance in low anxious youth, while greater striatal connectivity during cautious choice was associated with heightened risk-taking in those with low anxiety and risk avoidance in those with high anxiety.

Conclusions: Relative to non-anxious adolescents, anxious adolescents take longer to make decisions in the face of approach-avoidance conflict and demonstrate unique brain-behavior associations during decision-making. Together, results from this study identify a unique role of fronto-striatal circuitry in risky decision-making among adolescents who struggle with anxiety.

Body text (3997/4000 words)

Introduction

Anxiety disorders commonly emerge during adolescence (1,2) and demonstrate considerable heterogeneity in presentation and symptom course (3–8). A cardinal symptom of anxiety is behavioral avoidance which contributes to much of the interference of these disorders. Avoidance conflicts with the normative adolescent propensity for heightened approach behavior (9) and is linked to risk aversion in anxiety (10). Nonetheless, relations between risk aversion, risky decision-making, and the behavioral decision to avoid are poorly understood (11). This gap is important for understanding the mechanisms underlying one of the most defining features of anxiety disorders for both youth and adults. Here, we examined the neural correlates of inhibitory behaviors in 137 adolescents to elucidate the mechanisms driving avoidance and their implications for adolescent-onset anxiety.

Avoidance can be adaptive in situations with clear threats (12), such as braking at a red light to avoid a crash (e.g., response inhibition). Conversely, avoidance can prove maladaptive in situations with uncertain outcomes, such as choosing to stop or go at a yellow light (e.g., risky decision-making). Risk-taking, or the ability to make decisions in the face of uncertainty, is important for learning and exploration in adolescence (13). However, the uncertainty of risk can spur approach-avoidance conflict where the ability to engage in goal-directed behavior becomes difficult for anxious youth (14), contributing to impaired functioning (15–18) and risk aversion in anxious adults (19). Interestingly, it is precisely the uncertainty of risk that appeals to typical adolescents (20), which may explain why studies have found both decreased (21,22) and increased (23–25) risk-taking among anxious youth.

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4 Approach-avoidance conflict has been explained neurobiologically by the Triadic model
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6 in which approach (ventral striatum; VS), avoidance (amygdala), and regulatory (prefrontal)
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8 neural systems interact and compete to influence response to positive and aversive cues (26).
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10 When appetitive and aversive stimuli are pitted against each other in adolescence, this model
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12 posits that regulatory systems will bias behavior towards approach (26). While the striatum
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14 functions to promote approach behavior in neurotypical adolescents, anxious youth may exhibit a
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16 different phenotype. Increased striatal response and reduced fronto-striatal connectivity during
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18 peer feedback has been linked to impaired recall of positive feedback in adolescents with social
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20 anxiety (27), suggesting that fronto-striatal mechanisms may bias learning in anxiety. This bias
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22 may then contribute to avoidance, as research has identified a fronto-striatal circuit that controls
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24 anxious avoidance behaviors in mice (28) and striatal response during avoidance correlates with
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26 anxiety in adult humans (29). Despite work implicating the VS (30–33), amygdala (34–36), and
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28 prefrontal cortex (PFC) (36–38) in risk for anxiety, the role of anxiety on neural functioning
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30 during approach-avoidance conflict in adolescents is still poorly understood (11,39).
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38 Here, we measured anxiety, risk-taking, and response inhibition in 137 adolescents (9-
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40 13y/o) as they played the Driving Game, a decision-making task, during functional magnetic
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42 resonance imaging (fMRI). Participants were instructed to “go” at green lights, “stop” at red
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44 lights, and choose whether to stop or go at yellow lights, thereby measuring response inhibition
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46 (stopping a prepotent response when the light turns red) and risky decision-making in the same
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48 design. Participants ranged across a spectrum of normative anxiety levels with over-sampling
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50 from those at the cusp of clinical diagnosis who are most at risk for developing anxiety in
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52 adolescence. Given work linking anxiety to risk avoidance (19,40–42), we hypothesized that
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54 anxiety would correlate negatively with risk-taking. Given work reporting no differences in
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response inhibition ability in anxiety (43), we predicted anxiety would not affect false alarm rate. As anxiety can sharpen inhibitory ability (12,44), we hypothesized that higher anxious youth would demonstrate faster response time (RT) during response inhibition. As approach-avoidance conflict can interfere with decision-making in anxiety (14), we predicted that faster RT during response inhibition would be paralleled by longer RT during cautious choice. Given the role of approach-avoidance conflict and the VS in risk-taking and anxiety, we predicted that greater activity in areas linked to approach-avoidance conflict (e.g., inferior frontal gyrus; IFG) (45) and fronto-striatal connectivity during risk avoidance would explain the behavioral differences between high and low anxious youth.

Methods and Materials

Participants

171 youth were recruited from the Los Angeles area to complete a clinical interview and an fMRI scan. Participants were recruited to capture the full spectrum of anxiety symptom severity as measured by the Screen for Child Anxiety and Related Emotional Disorders (SCARED) (46). They were eligible if they were ages 9-13, right-handed, free of metal, had no medical or psychiatric conditions contraindicating study participation (e.g., suicidality, head trauma), did not currently use psychotropic medication, and were not claustrophobic. Informed consent and assent were obtained from all legal guardians and study participants in accordance with the Institutional Review Board. Youth were compensated \$100 and could win an additional \$10 during the fMRI tasks. Participants completed the Anxiety and Related Disorders Interview Schedule-IV (ADIS-IV) (47) with a clinician trained to criterion.

Of the 171 enrolled youth, 25 did not complete the scan: 13 visits were canceled due to the COVID-19 pandemic and 12 youth were uncomfortable with the MR environment. Data

from 7 participants were unusable due to too few trials, and data from 2 participants were unusable due to technical errors during data collection. Data were excluded if the participant exceeded 1 mm mean relative motion during the task (1 run for 1 participant; no youth excluded). Data are presented for 137 participants ($M_{\text{Age}}=11.3$, $SD_{\text{Age}}=1.41$; 61 girls; 35% white, 22.2% Latino, 20.4% Asian, 13.9% Black, 9.5% Mixed Race).

Anxiety severity

Participants completed the 41-item self-report SCARED (46) as a dimensional measure of anxiety severity. They rated statements describing anxiety symptoms (e.g., “I feel nervous around people I don’t know very well”) on a 3-point Likert scale ranging from 0 (*Not True or Hardly Ever True*) to 2 (*Very True or Often True*) based on how often the symptoms were true for them.

fMRI task

Participants played two 8-minute runs of the Driving Game, an adapted version of the Stoplight Task (48) involving making decisions at randomly presented traffic lights and trying to reach the finish line quickly to maximize monetary reward (\$5; Figure 1). Each trial (35-40 trials per run) begins with 2-4 green lights and ends with either a yellow light or a red light. Each light is presented for 1 s or until the participant responds and is followed by a jittered inter-trial interval (ITI; .5-5 s). Participants were instructed to press “1” to go at green lights and “2” to stop when the light turns red. Failure to stop resulted in a crash, adding 6 s to their route. At yellow lights, participants were given a choice to press “1” to go (risky choice) or “2” to stop (cautious choice). Stopping led to the light turning red, adding 3 s. Going led to a 50/50 chance of a safe crossing, resulting in a reward, or a crash, adding 6 s. In total, participants encountered

~35-40 yellow lights, ~35-40 red lights, and 200+ green lights. RT was measured as the duration in milliseconds from stimulus onset to participant response.

Figure 1. The Driving Game. Participants encountered green, red, and yellow stoplights in the laboratory task and were instructed to press “1” to go for green lights, “2” to stop for red lights, and either “1” to go (risky choice) or “2” to stop (cautious choice) for yellow lights. A jittered inter-trial (ITI) stimulus followed each event. All trials began with 2-4 green lights and ended with either a red or yellow light (50/50 chance). A false alarm at a red light was followed by a crash. A risky choice at a yellow light was followed by either a reward (50% chance), getting to the finish line faster and earning more money, or a crash (50% chance), adding a 6 s delay.

fMRI acquisition

A 20-channel head coil was used for scanning on a 3-Tesla Siemens Trio MRI machine.

Participants completed a mock scan to acclimate them to the scanner and were screened with a

metal detector before entering the scanner. The task was presented on E-Prime, which collects responses and RTs. A Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) scan (TR=1900ms, TE=2.26ms, FOV=250 mm, 176 slices, slice thickness 1 mm, in-plane voxel size 1.0x1.0 mm, interleaved) was used for registration. For B0 distortion correction, participants received 2 T2*-weighted gradient-echo field map scans with opposite phase encoding directions (AP, PA; TR=8000 ms, TE=66 ms, FOV=208 mm, 72 slices, slice thickness 2 mm, in-plane voxel size 2x2 mm, interleaved). Two runs of the T2*-weighted task fMRI sequence (TR=800 ms, TE=37 ms, FOV=208 mm, 72 slices, slice thickness 2 mm, in-plane voxel size 2x2 mm, interleaved) were acquired while participants played the task. A single-band reference (SBRef) image was acquired immediately before each run.

fMRI preprocessing

FEAT V6 within FSL (FMRIB Software Library; <https://fsl.fmrib.ox.ac.uk/fsl/>) (49) was used for preprocessing. Steps included non-brain removal using FSL BET, high-pass filtering (100 s), and spatial smoothing using a Gaussian kernel of FWHM 5 mm. Rigid body motion correction with 6° of freedom was performed using MCFLIRT. AP and PA field map images were combined using FSL's topup (50) and multiplied by 2π to convert to rad/s. A magnitude image was created by taking the mean of the unwarped field map and brain-extracted using BET. Rad/s and magnitude images were used for B0 unwarping in FEAT. Each participant's functional data was registered to their SBRef, then to the MPRAGE, and finally to Montreal Neurological Institute (MNI) stereotaxic space with 12° of freedom using FSL's nonlinear registration method FNIRT. One run for one participant exceeded 1 mm mean relative motion as determined using FSL motion parameters and was excluded. FSLMotionOutliers (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers>) detected timepoints corrupted by a

high degree of motion using the box-plot cutoff = $P75 + 1.5 * IQR$. The resulting confound matrices were entered as regressors of no interest in the general linear model (GLM), removing the effects of these timepoints.

Behavioral analysis

A multivariate analysis of variance (MANOVA) in SPSS was used to compare average task behavior with anxiety, sex, and age as covariates. RTs for each condition were compared using paired samples *t*-tests. Cautious RT and Inhibition RT were compared to anxiety to assess the impact of anxiety on RT across inhibitory contexts.

Before use in neuroimaging analyses, participant responses at all lights were entered into a Principal Components Analysis (PCA) in SPSS to reduce dimensionality and determine overall behavioral metrics for each participant. Responses were correlated, the Kaiser-Meyer-Olkin measure of sampling adequacy was above .5, and Bartlett's test of sphericity was significant ($\chi^2(15)=972.39, p<.001$). Variance maximizing rotation was used and components with eigenvalues >1 were extracted.

fMRI analysis

Whole-brain activation

A GLM was defined in FEAT with 11 regressors: Go ("1" at a green light), Inhibition ("2" at a red light), False Alarm ("1" at a red light), Red Crash (crash following false alarm), Risky ("1" at a yellow light), Cautious ("2" at a yellow light), Anticipation (period between risky choice and feedback), Yellow Crash (crash following risky choice), Reward (reward following risky choice), Finish (3 s finish line at end of run), and Junk (any trials of no interest or trials without responses). Events were modeled with a canonical double-gamma hemodynamic response function (HRF) for a variable duration dependent on participant behavior. Rest periods

and ITIs were not explicitly modeled and therefore served as the implicit baseline of interest. Temporal derivatives for all regressors, standard and extended motion parameters (6 standard motion parameters, their temporal derivatives, and squares of the above), and motion outliers were included as covariates of no interest. Individual-level models were defined with 3 contrasts: Inhibition vs. Baseline, Cautious vs. Baseline, and Cautious vs. Inhibition, chosen with the aim of identifying the neural correlates of inhibitory behaviors across conditions. First-level analyses were conducted using fixed-effects modeling with FLAME-1. Both runs were combined using a fixed effect voxel-wise second-level model in FEAT.

Group-level activation analyses were performed using FMRIB Local Analysis of Mixed Effects (51). Anxiety, risk-taking, response inhibition, and the interaction between anxiety and risk-taking were included in the design matrix as covariates of interest. Age and sex were included as covariates of no interest. Thresholded Z-statistic images were generated to visualize clusters determined by a corrected, cluster-forming threshold of $Z > 3.1$ and an extent threshold of $p < 0.05$ family-wise error (FWE) corrected using the Theory of Gaussian Random Fields (52). Statistical maps were projected onto a standard MNI brain; group activation maps were visualized using MRICron software (<http://www.sph.sc.edu/comd/rorden/mricron/>).

Striatal connectivity

Beta series correlation analyses (53) were conducted in FSL to examine differences in VS functional connectivity across task conditions. For each run, one GLM was defined for Cautious trials and another for Inhibition trials. Trials of interest were separated into their own regressor (resulting in n regressors for n trials). Trials of no interest were represented by one regressor per trial type to preserve the original task design. Parameter estimates for each trial were combined within conditions, registered to standard space, and extracted from a bilateral VS seed (Harvard-

Oxford subcortical probabilistic atlas, 50% probability). The resulting timeseries was correlated with every other voxel in the brain and Fisher transformed using 3dTcorrelate in AFNI (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dTcorrelate.html). Z-transformed correlation maps for Inhibition were subtracted from Z-transformed correlation maps for Cautious and combined across participants for group analysis.

Group-level analysis was performed using FSL's randomise (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide>) with Threshold-Free Cluster Enhancement and 5,000 permutations. Anxiety, risk-taking, response inhibition, and the interaction between anxiety and risk-taking were included in the design matrix as covariates of interest. Age and sex were included as covariates of no interest. Thresholded Z-statistic images were generated to visualize clusters ($Z > 3.1$, $p < .05$). Statistical maps were projected onto a standard MNI brain and visualized using MRICron software.

Results

Behavioral results

Anxiety

SCARED scores ranged from 0-52 ($M_{\text{Anx}}=19.27$, $SD_{\text{Anx}}=11.48$; Figure 2), with higher scores indicating greater anxiety severity. In community samples, a score ≥ 25 has been found to indicate the presence of an anxiety disorder, suggesting that 26.3% of participants showed signs of an anxiety disorder when using self-report to describe their symptoms (54,55). An independent samples t -test revealed a significant sex difference in anxiety ($t(135)=2.07$, $p=.04$) with girls reporting a mean score of approximately 4 points higher than boys. Anxiety was not associated with age ($r(137)=.13$, $p=.15$).

Figure 2. Histogram of total anxiety symptom severity scores on the SCARED. *Note:* a score of 18 or greater on the SCARED indicates elevated anxiety symptoms, while a score of 25 or greater may indicate the presence of an anxiety disorder.

Task behavior

Participants made an average of 13.54 risky choices, 18.41 cautious choices, 30.40 successful inhibitions, 3.14 false alarms, and 200.23 responses at green lights. MANOVA results revealed significant effects of sex ($p < .001$) and age ($p = .01$) on behavior, with boys taking more risks ($p = .003$) and going at more green lights ($p = .05$) as well as making more false alarms ($p < .001$) and fewer successful inhibitions ($p = .04$) than girls, and older participants successfully inhibiting more ($p = .02$) than younger participants.

Paired samples t -tests revealed significant differences between RT across task conditions (all p 's $< .001$). Participants spent an average of 0.52 s making risky choices, 0.63 s making cautious choices, 0.59 s inhibiting when instructed, 0.45 s making false alarms, and 0.46 s going at green lights. Overall, participants spent longer stopping than going and at yellow than at red lights.

Anxiety and behavior

Anxiety was neither associated with response inhibition ability ($r(137)=.08, p=.33$) nor risk-taking frequency ($r(137)=-.09, p=.29$). However, anxious youth took longer on Cautious choice (voluntary choice to inhibit; $r(137)=.24, p=.005$) and were faster at Inhibition (successfully inhibiting when instructed; $r(137)=-.20, p=.017$; Figure 3). These associations remained when controlling for age and sex ($r_{\text{Cautious}}(110)=.22, p=.012, r_{\text{Inhibition}}(110)=-.18, p=.043$), suggesting that while anxiety can improve inhibitory control, it may impede decision-making when faced with approach-avoidance conflict.

Figure 3. Anxiety and response time during Cautious vs. Inhibition. Youth with higher anxiety spent longer making cautious choices but were faster at inhibiting when instructed, suggesting that anxiety may aid in response inhibition, but interfere once outcomes are uncertain. RT=response time.

Principal Components Analysis

PCA revealed two components with eigenvalues >1 that together explained 83% of the variance in participant behavior. One, explaining 54.94% of the variance, was closely correlated with risk-taking frequency. The other, explaining 28.1% of the variance, was closely correlated with successful inhibitions (Table 1). Given the high positive loading of risky choice on Component 1, we refer to this component as “Risk-taking Frequency” or preference for risky behavior. Given the high positive loading of successful inhibitions (and negative loading of false alarms) on Component 2, this component is conceptualized as “Response Inhibition Ability” or ability to follow task instructions. Component scores were extracted for each participant and used to represent risk-taking and response inhibition in the neuroimaging analyses.

Table 1. Correlations between main study variables. * $p < .05$, ** $p < .01$, *** $p < .001$.

	1	2	3	4	5	6	7	8	9	10
1. # Risky	1									
2. # Cautious	-.81***	1								
3. # Inhibition	-.16 [†]	.47***	1							
4. # False alarm	.43***	-.38***	-.69***	1						
5. # Go	.21*	.23**	.62***	.08	1					
6. Component 1	.97***	-.88***	-.27**	.50***	.18*	1				
7. Component 2	.09	.30***	.92***	-.53***	.85***	0	1			
8. Age	.01	.16 [†]	.21*	-.12	.12	-.16	.19*	1		
9. Sex	-.26**	.13	.19*	-.36***	-.15 [†]	-.26**	.06	.03	1	
10. Anxiety	-.10	.09	.10	-.09	.09	-.08	.09	.13	.18*	1

fMRI results

Whole-brain activation

The main contrast of interest isolated inhibitory behaviors stemming from risk-taking processes (cautious choice at yellow lights) from inhibitory behaviors in a cognitive control context (inhibiting at red lights). Whole-brain GLM analysis of the Cautious>Inhibition contrast revealed activation of the dorsal anterior cingulate cortex (dACC), posterior cingulate cortex

(PCC), precuneus, anterior insula, IFG pars opercularis, angular/supramarginal gyri, paracingulate gyrus, middle frontal gyrus (MFG), precentral gyrus, and frontal pole, while the Inhibition>Cautious contrast revealed activation of the lingual gyrus, orbitofrontal cortex (OFC), IFG pars triangularis, lateral occipital cortex (LOC), and temporal fusiform gyrus (Figure 4, Table 2).

Figure 4. Whole-brain neural activation during Cautious vs. Inhibition. Whole-brain activation of Cautious vs. Inhibition revealed activation of the insula, posterior cingulate cortex (PCC), precuneus, dorsal anterior cingulate cortex (dACC), inferior frontal gyrus (IFG) pars opercularis, paracingulate gyrus, middle frontal gyrus (MFG), angular and supramarginal gyri, precentral gyrus, and frontal pole. Conversely, whole-brain activation for the Inhibition>Cautious contrasts revealed activation of the left IFG pars triangularis, lingual gyrus, lateral occipital cortex (LOC), temporal fusiform cortex, and orbitofrontal cortex (OFC). Cluster-corrected at $Z > 3.1$, $p < .05$.

Table 2. Neural activation for the Cautious vs. Inhibition contrast.

Region label	Peak MNI coordinates			Z-max	Voxels (mm ³)
	x	y	z		
a. Regions showing significant activation for Cautious > Inhibition					
Precuneus cortex	-8	-74	40	9.05	6802
R angular gyrus	37	-53	40	6.40	
L lateral occipital cortex	-30	-62	46	6.74	
L superior parietal lobule/supramarginal gyrus	-40	-46	46	5.58	
Paracingulate gyrus	10	32	26	8.96	2239
Dorsal anterior cingulate cortex	2	40	11	5.03	
R middle frontal gyrus	50	12	36	5.67	1207
L middle frontal gyrus	-52	12	42	5.29	821
L insular cortex	-32	20	8	6.71	609

L inferior frontal gyrus pars opercularis	-57	12	2	3.74	
Posterior cingulate cortex	4	-28	28	6.40	414
R lateral occipital cortex	34	-90	-8	5.22	174
R frontal operculum cortex	34	22	8	5.58	142
R superior/middle frontal gyrus	26	4	54	3.98	73
R inferior frontal gyrus pars opercularis	50	12	19	4.70	
R superior frontal gyrus	18	24	62	4.07	71
b. Regions showing significant activation for Inhibition > Cautious					
L postcentral gyrus	-14	-46	60	6.65	3149
R postcentral gyrus	18	-42	58	5.55	1344
R lingual gyrus	10	-78	-10	5.81	628
L superior temporal gyrus	-52	-6	-16	5.36	534
L superior frontal gyrus	-20	24	40	4.87	366
L orbitofrontal cortex	-36	34	-8	6.03	337
L posterior parahippocampal gyrus	-24	-38	-12	5.66	332
R precentral gyrus	22	-20	68	4.64	164
L precuneus cortex	-14	-56	8	5.30	148
L central opercular cortex	-40	0	18	5.01	144
R posterior parahippocampal gyrus	22	-26	-20	4.05	106
Occipital pole	12	-98	-16	4.59	97
Subcallosal cortex	4	16	-6	5.77	89
L superior frontal gyrus/frontal pole	-8	56	28	4.11	78
R planum polare	44	-16	-8	4.26	69

Risk-taking and anxiety did not show significant main effects on whole-brain Cautious>Inhibition activation. However, response inhibition showed both positive and negative effects, with greater activity in the occipital pole, intracalcarine cortex, and supplementary motor area (SMA) associated with better ability, and greater LOC activity associated with worse ability (Figure S1).

We found a significant interaction between risk-taking and anxiety on left IFG pars opercularis activation: greater IFG recruitment during Cautious>Inhibition was associated with *increased* risk-taking in higher anxious youth and *decreased* risk-taking in lower anxious youth (Figure 5), as revealed with a whole-brain analysis for the Cautious>Inhibition contrast.

Figure 5. Left IFG recruitment during Cautious>Inhibition differentially facilitates risk-taking depending on youth anxiety. A) The interaction between anxiety and risk-taking frequency on whole-brain activation for the Cautious>Inhibition contrast revealed a cluster encompassing the left inferior frontal gyrus (IFG) pars opercularis and extending into the anterior insula that showed opposing associations with risk-taking frequency in youth with high vs. low anxiety. B) Visual depiction of the interaction between anxiety and risk taking on left IFG activity in a peak voxel. More IFG recruitment is associated with greater cautious behavior in low anxious youth and more risky choices in higher anxious youth. *Note:* for visualization purposes only. Cluster-corrected at $Z > 3.1$, $p < .05$.

Striatal connectivity

Beta series correlation analysis of the Cautious>Inhibition contrast revealed main effects of risk-taking and response inhibition, as well as a significant interaction between anxiety and risk-taking, on VS functional connectivity. More cautious behavior was associated with greater connectivity between the VS and the right IFG pars triangularis, suggesting that regulation of the VS by the IFG promoted risk avoidance in this sample (Figure 6). Worse inhibition ability was associated with greater connectivity between the VS and a cluster in the left parietal lobe encompassing the LOC, superior parietal lobule, and supramarginal and angular gyri during Cautious>Inhibition, extending the activation results and highlighting the role of the LOC in instructed inhibition (Figure S2).

Figure 6. Main effects of risk-taking frequency on striatal functional connectivity during Cautious>Inhibition. A) More connectivity between the VS and the right IFG pars triangularis during Cautious>Inhibition was associated with more cautious behavior. B) Visual depiction of the association between risk-taking frequency and right IFG activity in a peak voxel. *Note:* for visualization purposes only. VS=ventral striatum, rIFG=right inferior frontal gyrus. Cluster-corrected at $Z>3.1$, $p<.05$.

There were no significant main effects of anxiety on striatal functional connectivity. However, there was a significant interaction between anxiety and risk-taking on striatal connectivity during Cautious>Inhibition: VS connectivity with a range of regions including the amygdala, putamen, OFC, hypothalamus, thalamus, medial PFC (mPFC), and insula was positively associated with risk-taking in low anxious youth and negatively associated with risk-taking in high anxious youth, suggesting that the VS may contribute differently to adolescent behavior depending on youth anxiety (Figure 7).

Figure 7. Interaction between anxiety and risk-taking frequency on VS functional connectivity. More VS connectivity with a range of regions during Cautious>Inhibition was associated with heightened risk taking in youth with low anxiety, whereas it was associated with heightened cautious behavior (risk avoidance) in youth with higher anxiety. VS=ventral striatum, STG=superior temporal gyrus, OFC=orbitofrontal cortex, mPFC=medial prefrontal cortex. Cluster-corrected at $Z > 3.1$, $p < .05$.

Discussion

We examined the neural mechanisms underlying inhibitory behaviors across risk and cognitive control contexts in adolescents across the anxiety continuum. As expected, anxiety was unrelated to response inhibition rate, but anxious youth were faster at inhibiting when instructed than when voluntarily avoiding risk. While anxiety was not linked to risk-taking frequency, the neural mechanisms driving risk-taking differed by anxiety such that greater left IFG recruitment was associated with greater risk-taking in high anxiety, while heightened striatal connectivity was associated with greater risk-taking in low anxiety. We also identified a circuit between the VS and the right IFG that promoted risk avoidance regardless of anxiety levels. Together, results point to a unique role of fronto-striatal circuitry in risk-taking in anxious adolescents.

Anxiety was neither related to risk-taking frequency nor response inhibition ability in this sample. Nonetheless, youth with more anxiety spent relatively longer making cautious choices

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4 than inhibiting when instructed, while youth with less anxiety showed the opposite pattern. This
5 provides initial support for the idea that avoidance can be adaptive when negative outcomes are
6 certain: higher anxious youth responded quickly when instructed. However, decisions involving
7 uncertainty—like risk-taking—can spur approach-avoidance conflict and impair decision-
8 making, which could explain the longer RT during cautious choice. There was also a nonlinear
9 trend in which youth with the highest anxiety struggled with response inhibition (longer RT
10 during instructed versus voluntary inhibition), suggesting that anxiety may interfere with
11 response inhibition once it becomes severe.
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15 Participants showed widespread activation in salience network and decision-making
16 regions such as the dACC, PCC, precuneus, angular gyrus, and anterior insula during
17 Cautious>Inhibition, while activity in regions such as the left IFG pars triangularis and LOC was
18 greater for Inhibition>Cautious. IFG pars triangularis is thought to mediate response inhibition
19 through bottom-up and top-down reprogramming of action plans (56), while occipital activity
20 may demonstrate visual attention to switching task demands. Activation was modulated by
21 response inhibition, with greater activation of the occipital pole, intracalcarine cortex, and SMA
22 to Cautious>Inhibition linked to better inhibitory ability, and greater LOC activation associated
23 with worse inhibitory ability. This aligns with work implicating IFG and SMA in response
24 inhibition (57) and work correlating LOC activation with RT to a planned stimulus (58).
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28 Crucially, the regions modulated by risk-taking were dependent on anxiety. Regulatory
29 systems in the left IFG pars opercularis played opposing roles in risk-taking depending on
30 anxiety: more IFG engagement was associated with more risk avoidance in low anxious youth,
31 but more risk-taking in high anxious youth. Previous work has identified dysregulation of the left
32 IFG in clinical anxiety associated with weaker connectivity between the IFG and the
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4 ventromedial PFC (vmPFC) where the IFG evaluates stimulus meaning and informs the vmPFC
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6 in inhibiting the amygdala (59). It is possible that increased IFG recruitment in higher anxious
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8 youth was compensatory and served to inhibit the amygdala, promoting risk-taking.
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11 Alternatively, perhaps bottom-up mechanisms drive risk-taking in neurotypical adolescents,
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13 while top-down processes guide risk-taking in anxious youth.
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16 Risk-taking and risk avoidance have both been linked to functioning of the VS, which is
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18 also implicated in anxiety. Here, striatal functional connectivity with the right IFG was
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20 associated with more cautious behavior in youth, regardless of anxiety severity. This is
21
22 consistent with previous research implicating the right IFG in inhibition (56): stimulation of the
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24 right IFG diminishes impulsive behavior (60) and IFG connectivity has been associated with
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26 adolescent self-control (61). The IFG is also implicated in approach-avoidance conflict (45),
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28 further highlighting its relevance for studies of decision-making and anxiety. Consistent with the
29
30 activation results, connectivity between the VS and the LOC was associated with poorer
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32 response inhibition ability, suggesting that occipital regions exert influence on inhibitory control
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34 through connections with the rest of the brain.
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41 More VS connectivity with a range of brain regions including the amygdala, putamen,
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43 OFC, hypothalamus, thalamus, mPFC, and insula was associated with greater risk-taking in
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45 lower anxious youth and risk avoidance in higher anxious youth. In lieu of behavioral differences
46
47 based on anxiety, these results suggest that individual differences in subclinical anxiety may not
48
49 show strong effects on adolescent behavior and may even involve the same brain regions, but
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51 these regions influence behavior in opposing ways. Future longitudinal work will probe how
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53 these mechanisms contribute to anxiety development over adolescence, and whether more
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55 pronounced behavioral differences emerge when anxiety reaches a clinical level.
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4 The VS translates evaluative signals from the amygdala (62) into value-based action
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6 (e.g., approach or avoid) (63). Here, greater VS-amygdala connectivity was associated with
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8 greater risk-taking in low anxious youth and greater risk avoidance in higher anxious youth,
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10 suggesting that amygdala signaling to the VS may be interpreted differently in adolescents with
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12 low versus high anxiety; perhaps the “thrilling” aspect of uncertainty inherent in risk drives risk-
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14 taking in low anxious adolescents but is perceived as threatening in higher anxiety. While VS
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16 response has been associated with increased risk-taking (64–66), it also plays a role in risk
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18 avoidance. In rodents, the striatum is necessary for scaling fear to degree of threat (67) and
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20 amygdala-striatal and fronto-striatal circuits control avoidant behavior (28,68). In human adults,
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22 degree of VS responding during avoidance is dependent on anxiety (29). The considerable
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24 development of amygdala-VS and fronto-striatal connections in adolescence may help explain
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26 both the emergence of anxiety and the refinement of motivated behavior.
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34 These findings should be interpreted in the context of several limitations. First, these
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36 analyses are cross-sectional and lacked experimental manipulation, limiting the ability to make
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38 causal inferences about the effects of anxiety on risk-taking or neural functioning. Second,
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40 participants did not provide information regarding why they made their decisions. Finally, while
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42 we did uncover effects of task on brain functional connectivity, we did not measure effective
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44 connectivity and therefore cannot speak to the direction or causality of these effects.
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49 Nonetheless, this study sheds light on the neural mechanisms driving avoidance in early
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51 adolescents at risk for developing anxiety. Although we did not find brain or behavioral
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53 differences based on anxiety, the findings suggest that anxious youth show altered associations
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55 between fronto-striatal functioning and risk-taking, highlighting the importance of a focus on
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57 these circuits in the study of adolescent-onset anxiety. Future longitudinal work will elucidate
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4 how these brain-behavior associations impact the development of anxiety in adolescence and
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Figure S1. Regions modulated by response inhibition ability during Cautious>Inhibition. Greater activity in the occipital pole, intracalcarine cortex, and supplementary motor area (SMA) to Cautious>Inhibition was associated with better inhibition ability, while greater activity in the lateral occipital cortex (LOC) to Cautious > Inhibition was associated with worse inhibition ability. Cluster-corrected at $Z > 3.1$, $p < .05$.

Figure S2. Main effects of risk-taking frequency on striatal functional connectivity during Cautious>Inhibition. More connectivity between the VS and the lateral occipital cortex (LOC), superior parietal lobule, and supramarginal gyrus was associated with worse inhibition ability. VS = ventral striatum. Cluster-corrected at $Z > 3.1$, $p < .05$.