Title
Neural mechanisms underlying the development of anxiety and risk taking in adolescence

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Publication Date
2022

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Neural mechanisms underlying the development of anxiety and risk taking in adolescence

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Amanda Elina Baker

2022

ABSTRACT OF THE DISSERTATION

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by

Amanda Elina Baker

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2022

Professor Adriana Galván, Chair

Anxiety is one of the most common disorders affecting children and adolescents worldwide. The average age of onset for clinical anxiety is in adolescence, a key period of brain and behavioral development that marks the transition from childhood to adult independence. Despite these overlapping developmental timelines, phenotypic anxiety is often characterized by persistent avoidant behavior which conflicts with normative hallmarks of adolescence such as risk taking and exploration. While research suggests that shared neural mechanisms contribute to both the rise of anxiety and risk taking in adolescence, the field has primarily studied these two topics in isolation, precluding the opportunity to understand how brain development contributes to *both* phenotypes during this period and identify factors that promote healthy development across decision-making and mental health domains. The studies presented in this dissertation aim to fill this gap in the literature by examining the concurrent development of anxiety symptoms and risky decision-making behaviors in a diverse sample of children and adolescents living in the greater Los Angeles Area over two timepoints separated by 1-3 years. At each timepoint,

participants completed a clinical interview and an fMRI scan while performing tasks aimed at measuring risky decision-making and cognitive control. Results from Study 1 suggest that anxious adolescents engage in a similar degree of risky behavior as their peers but report negative perceptions of their own decision-making and struggle with making decisions in the face of approach-avoidance conflict. Anxious adolescents also demonstrated altered associations between fronto-striatal circuitry and risky behavior such that reduced prefrontal regulation and heightened striatal connectivity was associated with risk avoidance in high anxiety, while these same neural markers were associated with risk taking in low anxiety. Study 2 investigated how approach motivations and anxiety interact to influence adolescent risky decision-making and neural functioning, revealing that the association between anxiety and risk taking is dependent on adolescent approach motivations: anxious adolescents with low approach motivations were risk averse and inhibited, while anxious adolescents with high approach motivations were risk taking and impulsive. Approach motivations and anxiety showed opposing associations with communication between the striatum, amygdala, and prefrontal cortex during risky decision-making and in the resting adolescent brain, highlighting the competing influences of both anxiety and approach motivations on brain and behavioral correlates of risk taking in adolescence. Whole-brain striatal connectivity patterns during risk taking and risk avoidance showed a high degree of overlap in adolescents with low anxiety but showed divergence in adolescents with high anxiety, again suggesting that the sensitized adolescent striatum plays an important role in anxiety and avoidance. In Study 3, longitudinal analyses revealed average group increases in risk taking and decreases in self-reported anxiety symptoms as participants progressed through adolescence, although clinician-rated anxiety scores increased over time. Adolescents who increased in anxiety reported decreases in positive perceptions and increases in negative

perceptions of their decision-making over time. Neural response during risk avoidance was linked to the development of both anxiety and risk taking such that increases in anxiety were reflected in increases in striatal connectivity during risk avoidance, while changes in risk taking were reflected in changes in amygdala connectivity during risk avoidance. Increases in anxiety were associated with increased neural generalization across risk avoidance and response inhibition and decreased conflict processing during risk avoidance, while increases in risky behavior were associated with increased neural generalization across risk avoidance and risk taking and heightened conflict processing during risk avoidance. Finally, amygdala and striatal response during risk avoidance interacted to predict the emergence of clinician-rated anxiety over time. Taken together, results from this dissertation help to delineate the shared behavioral and neural mechanisms that contribute to anxiety and risky decision-making in adolescents and highlight the potential of leveraging these shared mechanisms to promote positive approaches to decision-making amongst developing youth.

The dissertation of Amanda Elina Baker is approved.

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University of California, Los Angeles

2022

This dissertation is dedicated to my wonderful family.

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The research presented in this dissertation was generously funded by the National Institute of Mental Health (PI: Galván, Peris; R01MH110476) and American Psychological Association Dissertation Award. My graduate training was funded by the National Science Foundation Graduate Research Fellowship Program (DGE-2034835) and the National Institute of Child Health and Human Development T32 Training Fellowship (1T32HD091059), as well as the University of California, Los Angeles Graduate Summer Research Mentorship program.

My graduate training would not have been possible without my fearless mentor, Dr. Adriana Galván. Thank you for believing in me, for supporting my ideas, and for reminding me to never let perfection get in the way of excellence. You lead by example and I'm so lucky to have learned from you.

To Dr. Tara Peris, thank you for all your support on the DAYS project. To Dr. Andrew Fuligni, thank you for all the work you put into the community and for involving me in invaluable experiences like the Summer Institute and Adolescent Bootcamp that will stick with me forever. To Dr. Sarah Tashjian, thank you for all your guidance and generosity—life as a new graduate student wouldn't have been the same without you.

To Dr. Namita Tanya Padgaonkar, my research partner in crime: thank you for all the CCN giggles, for your love of food, animals, and kiddos, for being such a light in my life. I'm so lucky to have met you that first summer and I can't wait for all our good times to come.

To Julia Schorn, Maira Karan, Claudia Aguirre, and all the wonderful people in my cohort: thank you for making graduate school such a delight. To Dr. Cody Cushing: thank you for being the most glorious guy in town, for reminding me to relax once the workday is over, and for being such a great dad to two scampy kitties.

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Under review

Baker, A. E., Padgaonkar, N. T., Galván, A., Peris, T. Anxiety may alter the role of fronto-striatal circuitry in adolescent risky decision-making. *Manuscript under review*.

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In preparation

Baker, A. E., Padgaonkar, N. T., Peris, T., Galván, A. Shared neural mechanisms underlie the development of anxiety and risk taking in adolescence. *Manuscript in preparation*.

* Denotes equal contribution

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Recent poster presentations

Baker, A. E., Padgaonkar, N. T., Peris, T., & Galván, A. (2022). *Shared neural mechanisms underlie the development of anxiety and risk taking in adolescence.* Poster accepted to the 10th Annual Flux Congress, Paris, France.

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CHAPTER 1

Generation Introduction to the Dissertation

Adolescent-onset anxiety is pervasive

Anxiety often emerges in adolescence (Kessler et al., 2007; Merikangas et al., 2010) and can lead to negative outcomes such as depression, addiction, educational underachievement, and suicide (Chiu, Falk, & Walkup, 2016; Kendall, Swan, Carper, & Hoff, 2018). Despite their prevalence, pediatric anxiety disorders exhibit considerable heterogeneity in presentation and symptom course which can make them difficult to effectively diagnose and treat. Symptoms of pediatric anxiety can often seem ambiguous: instead of cognitive or conscious endorsement of anxiety, youth instead report behavioral and somatic manifestations of the symptoms themselves such as stomach aches (Dickstein, 2011). Symptom ambiguity combined with the decrease in routine medical visits that often occurs after childhood leaves anxious adolescents uniquely vulnerable to unmet health needs (Green et al., 2019).

Anxiety in adolescence: approach or avoid?

One potential cause for the heterogeneity in adolescent anxiety trajectories is the contrast between phenotypic anxiety and adolescence as a developmental period. While adolescence is often characterized by behavioral activation (Braams, van Duijvenvoorde, Peper, & Crone, 2015), or the motivation to *approach* novel stimuli, adolescent anxiety is often preceded by behavioral inhibition in childhood which involves fear, wariness, and avoidance of unfamiliar stimuli (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). Avoiding threatening stimuli can be adaptive early in development (Shechner et al., 2012); however, overly avoidant behavior can become reinforcing and habitual (LeDoux, Moscarello, Sears, & Campese, 2017) and contribute

to symptom maintenance and further anxiety development (Arnaudova, Kindt, Fanselow, & Beckers, 2017), especially in a critical time of life during which approach-motivated behaviors serve a vital role for promoting independence, learning, and goal-directed behavior (Casey, Getz, & Galvan, 2008; Spear, 2000). While inhibited children are almost four times as likely to develop anxiety disorders in adolescence (Chronis-Tuscano et al., 2009; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010; Schwartz, Snidman, & Kagan, 1999), not all inhibited individuals go on to develop anxiety later in life (Henderson, Pine, & Fox, 2015), suggesting that the developmental window of adolescence is crucial for determining pediatric anxiety trajectories.

Shared neural mechanisms contribute to anxiety and risk taking

During adolescence, subcortical regions signaling salience and valence such as the amygdala and the ventral striatum (VS) are especially sensitive and responsive to stimuli (Galván, 2013). The adolescent striatum receives direct input from the amygdala (Haber & Behrens, 2014) that allows it to translate evaluative signals into approach or avoidance decisions (Haber & Behrens, 2014)(Fareri & Tottenham, 2016). Connections form and strengthen between these subcortical hubs and frontal regulatory systems as cognitive control and complex decision-making abilities improve (Casey et al., 2008). This combination of subcortical sensitivity and ongoing regulatory development in adolescence is thought to contribute to both the rise in approach behaviors such as risk taking and the emergence of clinical anxiety in adolescence (Casey & Jones, 2010; Galvan et al., 2006).

Adolescent motivated behavior has been explained neurobiologically by the Triadic model in which approach (VS), avoidance (amygdala), and regulatory (prefrontal) neural systems interact and compete to influence response to positive and aversive cues (Ernst, Romeo, & Andersen, 2009). When appetitive and aversive stimuli are pitted against each other in

adolescence, this model posits that striatal sensitivity and developing regulatory systems will bias behavior towards approach responses (Ernst et al., 2009). However, the striatum and its connections are also crucial for aversive learning (Delgado, Li, Schiller, & Phelps, 2008) and play a critical role in adolescent anxiety (Bar-Haim et al., 2009; Benson, Guyer, Nelson, Pine, & Ernst, 2014; Guyer et al., 2012, 2006). While avoidance is often attributed to the threat-sensitive amygdala, animal models have demonstrated that habitual or persistent avoidance forgoes the amygdala and instead correlates with activity in the striatum and prelimbic cortex—or dorsal anterior cingulate cortex (dACC) in humans (Bravo-Rivera, Roman-Ortiz, Montesinos-Cartagena, & Quirk, 2015). Therefore, the combination of striatal sensitivity and still-developing fronto-striatal circuits that occurs in adolescence may contribute to both approach and avoidance phenotypes, perhaps depending on adolescent anxiety. Understanding how adolescent brain development contributes to both anxiety and risky decision-making trajectories is an important next step for delineating the shift from normative to pathological anxiety from a neurobiological perspective.

Adolescence as an intervention point for anxiety disorders

As a transitionary period that serves to prepare youth for adult independence, adolescence is a pivotal trajectory point that impacts health and well-being into adulthood (Dahl, 2004) and therefore has the potential to differentiate normative from pathological anxiety trajectories. Given the significance and complexity of this period, it is important to leverage what the field has already learned about the developing brain to maximize effectiveness of anxiety prevention and treatment. While studies of adolescent risk taking often focus on striatal functioning and its connections with the PFC (Galvan, 2010), the sensitized adolescent amygdala also plays an important role in risk taking through its connections with the striatum and prefrontal cortex

(Peters, Jolles, Duijvenvoorde, Crone, & Peper, 2015). Given the ongoing development of these dynamic systems, the uncertainty inherent in risk may be uniquely thrilling in adolescence compared to in other stages of life (Dahl, 2004).

The sensation of thrill is involved in many aspects of adolescent risk taking, including romance and sexual experimentation. To explore and learn from new and potentially scary experiences, it would greatly behoove the adolescent brain to have a nuanced perception of threat and uncertainty that can perceive potential danger as both frightening and rewarding. In line with this idea, adolescents tend to be more tolerant of uncertainty during risky decision-making than either children or adults (van den Bos & Hertwig, 2017) and are more willing to take risks when the risk is ambiguous rather than when risks are clearly stated (Tymula et al., 2012). Adolescence could serve as an ideal intervention point during which decision-making brain networks are uniquely malleable and tuned to uncertainty and reward, and therefore key targets for reward-based training aimed at promoting approach behaviors and extinguishing avoidant behavior loops.

The current research

In the following chapters, I present three studies that combine clinical psychology and cognitive neuroscience to answer open questions regarding the development of anxiety and motivated behavior in adolescents. In the first two chapters, I delve into the neurobiological mechanisms promoting approach and avoidance behaviors across risk and cognitive control contexts and their relation to anxiety in a sample of early adolescents. In the third chapter, I extend this line of inquiry to uncover neurobiological markers of anxiety development by probing within-person change as the sample progresses through adolescence.

Summary of Study 1: Neural correlates of avoidance and anxiety in adolescents

Avoidance is a cardinal symptom of anxiety disorders that conflicts with the normative adolescent propensity for heightened approach behavior (Galván, 2013). Although avoidance contributes to much of the interference observed in anxiety disorders, a tendency to avoid can have adaptive or maladaptive consequences for adolescents depending on the situation. For example, avoidance can be adaptive in situations with clear threats (Robinson, Krimsky, & Grillon, 2013), 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). Despite the importance of avoidance for adolescent anxiety development, relations between risky decision-making, response inhibition, and the behavioral decision to avoid are poorly understood (Peris & Galván, 2021). Understanding the neural and behavioral correlates of different forms of avoidance and their relation to anxiety in adolescents is an important next step for understanding the mechanisms underlying one of the most defining features of anxiety disorders for both youth and adults.

Chapter 2 examines neural mechanisms underlying avoidant behaviors across risk and cognitive control contexts in adolescents across the anxiety continuum. While anxious youth often perform well when given clear instructions, the uncertainty of risky decision-making can spur approach-avoidance conflict where the ability to engage in goal-directed behavior becomes difficult for anxious youth (Barker, Buzzell, & Fox, 2019), contributing to impaired functioning (Arnaudova et al., 2017) and risk aversion (Charpentier, Aylward, Roiser, & Robinson, 2017). In this chapter, we find that anxious youth were faster at response inhibition but slower when voluntarily avoiding a risk, highlighting the adaptive nature of anxiety when instructions are clear and suggesting interference during approach-avoidance conflict. Despite these differences

in response time, there was no direct link between anxiety and risk aversion in this sample. However, the neural mechanisms driving risk taking differed by anxiety such that greater left inferior frontal gyrus (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 from this chapter suggest that anxiety may be adaptive for response inhibition and maladaptive for risky decision-making in adolescents, highlighting the importance of understanding anxious decision-making across contexts of risk and cognitive control. Even further, this chapter suggests that fronto-striatal circuitry may play a unique role in risky decision-making amongst anxious adolescents.

Summary of Study 2: The interplay between anxiety and approach motivations in adolescent risk taking

While anxiety has been linked to risk aversion in adults (Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016), the heterogeneity of the disorder and its interaction with typical adolescent development adds nuance to this narrative. For example, latent class analysis in anxious adults suggests that there may be two subtypes of social anxiety—the avoidant subtype, characterized by behavioral inhibition and risk avoidance, and the approach-motivated subtype, characterized by impulsiveness, reward sensitivity, risk taking, and substance abuse (Nicholls, Staiger, Williams, Richardson, & Kambouropoulos, 2014). Given the frequency of approach-avoidance conflict in adolescence, it can be hypothesized that these subtypes might emerge in adolescence and influence the development of risky behavior during this period. However, the field has yet to identify how approach motivations and anxiety interact to impact decision-making and symptom development as youth enter adolescence.

The regulatory brain area that is most frequently implicated in decision-making under conflict or uncertainty is the dorsal anterior cingulate cortex (dACC) (B. W. Smith et al., 2009). While the VS and amygdala track value and salience, the dACC governs conflict monitoring and regulates risk-related values and behavior (Christopoulos, Tobler, Bossaerts, Dolan, & Schultz, 2009; Kolling, Wittmann, & Rushworth, 2014). In adolescents, blunted dACC response during social exclusion links anxiety to substance use, suggesting that altered conflict monitoring in the dACC may drive risk taking in anxious adolescents (Beard, Hastings, Ferrer, Robins, & Guyer, 2022). Furthermore, low dACC activation has been shown to mediate the link between high approach motivations and heightened risk taking in neurotypical adolescents (M. Li et al., 2019). Despite the importance of amygdala, VS, and dACC communication for both anxiety and risk taking in adolescence, the combined roles of approach motivations and anxiety on neural functioning of this network during risky decision-making has yet to be explored.

Chapter 3 focuses on the competing influences of sensitivity of the behavioral activation system (BAS) and anxiety on behavior and neural dynamics during adolescent risky decision-making. While studying neural dynamics during decision-making is important for clarifying which brain regions are involved in different processes, examining resting-state fMRI—or neural fluctuations in the *absence* of task—in conjunction with task fMRI can improve reliability of results by measuring neural function across modalities (Herting, Gautam, Chen, Mezher, & Vetter, 2018) and help clarify the scope of influence of individual difference measures on adolescent brain function. Therefore, this chapter also explores the influence of BAS sensitivity and anxiety on intrinsic communication between the amygdala, striatum, and dACC in the resting adolescent brain.

As the approach-motivated substyle of anxiety has been characterized by increased impulsivity, sensation seeking, and risk taking (Nicholls et al., 2014), we predicted that youth with high anxiety and high BAS would show excessive risk taking and decreased inhibitory control, while youth with high anxiety and low BAS would demonstrate risk aversion and improvements in inhibitory control. In line with these hypotheses, results from this chapter demonstrate that anxiety is not always synonymous with risk aversion in adolescents—rather, anxious adolescents with low BAS sensitivity were risk averse, whereas anxious adolescents with high on BAS sensitivity were risk seeking. Approach motivations were directly linked to amygdala-striatal-anterior cingulate dynamics during risky versus cautious choices and at rest. Youth with higher anxiety showed greater fronto-amygdala communication during risky versus cautious choice, and during risky decision-making overall. Although anxiety was not related to mean striatal connectivity levels, higher anxiety was associated with more neural differentiation in striatal connectivity during risky versus cautious choice, suggesting that multivariate analysis of neural response during decision-making may prove useful for understanding how anxiety affects striatal functioning and decision-making in adolescence.

Summary of Study 3: Shared neural mechanisms underlie the development of anxiety and risk taking in adolescence

Research suggests that shared mechanisms underlie adolescent changes in anxiety and risk taking; however, a neurobiological link contributing to the rise of both phenotypes remains elusive. The first two chapters of this dissertation connect brain response to behavior and elucidate neural mechanisms underlying risky decision-making in vulnerable youth by providing snapshots of neural development across different individuals at varying ages. However, research shows that the incidence of anxiety increases dramatically as youth progress through adolescence

as many risk-taking behaviors also onset during this time. Furthermore, while there are overarching commonalities in the adolescent experience, everyone has a unique journey from childhood to adulthood. To accurately track developmental change and capture the transition from normative to clinical anxiety from a neurobiological perspective, it is important to measure within-person change by assessing individuals across multiple timepoints.

According to the Triadic Model, regulatory systems in adolescence bias behavior towards approach responses in the face of an approach-avoidance conflict (Ernst et al., 2009). However, anxiety symptoms may interact with this bias to promote inhibitory behaviors in vulnerable youth. To date, no prospective longitudinal study has tested how changes in approach, avoidance, and regulatory neural response during risky decision-making function to promote normative or anxious trajectories in adolescence. Without this knowledge, the field cannot identify the precise neurobiological mechanisms that confer risk or resilience to anxiety development in the adolescent period.

Chapter 4 helps fill this gap in the literature by examining developmental changes in anxiety symptoms and decision-making in adolescents over the course of 1-3 years, depending on the COVID-19 pandemic. In this chapter, longitudinal analyses are used compare neural representations of risky choice, cautious choice, and response inhibition over adolescent development. As anxiety has been associated with excessive avoidant behavior, we predicted that youth whose anxiety worsened between Time 1 and Time 2 would show less neural differentiation between voluntary cautious decisions and instructed response inhibition, denoting a shift from goal-directed behavior to habit-based avoidance.

Results presented in this chapter show that participants showed increases in risk taking that were paralleled by increased neural similarity between risky and cautious choice and neural

dissimilarity between cautious choice and response inhibition. Conversely, increases in anxiety were paralleled by greater neural dissimilarity between risky and cautious choice and neural similarity between cautious choice and response inhibition. In this way, neural representations of cautious choice shifted towards risky choice or response inhibition depending on risk taking and anxiety trajectories.

Adolescents who increased in anxiety also demonstrated increased striatal response paralleled by decreased dACC response and increased striatal-dACC connectivity when making cautious decisions, while within-person increases in risk taking were positively associated with striatal and dACC activation and amygdala connectivity with the pre- and postcentral gyri and lateral occipital cortex and negatively associated with amygdala-prefrontal connectivity during cautious choices. Overall, results from the following chapters suggest that overlapping neural mechanisms—specifically, activation of and communication between the prefrontal cortex, amygdala, and striatum during cautious choice—underlie the development of risky decision-making and anxiety in adolescents. These shared neural mechanisms are therefore a key target for interventions and treatments to mitigate the development of anxiety in adolescence.

CHAPTER 2

Neural Correlates of Avoidance and Anxiety in Adolescents

Introduction

Anxiety disorders commonly emerge during adolescence (Kessler et al., 2007; Merikangas et al., 2010) and demonstrate considerable heterogeneity in presentation and symptom course (Hovenkamp-Hermelink, Jeronimus, Myroniuk, Riese, & Schoevers, 2021). 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 (Galván, 2013) and is linked to risk aversion in anxiety (Sonuga-Barke et al., 2016). Nonetheless, relations between risk aversion, risky decision-making, and the behavioral decision to avoid are poorly understood (Peris & Galván, 2021). 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 avoidance 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 (Robinson et al., 2013), 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 decisions made in the face of uncertainty, is important for learning and exploration in adolescence (Galván, 2013). However, the uncertainty of risk can spur approach-avoidance conflict where the ability to engage in goal-directed behavior becomes difficult for anxious youth (Barker et al., 2019), contributing to impaired functioning (Arnaudova et al., 2017) and risk aversion in anxious adults (Charpentier et

al., 2017). Interestingly, it is precisely the uncertainty of risk that appeals to typically-developing adolescents (Tymula et al., 2012) which may help explain the heterogeneity in behavior and symptom profiles observed during this developmental window.

Approach-avoidance conflict has been explained neurobiologically by the Triadic model in which approach (ventral striatum; VS), avoidance (amygdala), and regulatory (prefrontal) neural systems interact and compete to influence response to positive and aversive cues (Ernst et al., 2009). When appetitive and aversive stimuli are pitted against each other in adolescence, this model posits that regulatory systems will bias behavior towards approach (Ernst et al., 2009). While the striatum functions to promote approach behavior in neurotypical adolescents, anxious youth may exhibit a different phenotype. Increased striatal response and reduced fronto-striatal connectivity during peer feedback has been linked to impaired recall of positive feedback in adolescents with social anxiety (Jarcho et al., 2015), suggesting that fronto-striatal mechanisms may bias learning in anxiety. This bias may then contribute to avoidance, as research has identified a fronto-striatal circuit that controls anxious avoidance behaviors in mice (Loewke, Minerva, Nelson, Kreitzer, & Gunaydin, 2021) and striatal response during avoidance correlates with anxiety in adult humans (Levita, Hoskin, & Champi, 2012). Despite work implicating the VS (Bar-Haim et al., 2009; Benson et al., 2014; Lahat, Benson, Pine, Fox, & Ernst, 2016), amygdala (Galván & Peris, 2014; Guyer et al., 2008; Kessler et al., 2007), and prefrontal cortex (PFC) (Clauss, Benningfield, Rao, & Blackford, 2016; Guyer et al., 2008; Kenwood, Kalin, & Barbas, 2021) in risk for anxiety, the role of anxiety on neural functioning during approach-avoidance conflict in adolescents is still poorly understood (A. E. Baker & Galván, 2020; Peris & Galván, 2021).

Here, we measured anxiety, risk taking, and response inhibition in 137 adolescents (9-13y/o) as they played the Driving Game, a decision-making task, during functional magnetic resonance imaging (fMRI). Participants were instructed to "go" at green lights, "stop" at red lights, and choose whether to stop or go at yellow lights, thereby measuring response inhibition (stopping a prepotent response when the light turns red) and risky decision-making in the same design. Participants ranged across a spectrum of normative anxiety levels with over-sampling from those at the cusp of clinical diagnosis who are most at risk for developing anxiety in adolescence. Given work linking anxiety to risk aversion (Charpentier et al., 2017), we hypothesized that anxiety would correlate negatively with risk taking. Given work reporting no differences in response inhibition ability in anxiety (Lipszyc & Schachar, 2010), we predicted anxiety would not affect false alarm rate. As anxiety can sharpen inhibitory ability (Grillon et al., 2017), 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 (Barker et al., 2019), 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) (Zorowitz et al., 2019) 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) (B Birmaher et al., 1997). 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) (Silverman & Albano, 1996) 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_{Age}=11.3, SD_{Age}=1.41; 61 girls; 35% white, 22.2% Latino, 20.4% Asian, 13.9% Black, 9.5% Mixed Race; Table 2.1).

Table 2.1. Participant descriptive statistics.

	Mean (SD) or % (*N* = 137)
Age (years)	11.3 (1.41)
Sex	76M (55.5%), 61F (44.5%)
Race/ethnicity	34.3% white, 22.1% Latino, 20% Asian, 14.3% Black, 9.3% Mixed Race

Anxiety (SCARED total score)	19.27 (11.48)
# Risky	13.54 (8.11)
# Cautious	18.41 (8.72)
# Inhibition	30.40 (5.11)
# False alarm	3.14 (3.16)
# Go	200.23 (25.59)
Average relative motion	0.22 (0.12)

Anxiety severity

Participants completed the 41-item self-report SCARED (B Birmaher et al., 1997) 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.

Adolescent decision-making

Participants also completed the 30-item self-report Flinders Adolescent Decision Making Questionnaire (ADMQ) (Mann, Harmoni, Power, Beswick, & Ormond, 1988) to assess their approach to decision situations. Participants read a series of statements regarding their perceptions of their decision-making (e.g., "The decisions I make turn out well") and rated each statement on a 4-point Likert scale ranging from 0 (*not at all true of me*) to 3 (*almost always true*). The ADMQ is composed of 5 sub-scales that broadly measure decision self-esteem (confidence in one's decisions), vigilance (care one takes while making decisions), panic (panic

when making decisions), cop out (avoidance of decisions), and complacency (preferring others to make decisions).

fMRI task

Participants played two 8-minute runs of the Driving Game, an adapted version of the Stoplight Task (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011) 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.

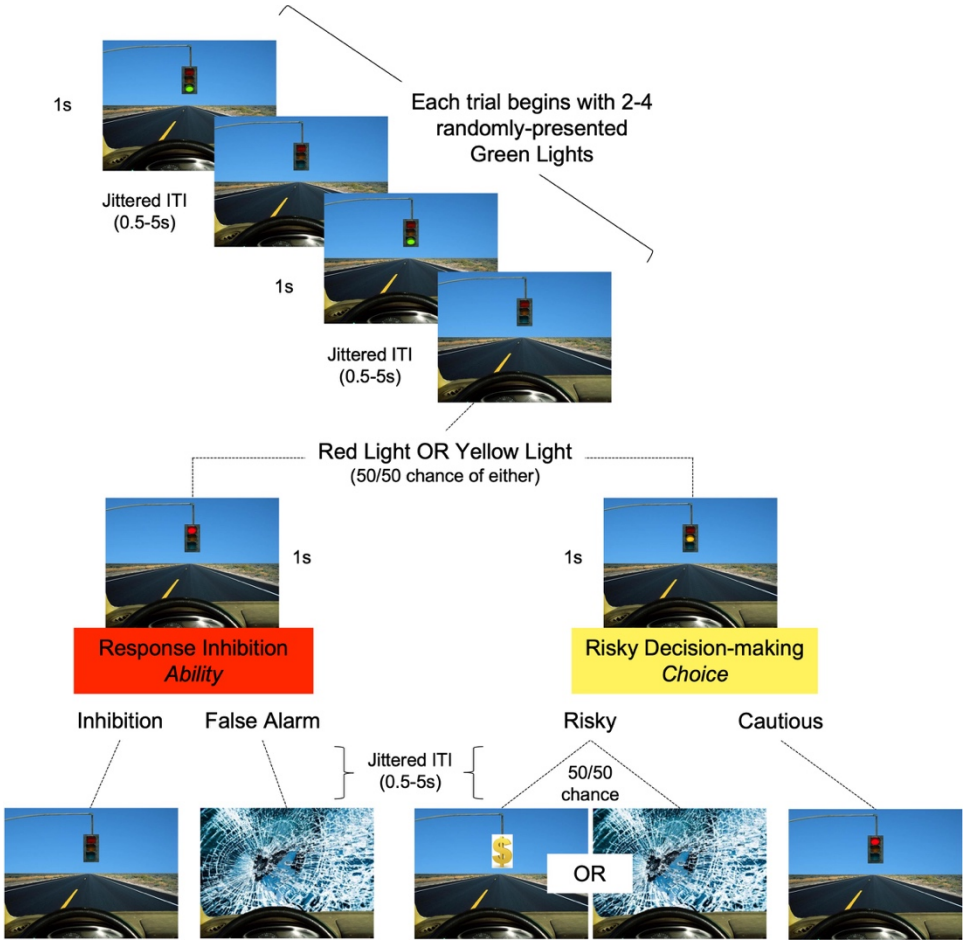

Figure 2.1. The Driving Game. Participants encountered green, red, and yellow stoplights in the laboratory task and were instructed to press "1" to go for green lights, "2" to stop for red lights, and either "1" to go (risky choice) or "2" to stop (cautious choice) for yellow lights. A jittered inter-trial (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/) (S. M. Smith et al., 2004) 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 (Andersson, Skare, & Ashburner, 2003) 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

To assess the association between anxiety severity and perceived decision-making capabilities, a multiple regression analysis was conducted in SPSS with ADMQ scores as predictors, age and sex as covariates, and anxiety as the outcome variable. 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 (Beckmann, Jenkinson, & Smith, 2003). 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 (Poline, Worsley, Evans, & Friston, 1997). 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 (Rissman, Gazzaley, & D'Esposito, 2004) 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 ($M_{Anx} = 19.27$, $SD_{Anx} = 11.48$; Figure 2.2), 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 (Boris Birmaher et al., 1999; Canals, Hernández-Martínez, Cosi, & Domènech, 2012). 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 ($r(137) = .13$, $p = .15$).

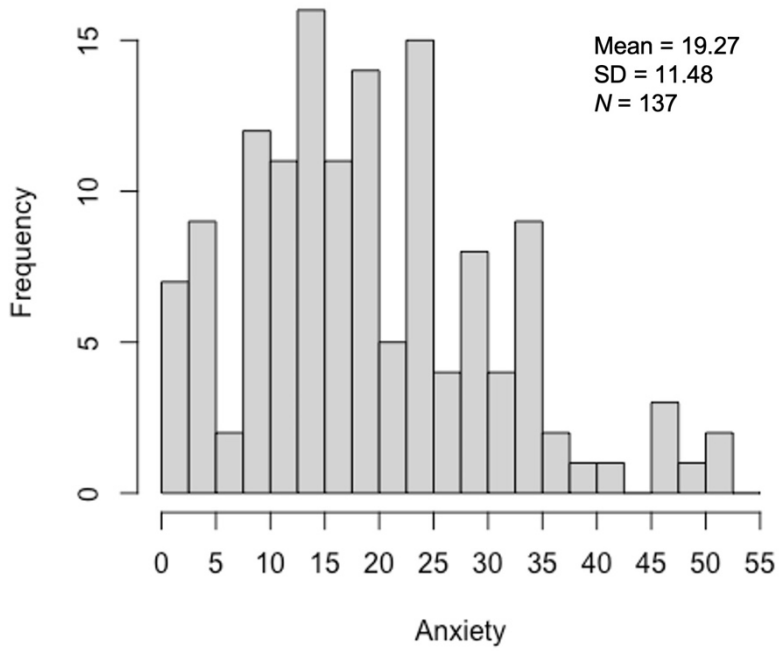

Figure 2.2. Histogram of total anxiety symptom severity scores on the SCARED. *Note:* a SCARED score ≥ 18 indicates elevated anxiety symptoms and risk for future disorder, while a score ≥ 25 may indicate the presence of an anxiety disorder.

Anxiety and perceived decision-making

ADMQ sub-scale scores were combined into a positive decision-making score (composed of decision self-esteem and vigilance) and a negative decision-making score (composed of decision panic, cop out, and complacency). Results of a multiple regression analysis revealed

that higher anxiety severity was associated with lower positive perceptions of decision situations (β=-.26, *p*=.006) and higher negative perceptions of decision situations (β=.28, *p*=.003; Figure 2.3), suggesting that anxiety may negatively impact the way that adolescents approach and perceive their decisions.

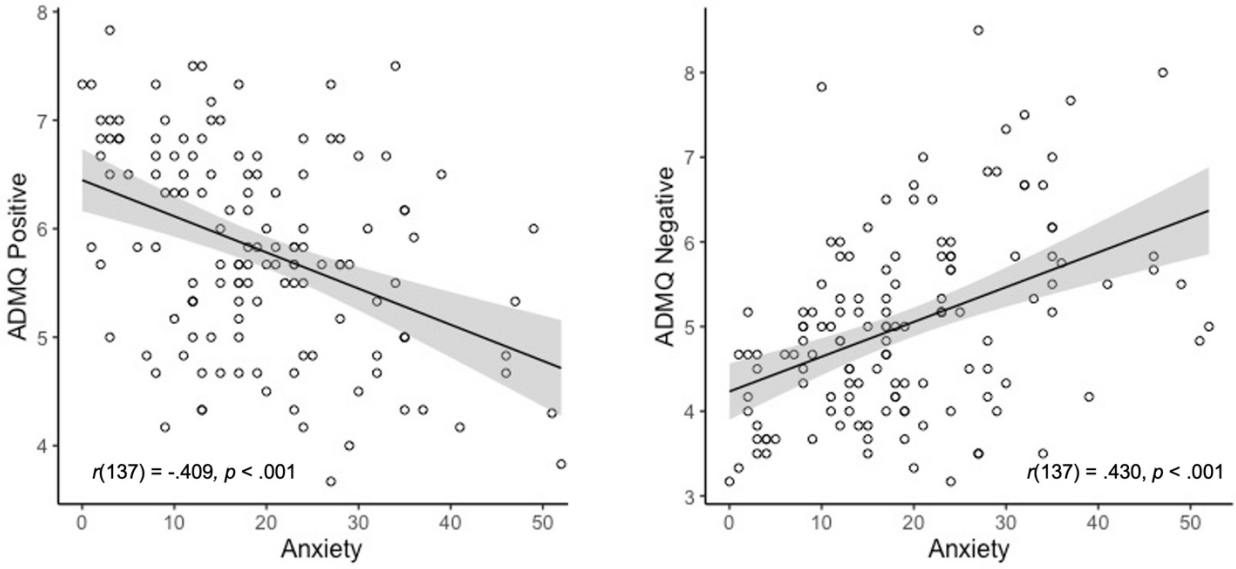

Figure 2.3. Anxiety is linked to decreased positive perceptions of decision-making and increased negative perceptions of decision-making. Youth with higher anxiety reported lower decision self-esteem and vigilance and higher decision panic, cop out, and complacency, suggesting that anxiety may negatively impact perceived decision-making capabilities in adolescence. *r* = Pearson correlation coefficient.

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 2.4). These associations remained when controlling for age and sex ($r_{Cautious}$(110)=.22, p=.012, $r_{Inhibition}$(110)=-.18, p=.043), suggesting that while anxiety can improve inhibitory control, it may impede decision-making when faced with approach-avoidance conflict.

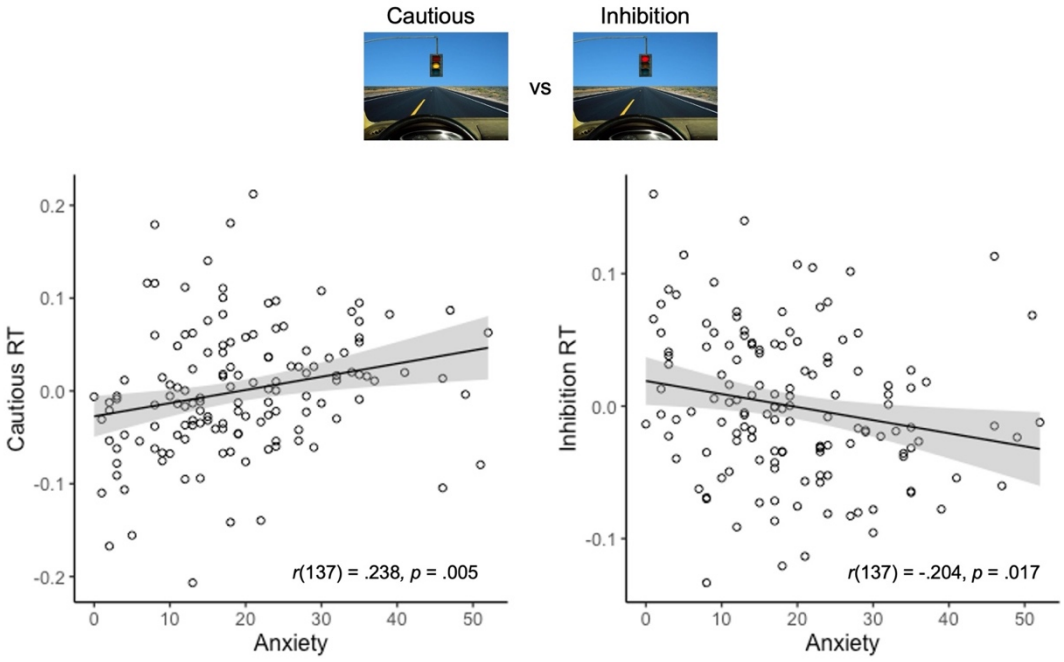

Figure 2.4. Anxiety and response time during Cautious vs. Inhibition. Youth with higher anxiety spent longer on cautious trials but were faster at inhibiting when instructed, suggesting that anxiety may aid in response inhibition, but interfere once outcomes are uncertain. RT = response time.

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 2.2). 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 2.2. Correlations between main study variables. †< .01, *p< .05, **p< .01, ***p<.001.

	1	2	3	4	5	6	7	8	9	10	11	12
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. Risk-taking Frequency	.97***	-.88***	-.27**	.50***	.18*	1						
7. Response Inhibition Ability	.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		
11. ADMQ Positive	.11	-.08	.01	.01	-.01	.09	.01	.03	-.00	-.41***	1	
12. ADMQ Negative	-.06	.12	.04	-.00	.11	-.07	.07	.10	-.01	.43***	-.56***	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 2.5, Table 2.3).

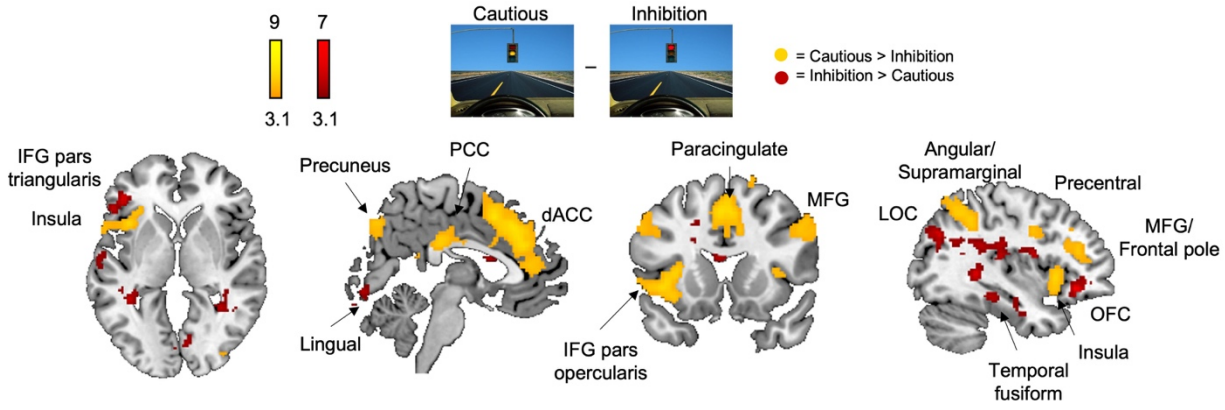

Figure 2.5. Whole-brain neural activation during Cautious vs. Inhibition. Whole-brain activation for the Cautious>Inhibition contrast revealed activation of the anterior insula, posterior cingulate cortex (PCC), precuneus, dorsal anterior cingulate cortex (dACC), inferior frontal gyrus (IFG) pars opercularis, 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 2.3. Neural activation during Cautious vs. Inhibition.

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 2.6).

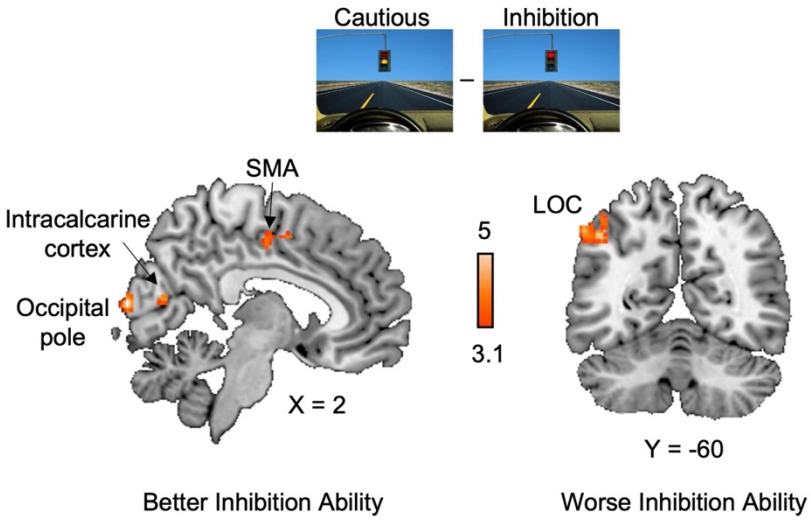

Figure 2.6. Regions modulated by response inhibition ability during Cautious vs. Inhibition. Greater activity in the occipital pole, intracalcarine cortex, and supplementary motor area (SMA) to Cautious > Inhibition was associated with better inhibition ability, while greater

activity in the lateral occipital cortex (LOC) to Cautious > Inhibition was associated with worse inhibition ability. Cluster-corrected at $Z > 3.1$, $p < .05$.

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 2.7), as revealed with a whole-brain analysis for the Cautious > Inhibition contrast.

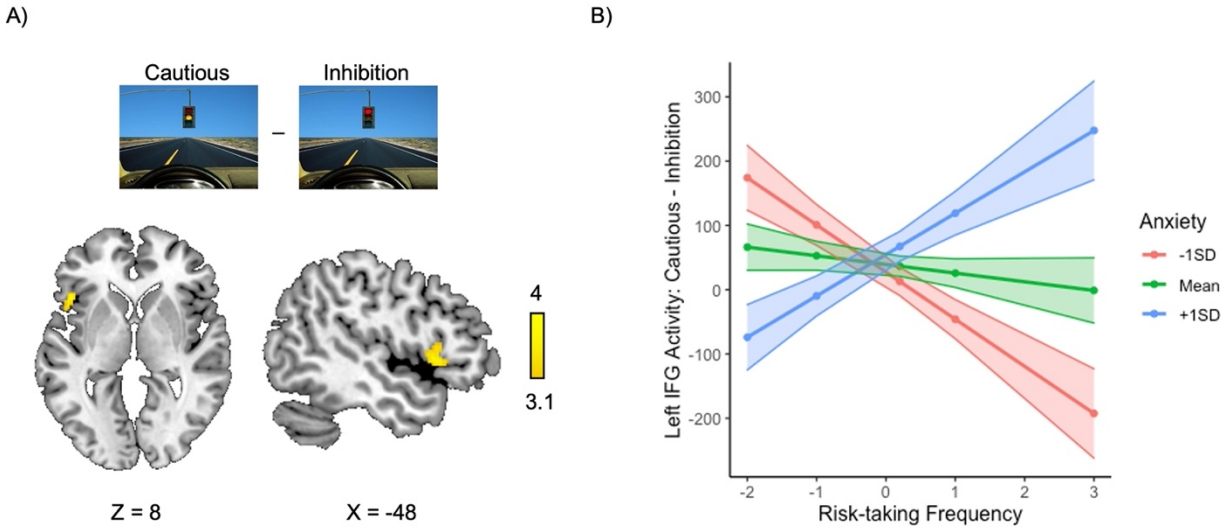

Figure 2.7. Left IFG recruitment during Cautious vs. Inhibition differentially facilitates risk taking depending on youth anxiety. A) The interaction between anxiety and risk-taking frequency on whole-brain activation for the Cautious > Inhibition contrast revealed a cluster encompassing the left inferior 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 $Z > 3.1$, $p < .05$.

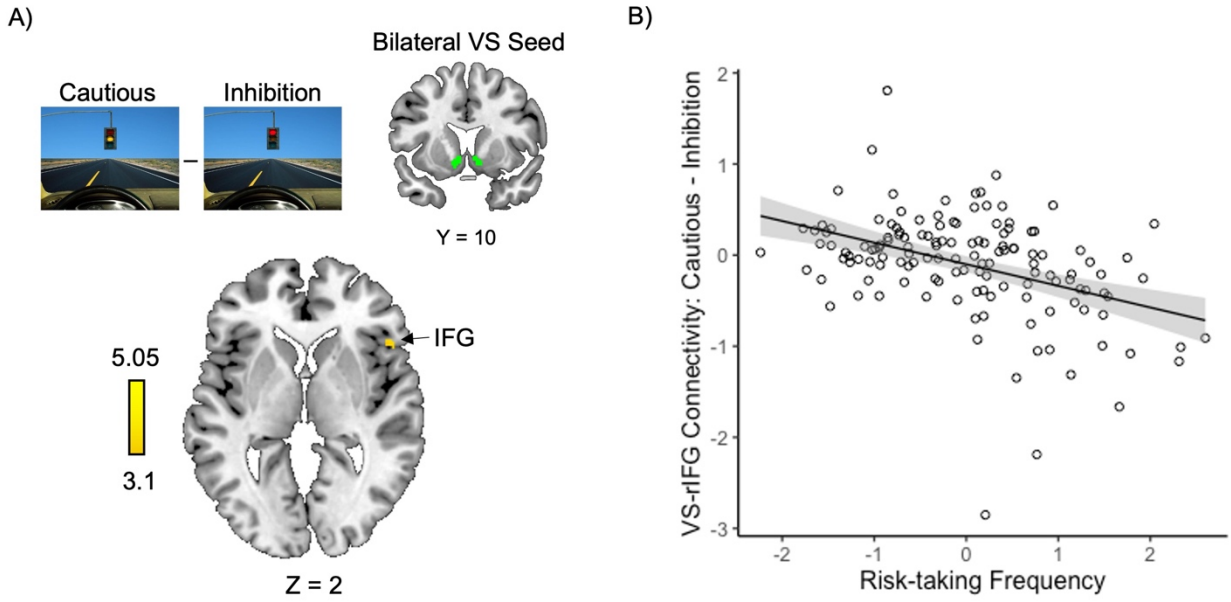

Figure 2.8. Main effects of risk-taking frequency on striatal functional connectivity during Cautious vs. Inhibition. A) More connectivity between the VS and the right IFG pars triangularis during Cautious > Inhibition was associated with more cautious behavior. B) Visual depiction of the association 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. $Z > 3.1$, $p < .05$.

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 2.8). 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 2.9).

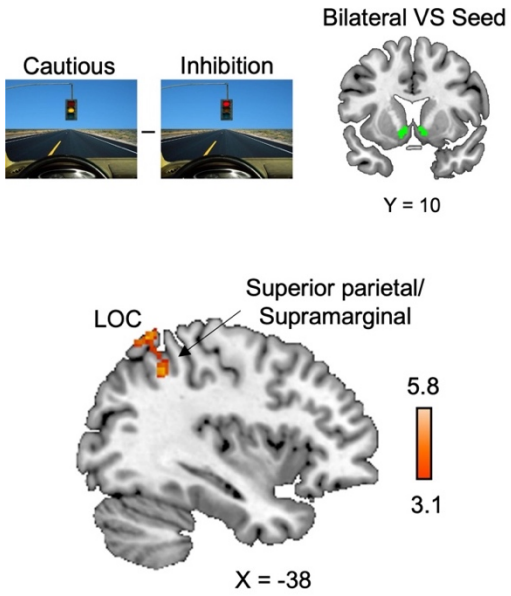

Figure 2.9. Main effects of response inhibition ability on striatal functional connectivity during Cautious vs. Inhibition. More connectivity between the VS and the lateral occipital cortex (LOC), superior parietal lobule, and supramarginal gyrus was associated with worse inhibition ability. VS = ventral striatum. Cluster-corrected at $Z > 3.1$, $p < .05$.

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 2.10).

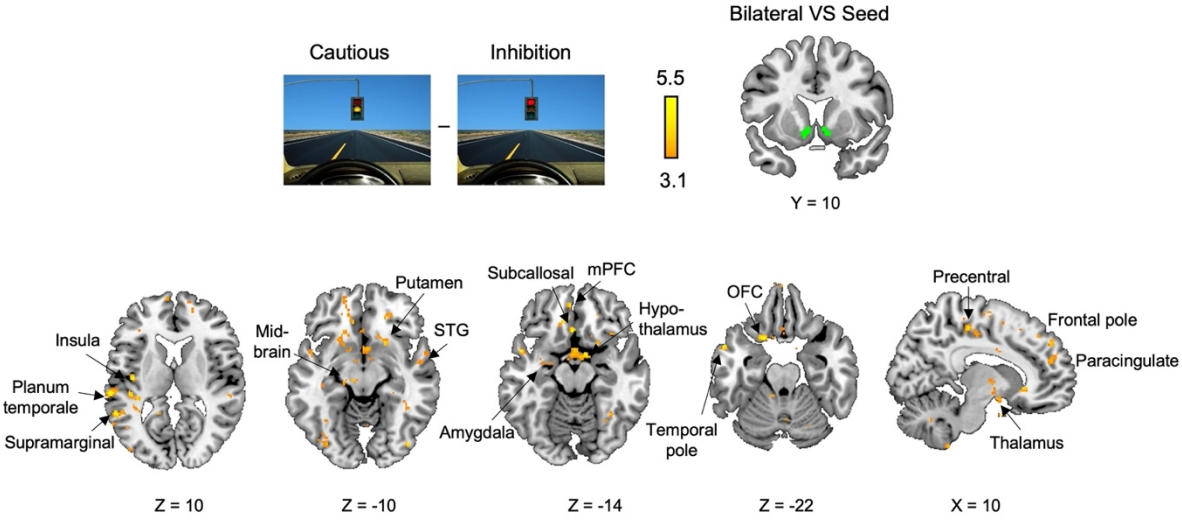

Figure 2.10. Interaction between anxiety and risk taking on VS functional connectivity. More VS connectivity with a range of regions during Cautious > Inhibition was associated with heightened risk taking in youth with low anxiety, whereas it was associated with heightened cautious behavior (risk avoidance) in youth with higher anxiety. VS = ventral striatum, STG = superior temporal gyrus, OFC = orbitofrontal cortex, mPFC = medial prefrontal cortex. $Z > 3.1$, $p < .05$.

Discussion

In this study, we examined the neural mechanisms underlying avoidance 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 than inhibiting when instructed, while youth with less anxiety showed the opposite pattern. This provides initial support for the idea that avoidance can be adaptive when negative outcomes are certain: higher anxious youth responded quickly when instructed. However, decisions involving uncertainty—like risk taking—can spur approach-avoidance conflict and impair decision-making, which could explain the longer RT during cautious choice. There was also a nonlinear trend in which youth with the highest anxiety struggled with response inhibition (longer RT during instructed versus voluntary inhibition), suggesting that anxiety may interfere with response inhibition once it becomes severe. As anxiety can co-occur with and show reciprocal associations with self-control issues such as attention-deficit/hyperactivity disorder (ADHD) (Murray et al., 2022), a task that involves both risk taking and cognitive control such as this one might prove useful for a study of comorbid trajectories.

Participants showed widespread activation in salience network and decision-making regions such as the dACC, PCC, precuneus, angular gyrus, and anterior insula during Cautious > Inhibition, while activity in regions such as the left IFG pars triangularis and LOC was greater

for Inhibition > Cautious. IFG pars triangularis is thought to mediate response inhibition through bottom-up and top-down reprogramming of action plans (Lenartowicz, Verbruggen, Logan, & Poldrack, 2011), while occipital activity may demonstrate visual attention to switching task demands. Activation was modulated by response inhibition, with greater activation of the occipital pole, intracalcarine cortex, and SMA to Cautious>Inhibition linked to better inhibitory ability, and greater LOC activation associated with worse inhibitory ability. This aligns with work implicating IFG and SMA in response inhibition (Zhang & Iwaki, 2019) and work correlating LOC activation with RT to a planned stimulus (Cohen et al., 2010).

Crucially, the regions modulated by risk taking were dependent on anxiety. Regulatory systems in the left IFG pars opercularis played opposing roles in risk taking depending on anxiety: more IFG engagement was associated with more risk avoidance in low anxious youth, but more risk taking in high anxious youth. Previous work has identified dysregulation of the left IFG in clinical anxiety associated with weaker connectivity between the IFG and the ventromedial PFC (vmPFC) where the IFG evaluates stimulus meaning and informs the vmPFC in inhibiting the amygdala (Cha et al., 2016). It is possible that increased IFG recruitment in higher anxious youth was compensatory and served to inhibit the amygdala, promoting risk taking. Alternatively, perhaps bottom-up mechanisms drive risk taking in neurotypical adolescents, while top-down processes guide risk taking in anxious youth.

Risk taking and risk avoidance have both been linked to functioning of the VS, which is also implicated in anxiety. Here, striatal functional connectivity with the right IFG was associated with more cautious behavior in youth, regardless of anxiety severity. This is consistent with previous research implicating the right IFG in inhibition (Lenartowicz et al., 2011): stimulation of the right IFG diminishes impulsive behavior (Jacobson, Javitt, & Lavidor,

2011) and IFG connectivity has been associated with adolescent self-control (Pyeon et al., 2021). The IFG is also implicated in approach-avoidance conflict (Zorowitz et al., 2019), further highlighting its relevance for studies of decision-making and anxiety. Consistent with the activation results, connectivity between the VS and the LOC was associated with poorer response inhibition ability, suggesting that occipital regions exert influence on inhibitory control through connections with the rest of the brain.

More VS connectivity with a range of brain regions including the amygdala, putamen, OFC, hypothalamus, thalamus, mPFC, and insula was associated with greater risk taking in lower anxious youth and risk avoidance in higher anxious youth. In lieu of behavioral differences based on anxiety, these results suggest that individual differences in subclinical anxiety may not show strong effects on adolescent behavior and may even involve the same brain regions, but these regions influence behavior in opposing ways. Future longitudinal work will probe how these mechanisms contribute to anxiety development over adolescence, and whether more pronounced behavioral differences emerge when anxiety reaches a clinical level.

The VS translates evaluative signals from the amygdala into value-based action (e.g., approach or avoid) (Fareri & Tottenham, 2016). Here, greater VS-amygdala connectivity was associated with greater risk taking in low anxious youth and greater risk avoidance in higher anxious youth, suggesting that amygdala signaling to the VS may be interpreted differently in adolescents with low versus high anxiety; perhaps the "thrilling" aspect of uncertainty inherent in risk drives risk taking in low anxious adolescents but is perceived as threatening in higher anxiety. While VS response has been associated with increased risk taking (Chein et al., 2011), it also plays a role in risk avoidance. In rodents, the striatum is necessary for scaling fear to degree of threat (Ray, Russ, Walker, & McDannald, 2020) and amygdala-striatal and fronto-striatal

circuits control avoidant behavior (Loewke et al., 2021; Ramirez, Moscarello, LeDoux, & Sears, 2015). In human adults, degree of VS responding during avoidance is dependent on anxiety (Levita et al., 2012). The considerable development of amygdala-VS and fronto-striatal connections in adolescence may help explain both the emergence of anxiety and the refinement of motivated behavior.

These findings should be interpreted in the context of several limitations. First, these analyses are cross-sectional and lacked experimental manipulation, limiting the ability to make causal inferences about the effects of anxiety on risk taking or neural functioning. Second, participants did not provide information regarding why they made their decisions. Finally, while we did uncover effects of task on brain functional connectivity, we did not measure effective connectivity and therefore cannot speak to the direction or causality of these effects.

Nonetheless, this study sheds light on the neural mechanisms driving avoidance in early adolescents at risk for developing anxiety. Although we did not find brain or behavioral differences based on anxiety, the findings suggest that anxious youth show altered associations between fronto-striatal functioning and risk taking, highlighting the importance of a focus on these circuits in the study of adolescent-onset anxiety. Future longitudinal work will elucidate how these brain-behavior associations impact the development of anxiety in adolescence and adulthood.

CHAPTER 3

The Interplay Between Anxiety and Approach Motivations in Adolescent Risk Taking

Introduction

The substantial brain and behavioral development that occurs in adolescence contributes to both the rise in approach behaviors such as risk-taking (Casey et al., 2008; Ernst, Pine, & Hardin, 2006) and the emergence of clinical anxiety (Gee et al., 2016; Zimmermann, Richardson, & Baker, 2019). Despite these overlapping developmental timelines, the typical phenotype of anxiety is characterized by avoidance and stands in stark contrast to the approach-motivated adolescent phenotype (Peris & Galván, 2021). As a transitionary period that serves to prepare youth for adult independence, adolescence is a pivotal trajectory point that impacts health and well-being into adulthood (Dahl, 2004). Therefore, an understanding of how risk-taking and anxiety develop in parallel and interact to influence behavior is crucial for promoting healthy development from adolescence into adulthood.

While adolescence is characterized by behavioral activation, or the motivation to *approach* a stimulus, adolescent anxiety is often preceded by behavioral inhibition characterized by fear, wariness, and avoidance of unfamiliar stimuli such as new people or situations (Fox et al., 2005). Inhibited children are almost four times as likely to develop anxiety disorders in adolescence (Chronis-Tuscano et al., 2009; Essex et al., 2010; Schwartz et al., 1999); however, not all inhibited individuals go on to develop anxiety later in life (Henderson et al., 2015). One potential reason for this may be that behavioral inhibition interacts with approach motivations during adolescence to influence behavior and symptom trajectories (A. E. Baker & Galván, 2020). Understanding this link is a critical next step understanding and preventing the development of anxiety in adolescence.

Situations involving uncertainty such as risk-taking can activate both approach and avoidance systems, causing an approach-avoidance conflict where motivations interact to influence behavior (Barker et al., 2019). While anxiety has been linked to risk aversion in adults (Sonuga-Barke et al., 2016), the heterogeneity of the disorder and its interaction with typical adolescent development adds nuance to this narrative. For example, latent class analysis in anxious adults suggests that there may be two subtypes of social anxiety—the avoidant subtype, characterized by behavioral inhibition and risk avoidance, and the approach-motivated subtype, characterized by impulsiveness, reward sensitivity, risk-taking, and substance abuse (Nicholls et al., 2014). Given the frequency of approach-avoidance conflict in adolescence, it can be hypothesized that these subtypes might emerge in adolescence and influence the development of risky behavior during this period. However, the field has yet to identify how approach motivations and anxiety interact to impact decision-making and symptom development as youth enter adolescence.

Shared neural mechanisms have been linked to adolescent risk-taking and anxiety symptoms and are therefore a key target for understanding behavioral and symptom profiles. In adolescence, subcortical brain regions signaling salience and valence such as the amygdala and the ventral striatum (VS) are especially sensitive and responsive to stimuli (Galván, 2013). Connections form and strengthen between these subcortical hubs and frontal regulatory systems as cognitive control and complex decision-making abilities improve (Casey et al., 2008). This combination of subcortical sensitivity and ongoing regulatory development in adolescence is thought to contribute to both the rise in approach behaviors such as risk-taking and the emergence of clinical anxiety.

Approach-avoidance conflict is explained neurobiologically by the Triadic model in which approach (ventral striatum; VS), avoidance (amygdala), and regulatory (prefrontal) systems interact and compete to influence response to positive and aversive cues (Ernst et al., 2009). The regulatory brain area that is most frequently implicated in decision-making under conflict or uncertainty is the dorsal anterior cingulate cortex (dACC) (B. W. Smith et al., 2009). While the VS and amygdala track value and salience, the dACC governs conflict monitoring and regulates risk-related values and behavior (Christopoulos et al., 2009; Kolling et al., 2014) and is therefore an important player in adolescent risky decision-making. The dACC has also been linked to risk-taking in anxiety: anxious adolescents demonstrating blunted dACC response during social exclusion were more likely to report substance use, suggesting that altered conflict monitoring in the dACC may drive risk-taking in anxious adolescents (Beard et al., 2022). However, the combined roles of approach motivation and anxiety on neural functioning between the VS, amygdala, and dACC has yet to be explored.

This study utilizes behavioral and fMRI data from a risky decision-making task in a sample of 127 early adolescents across a continuum of anxiety severity to examine 3 main preregistered aims. In Aim 1, we test whether self-reported sensitivity of the behavioral activation system (BAS) moderates the association between anxiety and risk-taking frequency and inhibitory control in adolescents to probe how approach motivations and anxiety interact during adolescent decision-making. As the approach-motivated substyle of anxiety has been characterized by increased impulsivity and sensation seeking, we predicted that youth with high anxiety and high BAS would show excessive risk-taking and decreased inhibitory control, while youth with high anxiety and low BAS would demonstrate risk aversion and improvements in inhibitory control. In Aim 2, we examined how individual differences in BAS and anxiety

severity relate to neural dynamics of the amygdala, VS, and dACC during task risk-taking to probe the links between individual difference measures and neural functioning during decision-making. As previous work has found increased amygdala activation in anxious youth during risky choice (Galván & Peris, 2014) and increased connectivity between the amygdala and PFC during viewing of emotional images (Poon, Thompson, & Chaplin, 2022), we predicted that higher anxiety would be associated with greater amygdala response and increased compensatory connectivity between the amygdala and the dACC during risk-taking. As BAS has been linked to heightened VS response during the receipt of rewards (Mohammadzadeh Ebrahimi, Rahimi Pordanjani, & Khorasaninia, 2015; Voigt et al., 2009), we predicted that BAS would be positively associated with VS response during risk-taking paralleled by decreased functional connectivity between the VS and dACC.

Studying neural dynamics during decision-making is important for clarifying which brain regions are involved in different processes. However, brain regions that work together during task often show associations in the absence of task, when the brain is "at rest". Examining resting-state in conjunction with task can improve reliability of results by measuring neural function across domains and help clarify the scope of influence of individual difference measures on adolescent brain function. With Aim 3, we sought to delineate the influence of these individual difference measures on brain functioning in the absence of decision-making by examining associations between the amygdala, VS, and dACC at rest. As work in adults has found decreased connectivity between the amygdala and dorsomedial prefrontal cortex at rest in anxiety (Kim, Gee, Loucks, Davis, & Whalen, 2011), we predicted that youth higher in anxiety would show decreased intrinsic functional connectivity between the amygdala and the dACC at rest. In adults, BAS has been linked to increased intrinsic connectivity between the striatum and

the orbitofrontal cortex (Angelides, Gupta, & Vickery, 2017) and between the ventral tegmental area (VTA) and prefrontal cortex (Adrián-Ventura, Costumero, Parcet, & Ávila, 2019). Therefore, we predicted that BAS would be positively correlated with intrinsic fronto-striatal connectivity at rest. Together, results from this study will shed light on the combined influence of approach motivations and anxiety on adolescent brain and behavioral functioning.

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) (B Birmaher et al., 1997). 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) (Silverman & Albano, 1996) 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 5 participants were unusable due to technical errors during data collection. fMRI data were excluded if the participant exceeded 1 mm mean relative motion during the task (1 run for 1 participant; no youth excluded) or did not have enough trials for analysis (n=14). Multiple

imputation (10 imputations) was used to account for missing questionnaire data in 6 participants. Data are presented for 127 participants (M_{Age}=11.24, SD_{Age}=1.37; 56 girls; 33.9% white, 22% Latino, 20.5% Asian, 14.2% Black, 9.4% Mixed Race; Table 3.1).

Table 3.1. Participant descriptive statistics.

	Mean (SD) or % (*N* = 127)
Age (years)	11.24 (1.37)
Sex	71M (55.9%), 56F (44.1%)
Race/ethnicity	33.9% white, 22% Latino, 20.5% Asian, 14.2% Black, 9.4% Mixed Race
Anxiety (SCARED total score)	19.06 (11.61)
Average # risky choices	14.54 (7.57)
Average # cautious choices	17.43 (8.03)
Inhibitory control (Stop RT – Go RT)	0.13 (0.06)
Average relative motion	0.24 (0.15)

Resting-state scan

Of the 127 participants with task risk-taking data, 117 also completed a resting-state fMRI scan. Data from 5 participants were unusable due to excessive motion (> 1 mm mean relative motion and/or > 5 mm mean absolute motion). Resting-state data are presented for the remaining 112 participants.

Anxiety severity

Participants completed the 41-item self-report SCARED (B Birmaher et al., 1997) as a dimensional measure of anxiety severity. They rated statements describing their 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 (Chein et al., 2011) involving making decisions at randomly presented traffic lights and trying to reach the finish line quickly to maximize monetary reward ($5; Figure 2.1). 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. Inhibitory control, or the ability to modify preplanned actions under changing task conditions, involves interconnected stop and go processes (Ma & Yu, 2016). Inhibitory control as measured in this task was calculated by subtracting average Go RT from average Stop RT for each participant, yielding a metric where higher numbers indicate longer Stop vs. Go RT and poorer inhibitory control.

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. After completing the task, participants underwent an 8-minute resting-state fMRI sequence (TR=800 ms, TE=37 ms, FOV=208 mm, 72 slices, slice thickness 2 mm, in-plane voxel size 2x2 mm, interleaved). A single-band reference (SBRef) image was acquired immediately before each functional sequence.

fMRI preprocessing

AP and PA field map images were combined using FSL's topup (Andersson et al., 2003) 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. FEAT V6 within FSL (FMRIB Software Library; https://fsl.fmrib.ox.ac.uk/fsl/) (S. M. Smith et al., 2004) was used for task fMRI 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. 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.

Resting-state preprocessing steps included non-brain removal using FSL BET and spatial smoothing using a Gaussian kernel of FWHM 6 mm. Rigid body motion correction with 6° of freedom was performed using MCFLIRT. 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. To remove potential confounds resulting from head motion, data were next denoised using Independent Component Analysis (ICA)-based Automatic Removal of Motion Artifacts (ICA-AROMA; Pruim et al., 2015). ICA-AROMA is a highly effective method for addressing head motion when compared to 18 other commonly employed denoising pipelines (Parkes, Fulcher, Yücel, & Fornito, 2018). Data were then high-pass filtered (100-s cutoff), and white matter and cerebrospinal (CSF) masks for each participant were created using FSL's Automatic Segmentation Tool (FAST).

Behavioral analysis

Moderation

Simple moderation analyses were performed using Model 1 of Hayes' PROCESS macro for SPSS (Hayes, 2012). Statistics were estimated using a bootstrapping method with 5000 samples, and significance was determined with 95% bias-corrected confidence intervals. Significant interactions were depicted using -1 SD, mean, and +1 SD as plotted values of the moderator (Aiken & West, 1991).

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 4 contrasts of interest: Risky vs. Baseline, Cautious vs. Baseline, Risky vs. Cautious, and (Risky + Cautious) vs. Baseline, chosen with the aim of identifying the neural correlates of risky decision-making across Risky and Cautious 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 (Beckmann et al., 2003). 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 (Poline et al., 1997). 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/).

Region-of-interest analysis

As the amygdala and the VS both have well-defined anatomical boundaries, seeds for these regions were created using the Harvard-Oxford subcortical probabilistic atlas thresholded at 50% probability. The dACC, on the other hand, is a large structure with less clearly defined boundaries. For the purposes of this study, our interest in the dACC came from its role in conflict processing during decision-making. Therefore, in the pre-registration for this study, we stated that we would choose an area of the dACC that had been most closely associated with conflict processing as determined using a meta-analysis of 337 studies involving the term "conflict" as generated from Neurosynth (https://neurosynth.org/analyses/terms/conflict/). To ensure that our seed was indeed located in the dACC, we used a conjunction map of the Neurosynth meta-analysis results and the Harvard-Oxford cortical probabilistic atlas of the dACC to pick center coordinates ($x = 0$, $y = 14$, $z = 34$). A 10-mm sphere was then created around this center. Amygdala, VS, and dACC seeds were all binarized before use.

Functional connectivity

Beta series correlation analyses (Rissman et al., 2004) were conducted in FSL to examine differences in functional connectivity between the amygdala, VS, and dACC across task conditions. For each run, one GLM was defined for Risky trials and another for Cautious 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 and registered to standard space, after which timeseries were extracted from the amygdala, VS, and dACC and correlated with one another using 1ddot in AFNI (https://afni.nimh.nih.gov/pub/dist/doc/program_help/1ddot.html). Correlation coefficients were Fisher transformed for use in group analysis.

Exploratory Analysis: Representational Similarity

Results from the second chapter of this dissertation suggest that striatal connectivity may contribute to risk-taking differently based on anxiety severity. In an exploratory (not pre-registered) analysis of striatal functional connectivity during risk-taking, we assessed neural similarity between Risky and Cautious decisions and its relationship with BAS and anxiety. To do this, parameter estimates from the VS timeseries were 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) for both Risky and Cautious conditions to generate whole-brain striatal connectivity maps for each subject for each condition. Next, we computed the voxel-wise dot-product between the whole-brain striatal connectivity maps for Risky and Cautious conditions using 3ddot in AFNI (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3ddot.html). Correlation coefficients were Z-transformed and used as the dependent variable in a multiple regression analysis with anxiety, BAS, age, and sex as predictor variables.

Table 3.2. Correlations between main study variables. †< .01, *p< .05, **p< .01, ***p<.001.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Anxiety	1															
2. BAS	.07	1														
3. Age	.13	.07	1													
4. Female sex	.19*	-.04	.04	1												
5. Risk-taking frequency	-.06	-.01	.01	-.32***	1											
6. Inhibitory control	-.10	-.05	-.09	-.20*	.47***	1										
Risky-Cautious																
7. Amy-dACC	.18*	-.16†	.02	.06	.17*	.09	1									
8. VS-dACC	-.08	.28**	-.04	.08	-.04	.12	.18*	1								
9. Amy-VS	-.18*	.11	-.06	-.05	.05	-.12	-.06	-.32***	1							
Risky+Cautious																
10. Amy-dACC	.27**	-.03	.02	.08	.05	.08	.72***	.10	-.02	1						
11. VS-dACC	.04	-.14	-.08	.07	.01	.16†	.08	.66***	-.18*	.18*	1					
12. Amy-VS	-.16†	.03	-.13	-.14	.02	-.17†	.10	-.11	.69***	-.01	-.24**	1				
Resting State																
13. Amy-dACC	-.14	-.04	-.20*	-.11	.05	.14	.04	.10	-.07	.06	.08	.11	1			
14. VS-dACC	-.07	.16†	-.07	-.10	-.12	.00	.09	.09	.03	.01	.01	.17†	.35***	1		
15. Amy-VS	-.02	.28**	.00	-.15	.00	.12	.02	.05	-.06	.04	.14	-.04	.17†	.18†	1	
Risky vs. Cautious																
16. Neural similarity	-.23**	-.07	.06	-.16†	.04	.03	.01	.01	.01	-.08	-.01	.10	.10	-.01	-.20*	1

Results

Behavioral results

BAS and the anxiety-risk relation

A simple moderation analysis using anxiety as the focal predictor, BAS total score as the moderator, risk-taking frequency as the outcome variable, and age and sex as covariates revealed that BAS significantly moderated the effect of anxiety on risk-taking behaviors (β = .25, p = .013; Fig. 3.1a). The positive slope of this interaction term suggests that as BAS increases, the effect of anxiety on risk-taking frequency becomes more positive (i.e., youth with high anxiety and high BAS show *increased* risk-taking rather than risk aversion).

BAS and the anxiety-inhibitory control relation

A simple moderation analysis using anxiety as the focal predictor, BAS total score as the moderator, inhibitory control as the outcome variable, and age and sex as covariates revealed that BAS significantly moderated the effect of anxiety on inhibitory control (β = .30, p = .003; Fig. 3.1b). Higher values of inhibitory control indicate more difficulty inhibiting when instructed. The positive slope of this interaction term suggests that as BAS increases, the effect of anxiety on inhibitory control becomes more positive (i.e., youth with high anxiety and high BAS show *impaired* rather than improved inhibitory control). Importantly, risk-taking frequency and inhibitory control were tightly correlated ($r(127)=.47$, $p<.001$) in this sample, suggesting that these two facets of adolescent behavior are intertwined.

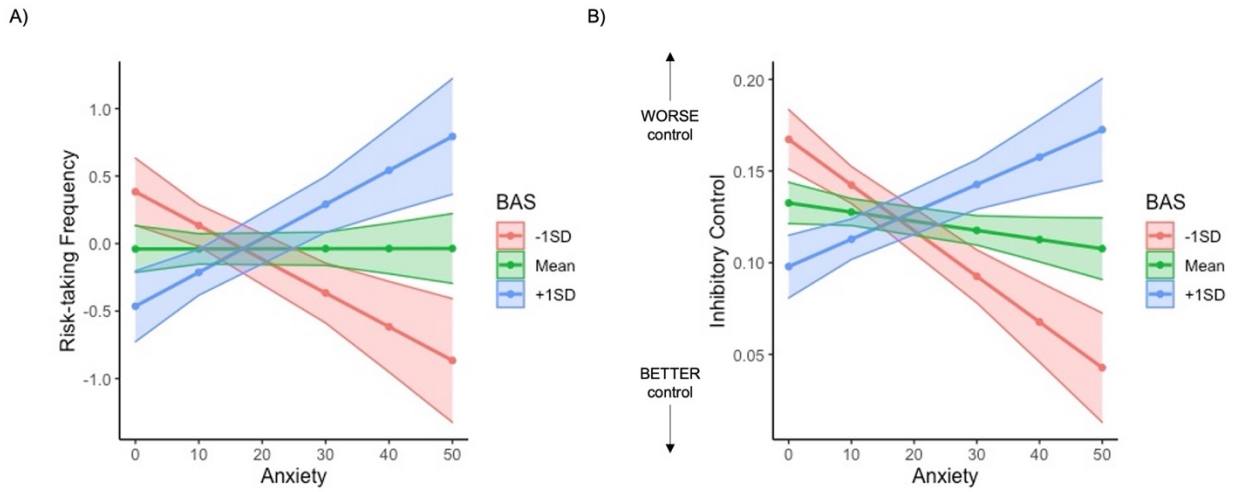

Figure 3.1. BAS moderates the association between anxiety and a) risk-taking frequency and b) inhibitory control. BAS = behavioral activation system sensitivity.

fMRI results

Whole-brain activation

Whole-brain GLM analysis of the Risky>Cautious contrast revealed activation of the occipital pole, lingual gyrus, cuneal and precuneus cortex, intracalcarine cortex, and thalamus, while the Cautious>Risky contrast revealed activation of the caudate, putamen, angular gyrus, lateral occipital cortex (LOC), postcentral and supramarginal gyri, and superior frontal gyrus (Figure 3.2, Table 3.3).

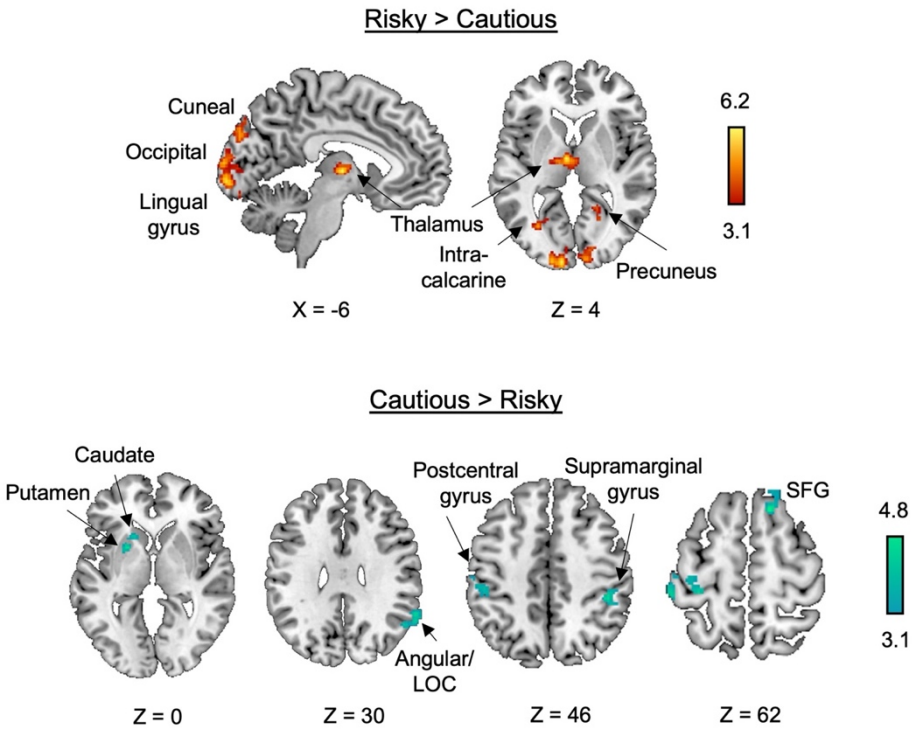

Figure 3.2. Whole-brain neural activation during Risky vs. Cautious. Cluster-corrected at $Z>3.1$, $p<.05$. LOC = lateral occipital cortex; SFG = superior frontal gyrus.

Table 3.3. Neural activation during Risky vs. Cautious.

Region label	**Peak MNI coordinates**			***Z*-max**	**Voxels (mm^3)**
	x	***y***	***z***		
a. Regions showing significant activation for Risky > Cautious					
L occipital pole	-12	-98	0	6.16	894
R occipital pole	14	-96	-2	5.11	887
R lingual gyrus	24	-40	-14	4.67	162
L thalamus	-6	-10	4	5.14	130

L temporal occipital fusiform cortex	-44	-54	-16	4.32	85
L intracalcarine cortex	-20	-72	8	4.43	77
b. Regions showing significant activation for Cautious > Risky					
L postcentral gyrus	-50	-32	62	4.11	208
L postcentral/precentral gyrus	-38	-26	68	4.22	116
R angular gyrus	62	-50	28	4.21	105
R supramarginal gyrus	44	-36	46	4.39	93
L putamen	-22	8	0	4.5	89
L caudate	-16	18	0	3.91	
R superior frontal gyrus	14	22	62	4.76	67

Region-of-interest activation

We hypothesized associations between anxiety and amygdala reactivity and BAS and VS reactivity during risk-taking. Therefore, to specifically assess activation of the amygdala and VS during risky decision-making, parameter estimates were extracted from both regions using the same structural seeds as used in the connectivity analyses. However, neither BAS nor anxiety was significantly associated with VS or amygdala activation during risk-taking ($r_{BAS,VS}(127) = .01$, $p = .91$; $r_{Anx,Amy}(127) = -.14$, $p = .12$).

Functional connectivity

Seed-based connectivity analyses resulted in two estimates of amygdala-dACC, VS-dACC, and amygdala-VS communication for each participant: one for Risky and Cautious trials

combined that signified average connectivity during risky decision-making, and one for Risky minus Cautious that signified differences in connectivity between the two decision conditions. MPlus version 8.2 (Muthén & Muthén, n.d.) was used to fit a model with seed-based connectivity estimates for each subject. Connectivity estimates were allowed to covary within participants and regressed on anxiety, BAS, age, sex, and mean relative motion during the fMRI task (Table 3.4). Risk-taking frequency and inhibitory control were also added to the model and regressed on anxiety, BAS, the anxiety*BAS interaction, age, and sex. Good model fit was assessed using the following criteria (Hu & Bentler, 1999): nonsignificant chi-square test of model fit, comparative fit index (CFI) greater than or equal to .95, Tucker–Lewis index (TLI) greater than or equal to .95, root mean squared error of approximation (RMSEA) less than or equal to .06, and standardized root mean squared residual (SRMR) less than or equal to .08. The model demonstrated excellent fit ($\chi^2(38, N = 127) = 35.03$, $p = .61$; RMSEA = 0.00; CFI = 1, TLI = 1.02; SRMR = 0.05).

Table 3.4. Model results for the Driving Game.

	Estimate (S.E.)	p-value
Risk-taking frequency ON		
Anxiety	-0.01 (0.09)	.878
BAS	0.04 (0.09)	.668
Anxiety*BAS	0.20 (0.09) *	.019
Age	0.05 (0.08)	.583
Female sex	-0.30 (0.08) ***	.000
Inhibitory control ON		
Anxiety	-0.06 (0.09)	.472
BAS	0.02 (0.10)	.863
Anxiety*BAS	0.22 (0.10) *	.020
Age	-0.04 (0.09)	.630
Female sex	-0.17 (0.09) *	.046
Risky - Cautious		
Amy-dACC ON		
Anxiety	0.18 (0.09) *	.032

BAS	-0.18 (0.09) *	.035
Age	-0.01 (0.09)	.910
Female sex	-0.01 (0.09)	.872
Motion	-0.13 (0.09)	.135
VS-dACC ON		
Anxiety	-0.07 (0.09)	.399
BAS	-0.25 (0.09) **	.003
Age	-0.04 (0.09)	.662
Female sex	0.06 (0.09)	.535
Motion	-0.12 (0.09)	.163
Amy-VS ON		
Anxiety	-0.18 (0.09) *	.040
BAS	0.12 (0.09)	.155
Age	-0.05 (0.09)	.601
Female sex	-0.01 (0.09)	.928
Motion	-0.01 (0.09)	.930
Risky + Cautious		
Amy-dACC ON		
Anxiety	0.27 (0.09) **	.001
BAS	-0.06 (0.09)	.508
Age	-0.03 (0.09)	.689
Female sex	-0.01 (0.09)	.907
Motion	-0.15 (0.09)	.087
VS-dACC ON		
Anxiety	0.05 (0.09)	.567
BAS	-0.13 (0.09)	.146
Age	-0.08 (0.09)	.358
Female sex	0.06 (0.09)	.549
Motion	0.01 (0.09)	.925
Amy-VS ON		
Anxiety	-0.13 (0.09)	.134
BAS	0.05 (0.09)	.580
Age	-0.11 (0.09)	.207
Female sex	-0.11 (0.09)	.216
Motion	-0.03 (0.09)	.741

Resting-state fMRI results

To assess the role that anxiety and BAS play on intrinsic functional connectivity in adolescence, the same circuits were next examined during a resting-state fMRI scan. The model demonstrated acceptable fit ($\chi^2(7, N = 112) = 10.23$, $p = .18$; RMSEA = 0.06; CFI = .96, TLI = .74; SRMR = 0.04; Table 3.5). Model results revealed significant positive associations between

BAS and both VS-dACC and Amy-VS connectivity at rest. However, contrary to hypotheses, anxiety did not show significant associations with functional connectivity at rest. Given prior literature, we had hypothesized that youth with higher anxiety would show reduced amygdala-dACC connectivity at rest. Although there were no main effects of anxiety on amygdala-dACC connectivity, there was a significant interaction between age and anxiety on amygdala-dACC connectivity such that older age was associated with decreased amygdala-dACC coupling *except* in youth with high anxiety, who evinced relatively low amygdala-dACC coupling at rest regardless of their age (Figure 3.3). This suggests that anxiety may interfere with normative developmental trends in amygdala-dACC connectivity, although longitudinal data are necessary for truly assessing developmental change.

Table 3.5. Model results for Resting State.

	Estimate (S.E.)	p-value
Resting State		
Amy-dACC ON		
Anxiety	-0.11 (0.09)	.211
BAS	0.02 (0.09)	.816
Age	-0.14 (0.09)	.113
Female sex	-0.06 (0.09)	.500
Motion	0.17 (0.09)	.071
Anxiety*Age	0.22 (0.09) *	.014
VS-dACC ON		
Anxiety	-0.04 (0.09)	.544
BAS	0.19 (0.09) *	.028
Age	-0.07 (0.09)	.385
Female sex	-0.07 (0.09)	.363
Motion	0.06 (0.09)	.558
Amy-VS ON		
Anxiety	-0.00 (0.09)	.980
BAS	0.30 (0.09) **	.001
Age	-0.03 (0.09)	.710
Female sex	-0.11 (0.09)	.211
Motion	0.11 (0.09)	.242

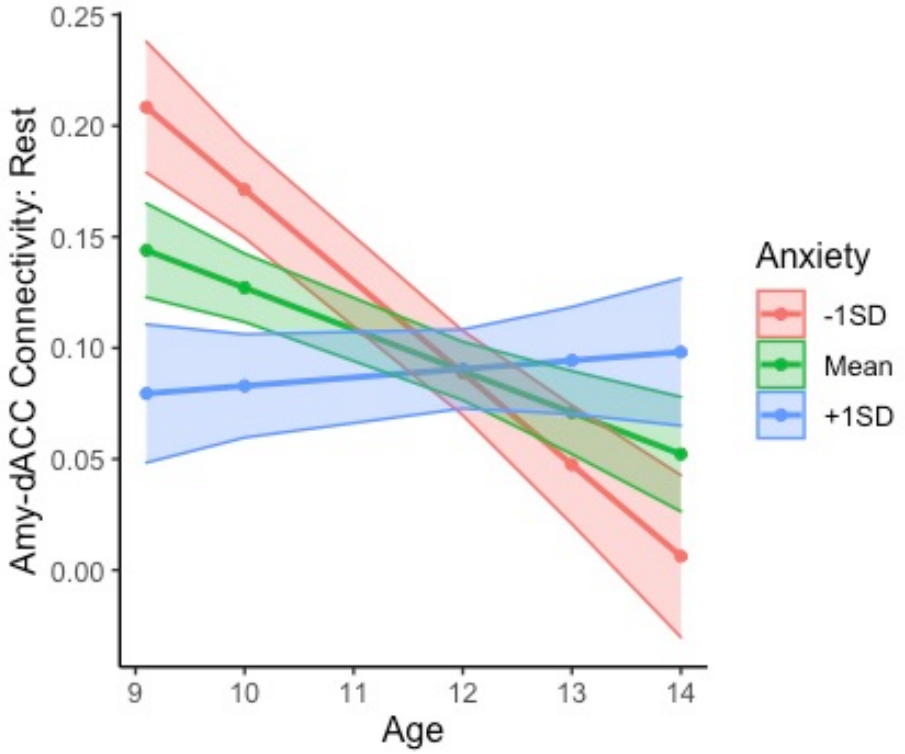

Figure 3.3. Youth with higher anxiety do not show age-related decreases in amygdala-prefrontal coupling at rest. dACC = dorsal anterior cingulate cortex.

Exploratory Analysis: Representational Similarity

Results from the analyses so far suggest anxiety and BAS show associations with amygdala-striatal-dACC connections during risky decision-making, while only BAS shows associations with VS connectivity at rest. However, results from the second chapter of this dissertation suggest that striatal connectivity patterns during risky decision-making may differentially contribute to risk-taking frequency depending on youth anxiety. Therefore, in an exploratory analysis, we next probed whether BAS and anxiety relate to striatal connectivity patterns during Risky versus Cautious choices. Using individual subject-level striatal connectivity maps, we computed the similarity of striatal connectivity patterns during Risky decisions to striatal connectivity patterns during Cautious decisions and found that anxiety, but

not BAS, was significantly associated with neural similarity between Risky and Cautious choices such that youth higher in anxiety showed more neural differentiation between Risky and Cautious choices, while youth lower in anxiety represented the two events more similarly (Figure 3.4).

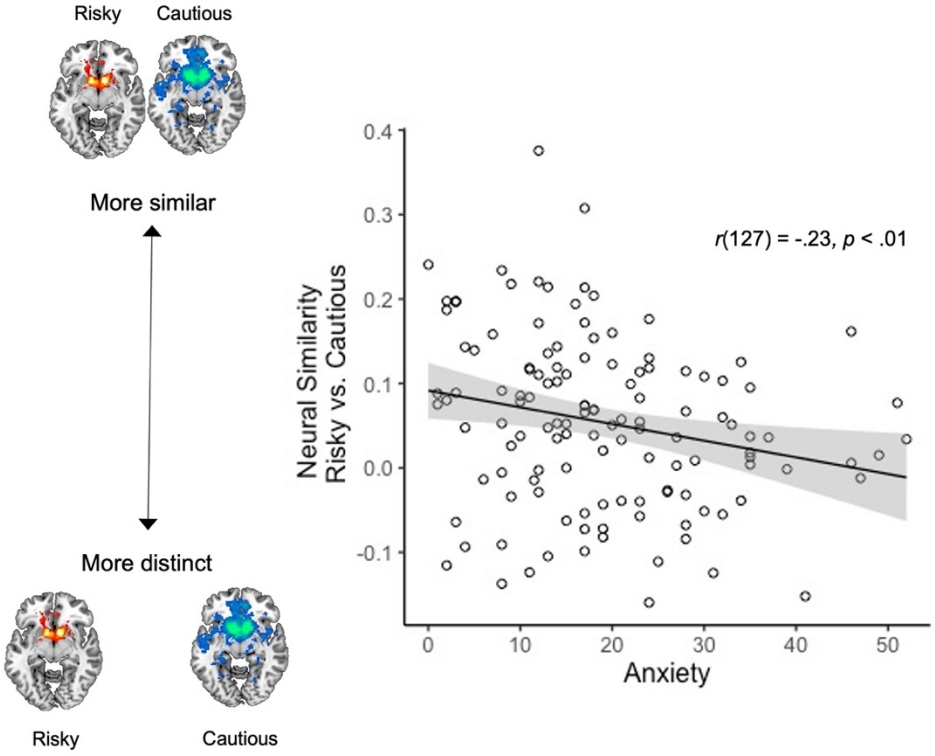

Figure 3.4. Anxiety is negatively associated with degree of overlap in whole-brain striatal connectivity patterns during Risky versus Cautious decisions. While adolescents with lower levels of anxiety showed similar striatal connectivity patterns across Risky and Cautious decisions, adolescents with higher anxiety showed more neural differentiation in striatal connectivity patterns during Risky and Cautious decisions, suggesting that striatal connectivity patterns may encode different aspects of decision situations depending on adolescent anxiety**.** r = Pearson correlation coefficient.

Discussion

In this chapter, we examined how anxiety and approach motivations influence adolescent risk-taking behaviors, inhibitory control processes, neural response during risk-taking, and intrinsic connectivity patterns at rest. As we hypothesized, sensitivity of the behavioral activation system (BAS) moderated the association between anxiety and task risk-taking such that youth with high anxiety and low BAS were risk-averse, while youth with high anxiety and high BAS were high risk-takers. This effect was also found with inhibitory control: high anxiety was beneficial for inhibitory control in youth with low BAS but was associated with poorer inhibitory control in youth with high BAS. In the brain, higher BAS sensitivity was associated with decreased prefrontal regulation of the amygdala and striatum during Risky versus Cautious choice paralleled by increased communication between these regions at rest, highlighting the role of approach motivations on neural functioning in adolescence. Conversely, higher anxiety was associated with heightened amygdala-prefrontal communication during risky decision-making and showed an interaction with age on amygdala-prefrontal communication at rest. Overall, results from this study shed light on the interplay between approach motivations and anxiety on decision-making and neural functioning in adolescence.

Although anxiety is often characterized by avoidant behavior, previous research has actually found evidence for two subtypes of anxiety—one characterized by risk aversion and avoidance and the other by risk-taking and impulsivity (Nicholls et al., 2014). Results from this study support this hypothesis by demonstrating that the influence of anxiety on risk-taking behaviors and associated metrics (e.g., inhibitory control) in adolescents may depend on individual differences in approach motivations. In the current sample of early adolescents, youth who reported high anxiety but low BAS sensitivity demonstrated risk aversion, while youth

scoring high on both anxiety and BAS sensitivity took an above-average amount of risks during the fMRI task. This pattern was also observed with inhibitory control, or the ability to switch from going to stopping when instructed: higher anxiety was associated with better inhibitory control only in youth with low BAS, whereas it was associated with worse inhibitory control in youth with the highest BAS. As inhibitory control and risk-taking frequency were tightly related in this task, it is possible that the combination of high anxiety and high BAS on neural functioning in adolescent has downstream effects on their inhibitory control, which then leads to increases in risk-taking behaviors. Future work will be important for probing the directionality of these effects over development.

Risky decision-making and anxiety development in adolescents have both been linked to functioning of the amygdala, ventral striatum (VS), and prefrontal cortex (PFC). Therefore, to probe how individual differences in anxiety and risk-related traits (e.g., approach motivations) relate to neural functioning during decision-making, we next tested whether individual differences in BAS and anxiety severity relate to communication between these brain regions during task risk-taking. As previous work has found increased amygdala activation in anxious youth during risky choice (Galván & Peris, 2014) and increased connectivity between the amygdala and PFC during viewing of emotional images (Poon et al., 2022), we predicted that higher anxiety would be associated with greater amygdala response and increased amygdala-PFC connectivity during risk-taking. Results from this chapter suggest that anxiety was not associated with heightened amygdala activation during risk-taking in this sample; however, anxiety was positively associated with amygdala-PFC connectivity during risky decision-making, suggesting that compensatory prefrontal regulation of the amygdala may have allowed anxious youth to take risks. With this line of thinking, perhaps the increased amygdala-PFC connectivity successfully

inhibited the amygdala, explaining the lack of association between anxiety and amygdala activity in this sample. Additionally, while youth in this study varied in anxiety symptoms, most participants did not reach clinical threshold for an anxiety disorder. As such, it is possible that heightened amygdala activation during risk-taking would be observed in a clinical sample.

As BAS has been linked to heightened VS response during the receipt of rewards (Mohammadzadeh Ebrahimi et al., 2015; Voigt et al., 2009), we predicted that BAS would be positively associated with VS response during risk-taking paralleled by decreased top-down regulation of the VS by the prefrontal cortex. Our activation hypotheses were not confirmed: BAS showed no association with VS activity during risky decision-making. However, higher BAS sensitivity was directly linked to decreased communication between the prefrontal cortex and the amygdala and VS during risky decision-making, suggesting that individual differences in adolescent approach motivations may impact neural communication between regions over and above reactivity of these regions.

Brain regions that work together during task often show associations in the absence of task, or when the brain is "at rest". Examining resting-state in conjunction with task-based fMRI can improve reliability by measuring neural function across domains and help clarify the scope of influence of individual difference measures on adolescent brain function. Given prior work (Adrián-Ventura et al., 2019; Angelides et al., 2017; Iadipaolo et al., 2017), we predicted that the reduced fronto-striatal connectivity evinced by youth with high BAS sensitivity during risk-taking would be paralleled by greater intrinsic fronto-striatal connectivity at rest, highlighting the frequent communication between these regions in approach-motivated individuals. Consistent with these hypotheses, we found that youth reporting higher BAS sensitivity showed greater fronto-striatal and amygdala-striatal connectivity at rest, suggesting that individual differences in

approach motivations are directly associated with intrinsic functioning of these circuits in adolescence.

While anxiety and BAS were both related to amygdala-PFC connectivity during task risk-taking, neither showed main effects on amygdala-PFC connectivity at rest. However, there was a significant interaction between age and anxiety on amygdala-prefrontal connectivity such that older age was associated with decreased amygdala-PFC coupling *except* in youth with high anxiety, who evinced relatively low amygdala-PFC coupling at rest regardless of their age. Previous work suggests that the typical developmental trajectory of amygdala-prefrontal intrinsic connectivity is characterized by positive amygdala-PFC coupling in childhood that begins to resemble the adult-like phenotype of negative coupling in adolescence (Gee, Humphreys, et al., 2013). However, early-life stress such as maternal deprivation can lead to earlier maturation of these circuits, with affected youth showing negative amygdala-PFC coupling earlier in childhood (Gee, Gabard-Durnam, et al., 2013). As age-related decreases in amygdala-PFC coupling were observed in all youth except those with high anxiety in the current sample, it is possible that anxiety and anxiety-related stress also leads to earlier maturation of amygdala-PFC circuits, although longitudinal data will be necessary for truly assessing developmental change.

It has been proposed that developmental changes in threat learning and threat generalization contribute to the development of anxiety in adolescence (Britton et al., 2013; Lau et al., 2011), while developmental changes in reward learning and risk tolerance have been used to explain the development of risky decision-making in adolescence. Neuroimaging studies commonly employ univariate methods that are helpful for understanding mean differences in brain response to different stimuli; however, these methods are not well suited for addressing questions regarding how the brain distinguishes between or generalizes across stimuli in

adolescence. A promising approach for tackling these types of generalization and representation questions is representational similarity analysis (RSA) (Kriegeskorte, Mur, & Bandettini, 2008) in which we leverage information contained in the *patterns* of activity across multiple voxels of the brain to characterize the unique neural representation of a stimulus. With this method, the similarity or dissimilarity of patterns is used to assess which representations of stimuli are alike and which diverge, allowing for a more nuanced examination of brain response that considers patterns of activity across regions. This approach has proven useful for delineating how the brain distinguishes between threat and safety in youth with and without anxiety (Glenn, Fox, Pine, Peters, & Michalska, 2020) and therefore seems a promising approach for parsing how the same brain regions encode decisions involving varying levels of risk and reward.

Findings from Study 1 of this dissertation revealed that VS connectivity was correlated with risk avoidance in youth with high anxiety and risk taking in youth with low anxiety, suggesting that VS connectivity with the rest of the brain during risky decision-making may encode both approach and avoidance motivations depending on anxiety levels. Therefore, we conducted an exploratory analysis using RSA to examine whether anxiety and approach motivations related to the degree of overlap in striatal connectivity patterns during Risky and Cautious decisions. We found that anxiety, but not BAS, was related to the degree of overlap between Risky and Cautious whole-brain striatal connectivity patterns. Specifically, adolescents with lower anxiety showed more overlap in striatal connectivity patterns during Risky and Cautious decisions, suggesting that the striatal processes going into risky decision-making in typically developing adolescents may be similar regardless of the ultimate decision reached. On the other hand, anxious adolescents showed more divergence in striatal connectivity patterns

during Risky and Cautious choices, suggesting that striatal connectivity may encode different aspects of decision situations depending on anxiety levels.

Along with the results from Study 1, these findings suggest that the striatal mechanisms contributing to risky decision-making in typically developing adolescents may show different associations with behavior in adolescents with anxiety. As the striatum is an important region for assessing expected value, it is possible that striatal connectivity during risky decision-making was indexing expected value of choice in lower anxious youth (relatively equal across Risky and Cautious choices) while indexing relative risk of choice in higher anxious youth. Of note, BAS sensitivity was not associated with neural similarity to Risky vs. Cautious, suggesting that while approach motivations may relate to mean differences in connectivity between brain regions, anxiety may have a greater impact on the multivariate representations of decisions themselves. Results of this exploratory analysis suggest that assessing whole-brain neural representations of events may be a fruitful line of research for understanding how anxiety shapes decision-making in adolescents.

These findings should be interpreted in the context of several limitations. First, these analyses are cross-sectional, limiting the ability to make causal inferences about the effects of anxiety or approach motivations on risk-taking or neural functioning. Additionally, while we did uncover effects of task on brain functional connectivity, we did not measure effective connectivity and therefore cannot speak to the direction or causality of these effects. Future research will be important for identifying how the dynamics of these neural circuits relate to anxiety and approach motivations in adolescents.

Nonetheless, this study sheds important light on the mechanisms by which anxiety and approach motivations impact risky decision-making in adolescents. Findings of this chapter

suggest that anxiety and approach motivations interact to influence risk-taking and inhibitory control and demonstrate distinct associations with amygdala-striatal-prefrontal communication during risk-taking and at rest. Even further, despite engaging in similar frequency of risk-taking as their peers, anxious youth showed greater whole-brain striatal differentiation between Risky and Cautious choices, highlighting the value of considering multivariate patterns of neural response in the study of adolescent-onset anxiety. Future longitudinal work is needed to elucidate how these brain-behavior associations impact the development of anxiety in adolescence and adulthood.

CHAPTER 4

Shared Neural Mechanisms Underlie the Development of Anxiety and Risk Taking in Adolescence

Introduction

The combination of subcortical sensitivity and ongoing regulatory development in the adolescent brain is thought to contribute to both the rise in approach behaviors such as risk taking and the emergence of clinical anxiety often observed during this period (Casey & Jones, 2010; Galvan et al., 2006). Despite these shared mechanisms, the field has primarily studied these two facets of adolescent development—namely, risk taking and anxiety—in isolation, precluding the opportunity to understand how brain and behavioral development contributes to *both* phenotypes during this period and identifying factors that promote healthy development across decision making and mental health domains. Here, we shed light on these open questions by examining how the neural circuits governing approach and avoidance behaviors in adolescence contribute to risky decision-making and anxiety symptoms in 106 children and adolescents.

Learning to avoid situations that trigger fear is a cardinal symptom of anxiety disorders that conflicts with the normative adolescent propensity for heightened approach behavior (Galván, 2013) and may be especially resistant to extinction during this period of development. In avoidance learning, an individual learns to avoid an aversive stimulus prior to the onset of the stimulus (Hofmann & Hay, 2018) which can prove useful for momentary reductions in anxiety and even give adolescents a feeling of control and safety that may have uses in therapy (Hofmann & Hay, 2018). However, over time, avoidance can become habitual and resistant to extinction, especially in adolescents (Klein, Shner, Ginat-Frolich, Vervliet, & Shechner, 2020).

In both human and animal models, adolescents show impairments in fear extinction (K. D. Baker, Bisby, & Richardson, 2016; K. D. Baker, Den, Graham, & Richardson, 2014). Compared to adults, adolescents demonstrate increased fear generalization and elevated fear responses to safety during avoidance learning (Klein, Berger, Vervliet, & Shechner, 2021; Klein et al., 2020), leading to greater vulnerability to persistent or habitual avoidance. Research suggests this overgeneralization of fear is moderated by trait anxiety in adolescents but not adults, suggesting that anxiety and avoidance learning may be especially linked in adolescence (Klein et al., 2020).

According to the Triadic Model of adolescent motivated behavior, heightened sensitivity of the ventral striatum (VS) coupled with still-developing regulatory systems in adolescence will bias behavior towards approach responses in the face of an approach-avoidance conflict (Ernst et al., 2009). However, anxiety symptoms may interact with this bias to promote inhibitory behaviors in vulnerable youth. Although studies of anxiety and avoidance often focus on the amygdala (Burghy et al., 2012; Pine, 2007), the striatum and its connections are also crucial for avoidance learning (Delgado et al., 2008) and play a critical role in adolescent anxiety (Bar-Haim et al., 2009; Benson et al., 2014; Guyer et al., 2012, 2006). While the amygdala shapes avoidance processes by sending evaluative signals through its direct projections to the ventral striatum, the ventral tegmental area (VTA)-ventral striatal dopaminergic pathway is responsible for controlling avoidance action selection processes (Anstrom, Miczek, & Budygin, 2009; Tian & Uchida, 2015). As avoidance becomes persistent or habitual, the involvement of the amygdala decreases further, with avoidance instead correlating with activity in the striatum and prelimbic cortex (or dorsal anterior cingulate cortex (dACC) in humans) (Bravo-Rivera et al., 2015). The striatum is also important for assessing safety: rats with striatal lesions show specific impairments in rapid uncertainty-safety discrimination, a skill that is necessary for survival and

disrupted in clinical anxiety (Ray et al., 2020). While these circuits have yet to be tested in adolescent rodents, it is possible that the plasticity and continued development of fronto-striatal circuits, as well as their connections with the amygdala, contribute to both the tolerance of uncertainty and increase in risk-taking as well as impairments in fear extinction and avoidance learning observed during adolescence (Tymula et al., 2012).

It has been proposed that developmental changes in threat learning and threat generalization contribute to the development of anxiety in adolescence (Britton et al., 2013; Lau et al., 2011). On the other hand, developmental changes in reward learning and risk tolerance have been used to explain the development of risky decision-making in adolescence. While neuroimaging studies commonly employ univariate methods that are helpful for understanding mean differences in brain response to different stimuli, these methods are not well suited for addressing questions regarding how the brain distinguishes between or generalizes across stimuli in adolescence. A promising approach for tackling these types of generalization and representation questions is representational similarity analysis (RSA) (Kriegeskorte et al., 2008) in which we leverage information contained in the *patterns* of activity across multiple voxels of the brain to characterize the unique neural representation of a stimulus. With this method, the similarity or dissimilarity of patterns is used to assess which representations of stimuli are alike and which diverge, allowing for a more nuanced examination of brain response that considers patterns of activity across regions. This approach has proven useful for delineating how the brain distinguishes between threat and safety in youth with and without anxiety (Glenn et al., 2020) and therefore seems a promising approach for parsing subtle differences in approach to decision situations involving varying levels of risk and reward. As the neural circuits involved in anxiety and decision-making overlap, an approach that considers whole-brain representations of events

may be especially sensitive to differences in neural computations. For example, adolescents who show worsening anxiety over time may exhibit an overgeneralization across decision situations involving inhibition or safety regardless of potential rewarding outcomes. While avoiding a loss is always beneficial, avoiding a situation involving potential reward can preclude learning and positive outcomes. Therefore, greater similarity between neural response during risk avoidance and loss avoidance would suggest less of an emphasis on outcome weighing or conflict processing and more habitual avoidance in the higher anxiety group. On the other hand, a bias towards approach behavior in adolescence may be represented by generalization across approach and avoidance decisions in situations involving potential reward, highlighting the similar neural computations involved in assessing potential outcomes regardless of the decision reached. Characterizing these shifts in neural processing and their downstream effects on behavior would give the field important insight on how anxiety and motivated behavior develop reciprocally during adolescence and would help distinguish adaptive from maladaptive avoidance behaviors.

Chapter 4 helps fill this gap in the literature by examining developmental changes in anxiety symptoms and decision-making in adolescents over the course of 1-3 years depending on the COVID-19 pandemic. In this chapter, we use multiple complementary approaches to characterize longitudinal change over two timepoints. In Aim 1, we assess change in anxiety, decision-making, and neural metrics by calculating difference scores between the time points and conducting *t*-tests to determine which measures changed significantly between time points. In Aim 2, we conduct whole-brain activation and connectivity analyses to identify how neural response during decision-making relates to these difference scores, as well as employing RSA to test for differences in representations of approach and avoidance decisions and the role of approach-avoidance conflict in adolescent decision-making. In Aim 3, we employ multivariate

latent change score modeling to examine how change in different facets of adolescent development relate to each other over time.

Methods and Materials

Participants

Year 1 sample

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) (B Birmaher et al., 1997). 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) (Silverman & Albano, 1996) with a clinician trained to criterion.

Year 2 sample

108 participants returned to UCLA for their Year 2 assessment approximately 1.3 years following their Year 1 assessment. Roughly half the sample (57/108) completed their Year 2 assessment prior to the COVID-19 shutdown, while the other half (51/108) returned once data collection was continued after the shutdown, although the two groups did not differ significantly in amount of time between assessments ($t(106) = -1.28$, $p = .20$). Of the 108 returning participants, 2 participants moved more than 1 mm mean relative motion (as determined via

motion parameters output from FSL's MCFLIRT) and were therefore excluded from analyses. Data are presented for the remaining 106 participants (M_{Age}=12.6, SD_{Age}=1.48; 46 girls; 34.9% white, 23.6% Latino, 19.8% Asian, 13.2% Black, 8.5% Mixed Race; Table 4.1).

Anxiety severity

Participants completed the 41-item self-report SCARED (B Birmaher et al., 1997) 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. SCARED scores at Time 2 ranged from 0-54 (M_{Anx} =14.76, SD_{Anx} =11.56; Figure 4.1), with higher scores indicating greater anxiety severity.

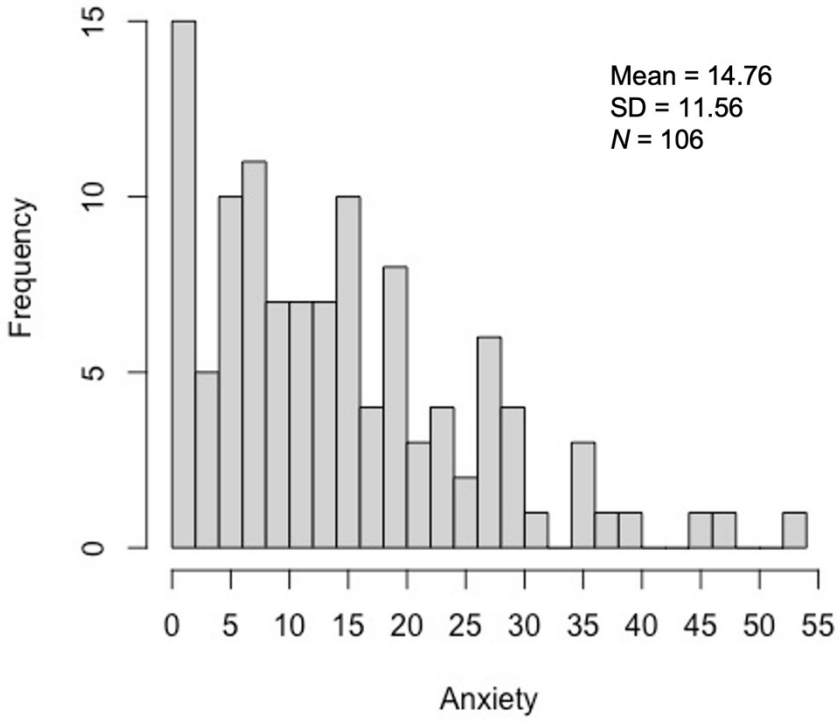

Figure 4.1. Histogram of total anxiety symptom severity scores on the SCARED at Year 2.

Note: a SCARED score ≥ 18 indicates elevated anxiety symptoms and risk for future disorder, while a score ≥ 25 may indicate the presence of an anxiety disorder.

Approach and avoidance motivations

Approach and avoidance motivations were assessed using the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales (Carver & White, 1994) designed to measure two motivational systems: the behavioral inhibition system (BIS), which corresponds to motivation to avoid aversive outcomes, and the behavioral activation system (BAS), which corresponds to motivation to approach goal-oriented outcomes. Participants responded to 24 questions on a 4-point Likert scale ranging from 1 (*very true for me*) to 4 (*very false for me*).

Adolescent decision-making

Participants also completed the 30-item self-report Flinders Adolescent Decision Making Questionnaire (ADMQ) (Mann et al., 1988) to assess their approach to decision situations. Participants read a series of statements regarding their perceptions of their decision-making (e.g., "The decisions I make turn out well") and rated each statement on a 4-point Likert scale ranging from 0 (*not at all true of me*) to 3 (*almost always true*). The ADMQ is composed of 5 sub-scales that broadly measure decision self-esteem (confidence in one's decisions), vigilance (care one takes while making decisions), panic (panic when making decisions), cop out (avoidance of decisions), and complacency (preferring others to make decisions).

fMRI task

Participants played two 8-minute runs of the Driving Game, an adapted version of the Stoplight Task (Chein et al., 2011) involving making decisions at randomly presented traffic lights and trying to reach the finish line quickly to maximize monetary reward ($5; Figure 2.1). 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.

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/) (S. M. Smith et al., 2004) 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 (Andersson et al., 2003) 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.

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 contrasts for all main regressors against the resting baseline (e.g., Cautious versus Baseline). Recent work has demonstrated greater reliability and stability across sessions when using condition versus baseline conditions relative to condition versus condition (Kennedy et al., 2022). 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 (Beckmann et al., 2003). 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 (Poline et al., 1997). 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/).

Representational similarity analysis

To assess how neural representations of adolescent behaviors relate to behavioral and anxiety development, we computed the voxel-wise dot-product between whole-brain neural activation maps for Cautious, Risky, and Inhibition trials using 3ddot in AFNI (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3ddot.html). Pairwise correlations between the conditions were Z-transformed and used as the dependent variable in a multiple regression analysis with anxiety, risk-taking, age, sex, and COVID group as predictor variables.

Neural metrics of conflict processing

In addition to comparing across task conditions, we also specifically targeted areas involved in approach-avoidance conflict using an association test map from a Neurosynth meta-

analysis of 337 studies involving the term "conflict" (Figure 4.2). Conflict processing during cautious choices was assessed by comparing similarity in whole-brain neural response to cautious decisions to the whole-brain Neurosynth conflict map. Correlation coefficients were Z-transformed and used as the dependent variable in a multiple regression analysis with anxiety, risk-taking, age, sex, and COVID group as predictor variables.

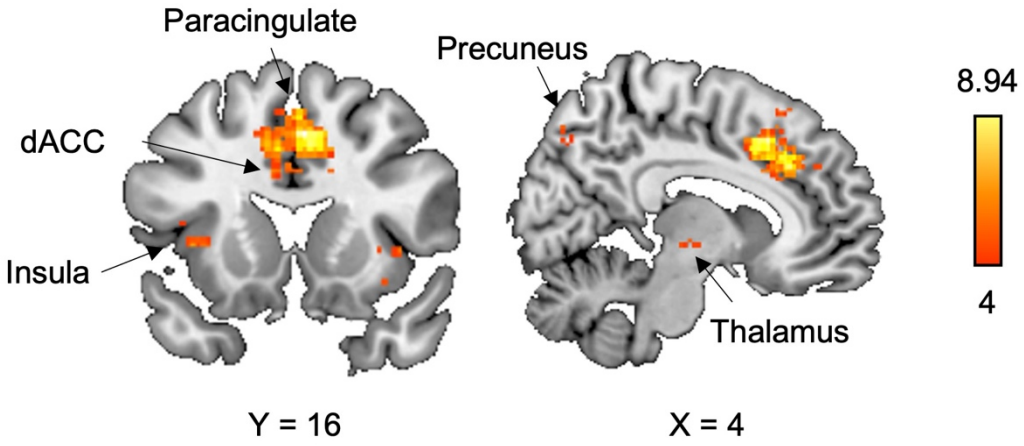

Figure 4.2. Brain regions preferentially related to the term "conflict" as generated using a Neurosynth meta-analysis of 337 studies. A Neurosynth meta-analysis of 337 studies involving the term "conflict" was used to generate an association test map which included brain regions such as the dorsal anterior cingulate cortex (dACC), paracingulate, insula, thalamus, and precuneus.

Whole-brain functional connectivity

Beta series correlation analyses (Rissman et al., 2004) were conducted in FSL to examine differences in whole-brain VS and amygdala functional connectivity during cautious choices. For each run, one GLM was defined for Cautious 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 bilateral VS and amygdala seeds (Harvard-Oxford subcortical probabilistic atlas, 50% probability). The resulting timeseries were 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 Cautious trials were 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. 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. As we ran two separate analyses (one with the VS seed and one with the amygdala seed), we corrected for multiple comparisons by requiring a *p*-value of .05/2 = .025 to survive.

Latent change score model

While difference scores and t-tests can help answer questions in developmental cognitive neuroscience, they are limited in their ability to quantify how change in one construct relates to change in another construct over time. Another method, the latent change score model, is a powerful and flexible type of structural equation model that can answer specific questions regarding how behavioral and neural measures change together over time, in addition to how starting values can influence trajectories, even with just two timepoints (Kievit et al., 2018). Therefore, for our final analysis, we used a multivariate latent change score model to a) model change in anxiety severity, risk-taking behaviors, response time during task, positive and

negative perceptions of adolescent decisions, and neural conflict processing during Cautious choices from Year 1 to Year 2 and b) assess how starting points and change scores related to each other over time. With two timepoints, we can conceptualize the scores of each participant on the construct of interest (e.g., anxiety) at some time *t* as being a function of an autoregressive component and residual. We fix the regression weight of the Y2 variable on the Y1 variable to 1, making the change score which is measured by time point with a factor loading fixed to 1, creating a latent factor that captures the change between Y1 and Y2. In a final step, we can add a path from Y1 to the change score, allowing us to examine how degree of change depends on starting values of the variable.

Good model fit was assessed using the following criteria (Hu & Bentler, 1999): nonsignificant chi-square test of model fit, comparative fit index (CFI) greater than or equal to .95, Tucker–Lewis index (TLI) greater than or equal to .95, root mean squared error of approximation (RMSEA) less than or equal to .06, and standardized root mean squared residual (SRMR) less than or equal to .08.

Results

Behavioral results

Year 2 sample

SCARED scores at Time 2 ranged from 0-54 (M_{Anx} =14.76, SD_{Anx} =11.56; Figure 4.1), 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 19.8% of participants showed signs of an anxiety disorder when using self-report to describe their symptoms (Boris Birmaher et al., 1999; Canals et al., 2012). An independent samples *t*-test revealed a significant sex difference in anxiety ($t(104) = 3.66$, $p < .001$) with girls reporting a mean score of

approximately 7.3 points higher than boys. Anxiety was not associated with age ($r(106) = .14$, $p = .14$). While self-reported SCARED scores decreased on average over time, clinician-rated anxiety severity measured using the Anxiety and Related Disorders Interview Schedule-IV (ADIS-IV) (Silverman & Albano, 1996) increased on average from Time 1 to Time 2 (Table 4.1). Self-reported and clinician-rated anxiety levels were significantly correlated at both time points.

As fifty of the 106 participants returned for their second visit after the COVID-19 shutdown, we also examined whether anxiety development across subscales differed based on whether the follow-up visit occurred before or after the COVID-19 shutdown. The only subscale that showed marginal differences before and after COVID was the Significant School Avoidance scale ($t(104) = 1.72$, p(one-sided) = .04, p(two-sided) = .08). Example items for this subscale include "I get headaches when I'm at school" and "I worry about going to school." As the pandemic shutdown involved virtual schooling for many participants, this may reflect a general decrease in in-person school-based anxieties due to lack of time spent in school. Future longitudinal analyses with the full 3 time points will be able to tease apart how these trajectories shift again once youth re-entered the school settings after the shutdown.

Table 4.1. Descriptive statistics of study variables across both time points. PD = Panic Disorder, GAD = Generalized Anxiety Disorder, SAD = Separation Anxiety Disorder, SOCAD = Social Anxiety Disorder, SSA = Significant School Avoidance; CGI-S = Clinical Global Impression Scale-Severity ranging from 1 (not at all ill) to 7 (extremely ill).

N = 106	Y1	Y2	Difference score	Two-sided p-value
Anxiety				
Total SCARED	19.11 (12.10)	14.76 (11.56)	-4.50 (11.56)	<.001

PD	3.92 (3.78)	3.10 (3.83)	-0.83 (3.53)	.019
GAD	4.77 (4.00)	4.05 (3.98)	-0.72 (4.00)	.069
SAD	3.90 (3.06)	2.07 (2.41)	-1.84 (2.97)	<.001
SOCAD	5.38 (3.64)	4.54 (3.32)	-0.85 (3.47)	.014
SSA	1.34 (1.37)	0.99 (1.19)	-0.35 (1.38)	.012
CGI-S	2.15 (0.99)	2.39 (1.12)	0.24 (0.95)	.014
Age	11.34 (1.50)	12.60 (1.48)	1.31 (0.44)	<.001
Risky	14.16 (8.40)	16.03 (7.26)	1.87 (10.31)	.020
Cautious	18.02 (8.62)	18.23 (7.76)	0.21 (10.26)	.834
Inhibition	30.49 (5.19)	30.53 (5.21)	0.04 (6.48)	.952
False alarm	3.12 (3.25)	4.00 (3.85)	0.88 (4.61)	.053
Go	199.62 (27.67)	207.27 (16.57)	7.65 (30.78)	.013
Mean RT	0.49 (0.08)	0.45 (0.06)	-0.05 (0.06)	<.001
BIS	19.26 (3.85)	19.37 (4.12)	0.11 (3.63)	.767
BAS	39.21 (4.97)	38.65 (5.34)	-0.56 (6.48)	.403
ADMQ Positive	5.88 (0.97)	5.95 (0.99)	0.07 (0.91)	.469
ADMQ Negative	4.97 (1.11)	5.07 (1.20)	0.10 (1.15)	.405

Anxiety and approach-avoidance motivations

Increases in anxiety from Year 1 to Year 2 were associated with increases in avoidance motivations measured using the BIS ($r = .33$, $p < .001$) but were not associated with approach motivations measured using the BAS ($r = .01$, $p = .90$). Changes in risk-taking frequency were not associated with change in BIS or BAS ($r = .06$, $p = .58$; r = .06, $p = .58$). Change in BIS and change in BAS were positively correlated ($r = .33$, $p < .001$).

Anxiety and perceived decision-making

Increases in anxiety were associated with decreases in positive perceptions of decision situations ($\beta = -.26$, $p = .008$) and increases in negative perceptions of decision situations ($\beta = .21$, $p = .021$; Table 4.2), suggesting that anxiety may negatively impact the way that adolescents approach and perceive their decisions. As many of the participants in this study showed *decreases* in anxiety over time, this also means that improvements in mental health corresponded with more positive approaches to making decisions as youth entered adolescence. Changes in positive perceptions of decision situations were negatively correlated with changes in BIS and

positively correlated with changes in BAS (r = -.24, p = .018; r = .26, p = .011), while changes in negative perceptions were only positively correlated with change in BIS (r = .27, p = .008). Change in positive and negative perceptions of decision situations were negatively correlated (r = -.38, p < .001). Interestingly, BAS moderated the association between anxiety and negative perceptions of decision situations such that youth reporting increases in anxiety and decreases in BAS reported increases in negative perceptions of decision situations (β = 0.42, p = .003), whereas youth who increased in both anxiety and BAS did not show the downstream increases in negative perceptions of decision situations (β = -0.06, p = .70). This suggests that adolescent increases in approach motivations (e.g., fun seeking) may be protective against the effects of anxiety on decision panic and complacency.

Table 4.2. Associations between change in anxiety and change in approach to decision situations. *p < .05, **p < .01, ***p < .001.

Δ T1-T2	Self-esteem	Vigilance	Panic	Cop out	Complacency	Total Positive	Total Negative	Positive-Negative
Anxiety	-.23*	-.20*	.16	.10	.26**	-.26**	.21*	-.28**

Anxiety and task decision-making

Changes in anxiety were not related to changes in risk-taking frequency (r(106) = -.03, p = .74) or average risks taken on average over the two timepoints (r(106) = -.19, p = .06) in the current sample, although participants who took relatively more risks than others on average showed more significant decreases in the Significant School Avoidance subscale of anxiety over time (r(106) = -.25, p = .01). Interestingly, participants reporting higher average anxiety across the time points showed more robust increases in risky behavior between the time points (r(106) = .22, p = .02). Hierarchical cluster analysis revealed that participants clustered into 3 groups based

on their change in anxiety and risk taking over time, after which k-means cluster analysis was conducted to determine group membership for each participant. Group 1 showed no change to mild decreases in anxiety and decreases in risk-taking frequency, group 2 showed decreases in anxiety and increases in risk-taking frequency, and group 3 showed increases in anxiety and either increases or decreases in risk-taking frequency between Year 1 and Year 2 (Figure 4.3).

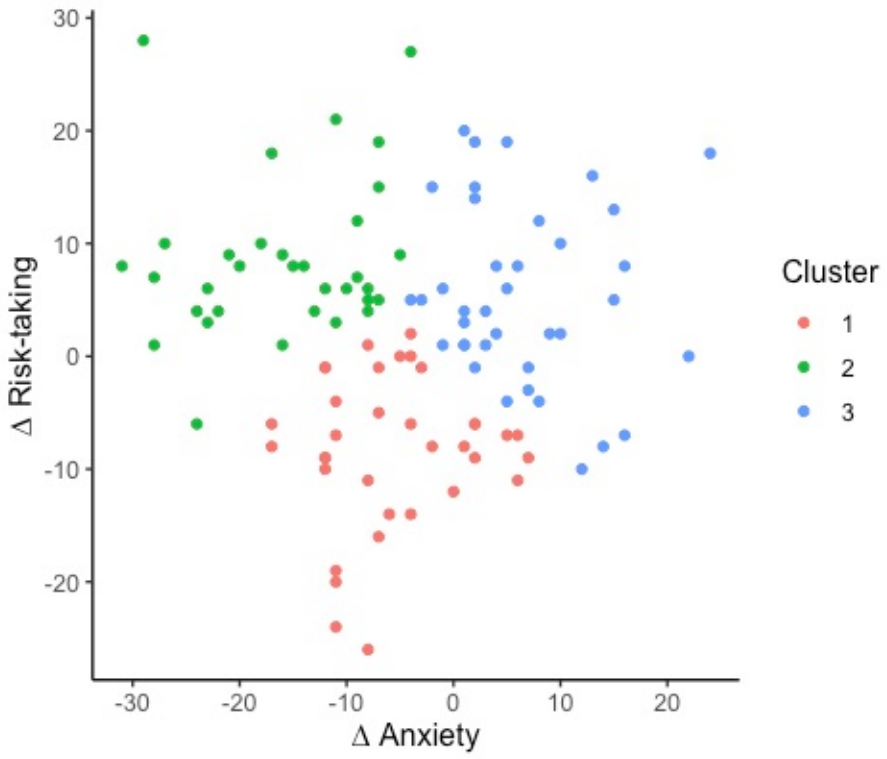

Figure 4.3. Hierarchical cluster analysis revealed that participants clustered into 3 groups based on within-person change in anxiety and risk taking from Year 1 to Year 2. Group 1 had no change to mild decreases in anxiety and decreases in risk taking, group 2 had decreases in anxiety and increases in risk taking, and group 3 had increases in anxiety and either increases or decreases in risk taking from Year 1 to Year 2.

Similarity in neural response across task conditions

In line with our hypotheses, increases in risk-taking frequency were paralleled by increased similarity between risky and cautious choices ($\beta = .50$, $p < .001$), while increases in anxiety symptoms were paralleled by increased similarity between cautious choices and instructed response inhibition ($\beta = .22$, $p = .03$). This suggests that neural generalization across scenarios involving uncertain outcomes regardless of participant response may be conducive to risk taking. While anxiety was not associated with overly avoidant behavior in the task, anxious adolescents distinguished more between risky and cautious choices and less between cautious choices and response inhibition. Even further, this neural generalization across cautious and inhibition was positively correlated with change in negative perceptions of decision situations ($r = .24$, $p = .02$) and explained the link between anxiety and increases in negative perceptions of decision-making from Year 1 to Year 2. When probing anxiety subtypes (as measured using the SCARED), Significant School Avoidance was the most tightly aligned with these neural changes ($\beta = .32$, $p = .001$), suggesting that although anxious participants did not demonstrate persistent risk avoidance during the task, avoidant behavior may be apparent in (and interfering with) other aspects of their life.

Table 4.3. Longitudinal change in anxiety symptoms and risky behaviors is associated with shifts in neural discrimination between task conditions. Summary statistics for multiple regression analyses with change in neural similarity between Year 1 and Year 2 as dependent variables and change in anxiety, risk-taking frequency, age, average relative motion, female sex, and COVID-19 group as predictor variables. *$p < .05$, **$p < .01$, ***$p < .001$.

	Dependent variables: Δ Similarity from Year 1 to Year 2			
	Cautious, Inhibition	Cautious, Risky	(Cautious, Inhibition) – (Cautious, Risky)	Cautious, Conflict (Neurosynth)
Δ Anxiety	.23*	-.15	.25*	-.29**

Δ Risky	.12	.50***	-.32**	.26**
Δ Age	.08	.968	.01	.19*
Δ Motion	-.14	-.07	.07	-.03
Female sex	-.12	-.12	.05	.04
COVID	-.07	.08	-.10	.03

Approach-avoidance conflict during cautious decision-making

To specifically test how conflict processing during risk avoidance relates to anxiety and risk taking, we next examined how change in anxiety symptoms and risk-taking behaviors related to the similarity between neural response during risk avoidance and the Neurosynth conflict map. While increases in risk taking were associated with increased neural similarity between cautious choices and the Neurosynth conflict map (β = .26, p = .008), increases in anxiety were associated with decreased neural similarity between cautious choices and the Neurosynth conflict map (β = -.29, p = .003; Table 4.3), suggesting that conflict processing during risky decision-making supports both risk taking and mental health development. As many of the participants in this study showed improvements in mental health over time, more conflict processing during risk avoidance was associated with better anxiety outcomes.

Region-of-interest analysis: dACC

As we discussed in Chapter 3 of this dissertation, the dorsal anterior cingulate cortex (dACC) is a primary region associated with conflict processing and is a predominant feature of the Neurosynth conflict map. We next conducted an exploratory region-of-interest analysis using our dACC seed from Chapter 3 to examine whether conflict processing during cautious choices could be summarized using change in mean activation of the dACC during cautious choices over the two timepoints. Indeed, change in mean dACC activation was tightly correlated with similarity scores between cautious choices and the Neurosynth conflict map (r = .62, p < .001), suggesting that change in mean activation was at least partially representative of neural conflict

processing. While increases in risk taking were linked to increased dACC recruitment during cautious choice over time (β = .25, p = .009), increases in anxiety were associated with decreased recruitment of the dACC during cautious choice over time (β = -.35, p < .001), highlighting the role of neural conflict processing systems—and the dACC in particular—in both anxiety and behavioral development in adolescence (Figure 4.4).

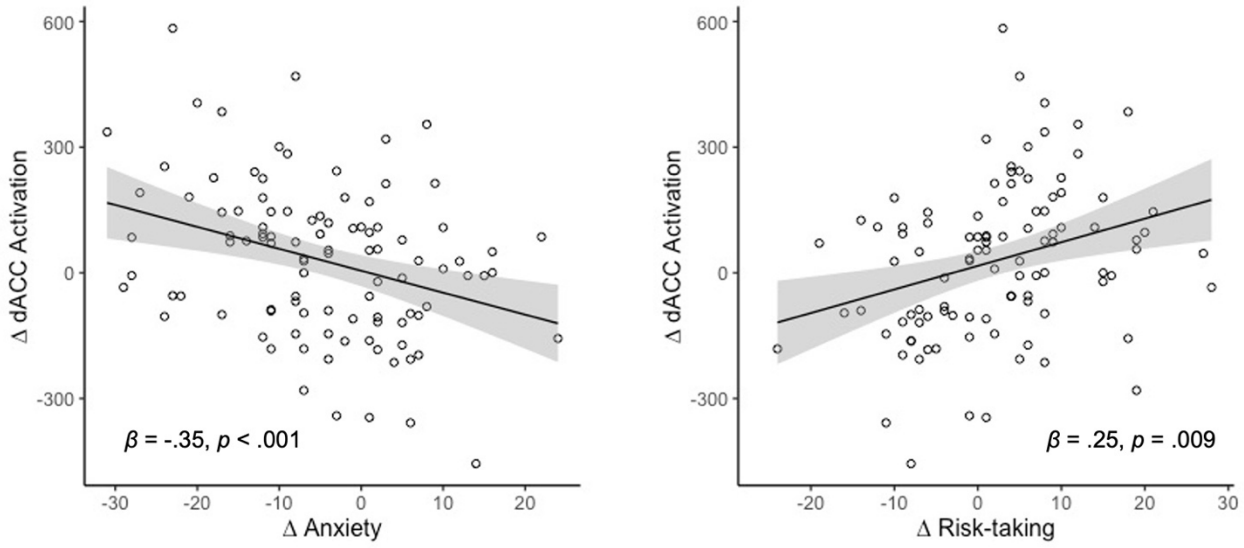

Figure 4.4. Changes in anxiety and risk taking over time are associated with changes in dACC recruitment during risk avoidance.

Whole-brain striatal connectivity

Results of a whole-brain analysis of striatal connectivity during Cautious choices revealed that changes in anxiety, but not risk-taking frequency, modulated connectivity between the ventral striatum and a range of regions including the dACC and thalamus (Figure 4.5).

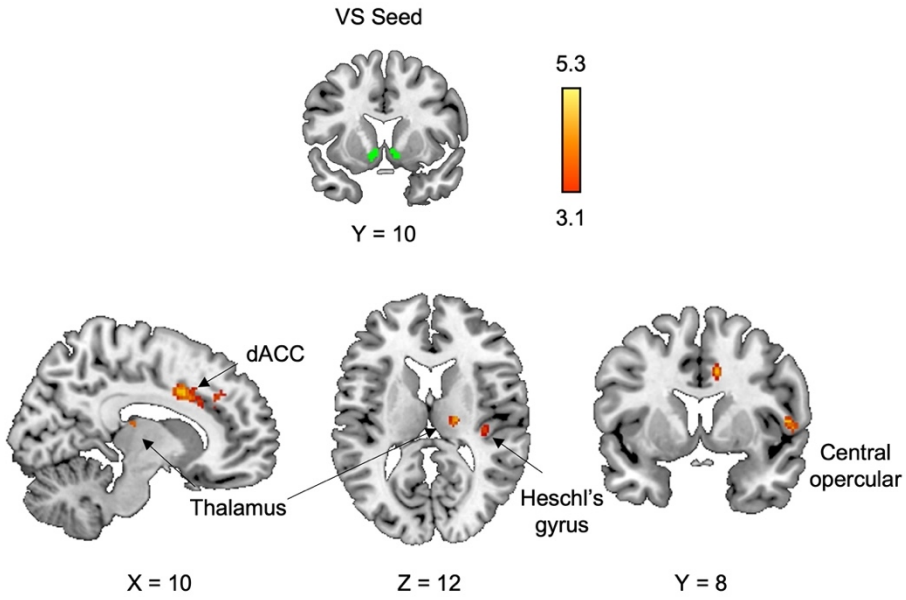

Figure 4.5. Anxiety development in adolescence is associated with increases in VS connectivity during risk avoidance. Increases in anxiety symptoms over time were associated with increases in VS connectivity with a range of brain regions including the dorsal anterior cingulate cortex (dACC), paracingulate cortex, thalamus, Heschl's gyrus, and central and parietal opercular cortices during cautious choices. $Z > 3.1$, $p < .025$.

Whole-brain amygdala connectivity

Results of a whole-brain analysis of amygdala connectivity during Cautious choices revealed that changes in risk taking, but not anxiety severity, modulated amygdala connectivity during Cautious choices—greater risk taking at Time 2 was associated with more connectivity between the amygdala and the pre- and postcentral gyri and superior parietal lobule and more negative coupling between the amygdala and the frontal pole (Figure 4.6).

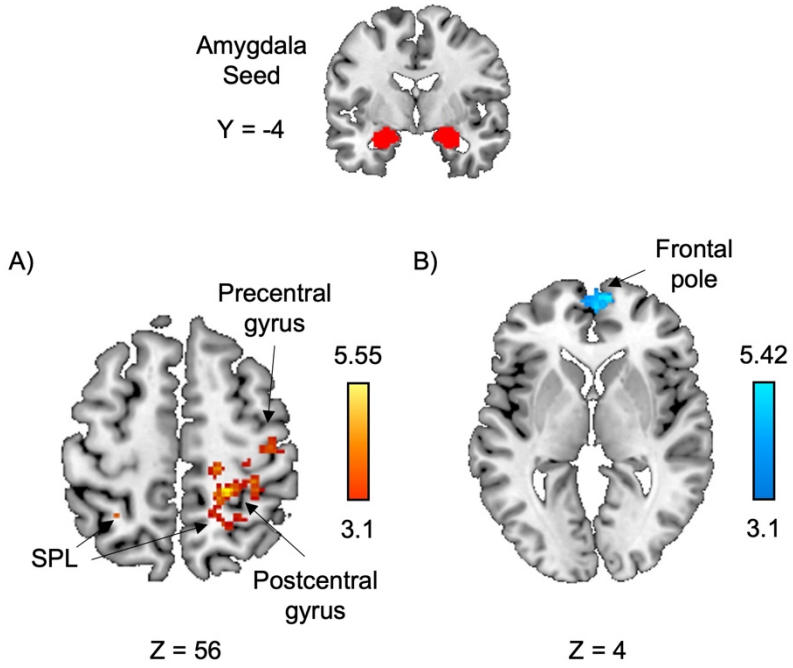

Figure 4.6. Changes in risk taking in adolescence are associated with changes in amygdala connectivity during risk avoidance. Increases in risk-taking frequency over time were positively associated with amygdala connectivity with the superior parietal lobule (SPL) and pre- and postcentral gyri and negatively associated with amygdala-frontal pole connectivity during cautious choices. $Z > 3.1$, $p < .025$.

Latent change score model

Risk-taking frequency, anxiety severity, positive and negative perceptions of decision situations, average task RT, and mean dACC activation during cautious choices for both time points were used to fit a multivariate latent change score which included latent variables representing change in each of the constructs, as well as paths from observed scores in each construct at Year 1 to these latent change variables to assess how change in one factor depended on starting points in another. The model demonstrated excellent fit ($\chi^2(1, N = 106) = 0.047$, $p = .83$; RMSEA = 0.00; CFI = 1, TLI = 1.18; SRMR = 0.002). Results from this model indicate

that more negative perceptions of decision situations (e.g., panic, cop out, and complacency), greater dACC recruitment during cautious choice, and longer deliberation time during decision-making at baseline were all predictive of worsening anxiety; higher anxiety at baseline was predictive of increasing risk taking; greater positive perceptions of decision-making at baseline predicted decreases in negative perception of decision-making; longer deliberation during decision-making at baseline was marginally predictive of decreases in positive perceptions of decision-making; more risk taking at baseline was predictive of faster deliberation over time; and higher baseline anxiety was predictive of greater decreases in dACC recruitment while longer RT at baseline predicted more dACC recruitment over time (Table 4.4). Additionally, correlations between the latent change scores demonstrated that change in anxiety was directly associated with change in perceptions to decision situations, increases in risk taking were directly associated with decreases in RT and increases in dACC recruitment over time, and greater dACC recruitment was directly linked to faster RT during decision-making (Table 4.5). Y1 anxiety was negatively correlated with dACC recruitment and positive perceptions of decision-making and positively correlated with negative perceptions of decision-making at Y1, while risk taking at Y1 was associated with faster RT and greater dACC recruitment at Y1 (Table 4.6). Overall, results from this model underscore the idea that anxiety and risk taking develop together through shared mechanisms but are not directly related in adolescence.

Table 4.4. Multivariate latent change score model. Positive = ADMQ positive score, Negative = ADMQ negative score, RT = average task response time.

Δ Anxiety ON		
Y1 Anxiety	-0.657 (0.076)	<.001
Y1 Positive	-0.130 (0.096)	.179

Y1 Negative	0.307 (0.097)	.002
Y1 Risky	-0.095 (0.081)	.245
Y1 RT	0.216 (0.082)	.008
Y1 dACC	0.165 (0.084)	.049
Δ Risky ON		
Y1 Risky	-0.667 (0.057)	<.001
Y1 Anxiety	0.176 (0.075)	.020
Y1 Positive	0.026 (0.086)	.761
Y1 Negative	-0.075 (0.088)	.391
Y1 RT	0.083 (0.072)	.248
Y1 dACC	-0.049 (0.069)	.476
Δ Negative ON		
Y1 Negative	-0.615 (0.098)	<.001
Y1 Positive	-0.268 (0.105)	.011
Y1 Anxiety	0.050 (0.095)	.599
Y1 Risky	-0.075 (0.090)	.405
Y1 RT	0.094 (0.089)	.290
Δ Positive ON		
Y1 Positive	-0.525 (0.100)	<.001
Y1 Negative	-0.154 (0.113)	.172
Y1 Anxiety	0.039 (0.097)	.684
Y1 Risky	0.023 (0.092)	.800
Y1 RT	-0.175 (0.090)	.051
Δ RT ON		
Y1 RT	-0.575 (0.067)	<.001
Y1 Negative	-0.044 (0.096)	.645
Y1 Positive	-0.010 (0.094)	.914
Y1 Anxiety	-0.076 (0.082)	.354
Y1 Risky	0.193 (0.076)	.011
Δ dACC ON		
Y1 dACC	-0.699 (0.062)	<.001
Y1 Anxiety	0.171 (0.078)	.029
Y1 Risky	0.023 (0.074)	.758
Y1 Positive	-0.010 (0.090)	.954
Y1 Negative	0.005 (0.091)	.913
Y1 RT	-0.191 (0.075)	.011

Table 4.5. Correlations between latent change across domains. *$p < .05$, **$p < .01$, ***$p < .001$.

	Δ Anxiety	**Δ Risky**	**Δ Positive**	**Δ Negative**	**Δ RT**	**Δ dACC**
Δ Anxiety	1					
Δ Risky	.025	1				
Δ Positive	-.279**	.096	1			
Δ Negative	.430***	-.059	-.500***	1		
Δ RT	.092	-.364***	-.021	.068	1	
Δ dACC	-.086	.342***	.068	.053	-.244**	1

Table 4.6. Correlations between starting points across domains. *$p < .05$, **$p < .01$, ***$p < .001$.

	Y1 Anxiety	Y1 Risky	Y1 Positive	Y1 Negative	Y1 RT	Y1 dACC
Y1 Anxiety	1					
Y1 Risky	-.114	1				
Y1 Positive	-.414***	.072	1			
Y1 Negative	.420***	-.112	-.585***	1		
Y1 RT	.047	-.306**	.007	-.126	1	
Y1 dACC	-.231*	.294**	.193*	-.028	-.336***	1

In a final step, we added four between-person covariates to the latent change score model to assess whether change in the modeled constructs differed by 1) sex, 2) time between visits, 3) age at Year 2, and/or 4) the COVID-19 shutdown. In line with previous research, latent change scores for anxiety significantly differed by sex, with girls showing greater worsening of anxiety over time ($\beta = 0.50$, $p = .001$). The only latent change variable showing significant differences based on the COVID-19 pandemic was negative perceptions of decision situations: youth who had experienced the COVID-19 pandemic reported increases in negative perceptions of decision-making over time ($\beta = 0.34$ $p = .033$), suggesting that the pandemic may have negatively contributed to adolescents' approach to decision situations, perhaps due to decreased practice due to the pandemic shutdown. On a more hopeful note, there was a significant interaction between the COVID-19 pandemic and baseline positive perceptions of decision-making on change in negative perceptions such participants with high baseline positive scores who experienced the pandemic were buffered against increases in negative decision perceptions ($\beta = 0.34$ $p = .034$).

Anxiety as an outcome

In the analyses so far, anxiety symptoms were considered alongside other measures of adolescent development to identify the ways in which these domains develop together. However, there is also interest in predicting outcomes—i.e., determining who will develop an anxiety

disorder in adolescence. At the time of these analyses, 84 of the 106 youth had completed the SCARED at a third time point (one year following the second visit). Using this anxiety score as the outcome of interest, we tested how starting values and change in the different domains predicted improvements in or worsening of anxiety at Year 3. To do this, we regressed Y3 anxiety on starting values and change scores for all model variables. Higher anxiety at baseline ($\beta = 0.54$ $p < .001$) and female sex ($\beta = 0.32$ $p < .001$) predicted higher anxiety at Y3. However, increases in dACC recruitment from Y1 to Y2 were protective against future anxiety ($\beta = -0.39$, $p = .001$) over and above changes in the other domains, suggesting that neural conflict processing during decision-making may be an important factor determining risk and resilience to anxiety in adolescence.

Finally, as clinician-rated anxiety severity increased from Year 1 to Year 2, we conducted an additional analysis testing whether amygdala and striatal response during risk avoidance interact to predict clinical anxiety diagnosis in adolescence. We tested 2 models: one testing whether Year 1 amygdala and striatal responding interact to predict Year 2 CGI-S score (controlling for Year 1 CGI-S and Year 2 amygdala and striatal activity), and another model testing whether *change* in amygdala and striatal responding over time interaction to predict change in CGI-S over time. Results from model 1 revealed that participants demonstrating low amygdala response coupled with high VS response—a marker of maladaptive avoidance (Diehl, Bravo-Rivera, & Quirk, 2019)—had higher clinician-rated anxiety at Year 2 ($\beta = -0.17$, $p = .018$; Figure 4.7a), while results from model 2 revealed that participants who decreased in amygdala activation and increased in VS activation during risk avoidance over time showed the greatest increases in clinician-rated anxiety over time ($\beta = -0.26$, $p = .009$; Figure 4.7b).

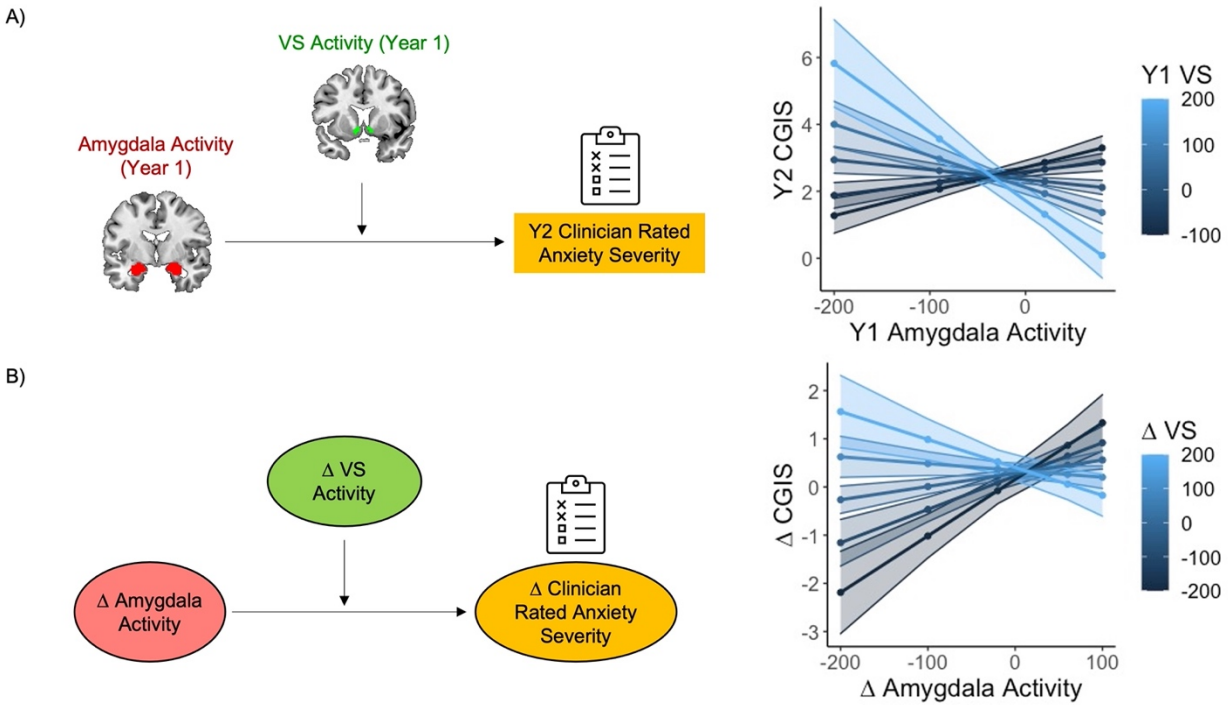

Figure 4.7. Amygdala and striatal response during risk avoidance interact to predict clinical anxiety development in adolescence. A) Participants demonstrating low amygdala coupled with high VS response during risk avoidance at Year 1 had a higher probability of clinical anxiety diagnosis at Year 2. B) Participants demonstrating decreased amygdala coupled with increased VS response during risk avoidance over time showed the most severe increases in clinical anxiety from Y1-Y2. VS=ventral striatum; CGIS=clinical global impressions scale.

Discussion

In this chapter, we shed light on the mechanisms that relate to the development of anxiety and risk taking in adolescence by examining longitudinal change in anxiety symptoms and neural and behavioral correlates of risk avoidance in 106 youth over a period of approximately 1.3 years. Contrary to hypotheses, participants in this study reported significantly lower anxiety at follow-up, although clinician-rated anxiety scores increased over time. As expected, the group

increased in risk-taking frequency over time, and both decreases in anxiety and increases in risk-taking behaviors were more robust in boys than in girls. Changes in anxiety over time were directly associated with changes in the way in which adolescents approach decision situations, with worsening anxiety predicting decreased decision confidence and increased decision panic and complacency over time. Change in approach motivations, such as drive to achieve goals and fun seeking, developed alongside positive perceptions of decision situations. Neural response during risk avoidance was linked to the development of both anxiety and risk taking: increases in anxiety were reflected in increases in striatal connectivity during risk avoidance, while changes in risk taking were reflected in changes in amygdala connectivity during risk avoidance. Even further, changes in anxiety and risk taking differentially impacted the way in which risk avoidance was represented in the brain, with increases in anxiety predicting more overlap in neural representations of risk avoidance and loss avoidance and more neural discrimination between risk avoidance and risk taking and increases in risky behavior predicting more overlap in neural representations of risk avoidance and risk taking. Taken together, results from this chapter help to delineate the shared behavioral and neural mechanisms that contribute to anxiety and risky decision-making in adolescents and highlight the potential of leveraging these shared mechanisms to promote positive approaches to decision-making amongst developing youth.

Anxiety and decision-making in adolescents

The first two chapters of this dissertation connect fronto-striatal and amygdala circuits to behavior and elucidate neural mechanisms underlying risky decision-making in youth by providing snapshots of development across different individuals at varying ages. However, research shows that the incidence of anxiety increases as youth progress through adolescence as many risk-taking behaviors also onset during this time. Furthermore, while there are overarching

commonalities in the adolescent experience, everyone has a unique journey from childhood to adulthood. In this chapter, we extend and expand on the questions from the first chapters by measuring within-person change in neural and behavioral correlates of anxiety and risk taking as youth progress through adolescence.

While anxiety has been linked to risk aversion in adults (Sonuga-Barke et al., 2016), we did not find associations between anxiety and risk aversion in the current study. Youth broadly clustered into three groups based on their anxiety and risk taking development, with the first group showing no change to mild decreases in anxiety and decreases in risk-taking frequency, the second group showing decreases in anxiety and increases in risk-taking frequency, and the third group showing increases in anxiety and either increases or decreases in risk-taking frequency from Year 1 and Year 2. Along with chapters 2 and 3 of this dissertation, these results suggest that the association between anxiety and risk taking in adolescence is more nuanced than we may tend to believe, and anxious adolescents vary in their tendencies for risk taking, perhaps due to the unique brain dynamics and development occurring during this time. While anxiety did not show direct associations with task risk aversion, youth reporting more anxiety at Year 2 also reported decreases in positive perceptions of decision situations (e.g., confidence in making decisions), while they reported increases in negative perceptions of decision situations (e.g., panicking when or putting off making decisions). This highlights the intertwined nature of anxiety symptoms and decision-making in adolescents: despite showing no actual behavioral differences in the decision-making task, youth with more anxiety felt worse about making decisions, doubted their ability to make decisions, and avoided making decisions more than their peers. Interestingly, perceptions of decision capabilities were not associated with actual decision-making accuracy or response time on the task, suggesting that these negative perceptions were

driven by (or at least related to) anxiety and not grounded in real ability. As adolescence is an important time for the development of complex decision-making skills, this downstream effect on self-assessment is concerning and may contribute to avoidance loops in anxiety. However, this is also a potential area for intervention, as *positive* assessments of decision situations were not affected by negative assessments, and in fact predicted decreases in negative perceptions and anxiety over time. Positive approaches to decision situations were also positively linked to adolescent approach motivations and negatively linked to adolescent avoidance motivations, highlighting the ways in which approach and avoidance motivations develop alongside self-perceptions of one's own decision-making capabilities.

Although anxious adolescents in this sample did not show risk aversion, they demonstrated differences in response time during decision-making. In Chapter 2 of this dissertation, we found that adolescents reporting higher anxiety at Year 1 took longer to make voluntary cautious decisions in the face of approach-avoidance conflict and were faster at inhibiting when instructed in tests of cognitive control. Here, we find continuation of this pattern: while most adolescents got faster on all trial conditions over time, anxious adolescents only improved on the instructed conditions and actually took longer to make a choice during risky decision-making over time. Increases in risk-taking frequency were negatively correlated with response time such that greater risk taking was associated with faster response times from Year 1 to Year 2. Although anxiety and risk taking were not directly linked, the opposing associations with response time again suggesting that shared mechanisms may be driving these differences in behavior and mental health.

Neural correlates of anxiety and risk taking

The amygdala, ventral striatum, and dACC go through changes in adolescence, have been implicated in clinical anxiety and adolescent approach behavior, and work closely with one another during decision-making. According to the Triadic Model of adolescent behavior, striatal sensitivity coupled with still-maturing regulatory systems in adolescence will bias behavior towards approach responses in the face of an approach-avoidance conflict (Ernst et al., 2009). However, as the striatum and its connections are also crucial for aversive learning and avoidant behavior (Delgado et al., 2008) and play a critical role in adolescent anxiety (Bar-Haim et al., 2009; Benson et al., 2014; Guyer et al., 2012, 2006), anxious adolescents may display a different phenotype not captured by the current model. The amygdala helps shape avoidance processes by sending evaluative signals through its direct projections to the ventral striatum, but it is the VTA-ventral striatal dopaminergic pathway controls avoidance action selection processes (Anstrom et al., 2009; Tian & Uchida, 2015). As avoidance becomes persistent or habitual, the involvement of the amygdala decreases further, with avoidance instead correlating with activity in the striatum and prelimbic cortex (or dACC in humans) (Bravo-Rivera et al., 2015). The striatum is also important for assessing safety: rats with striatal lesions show specific impairments in rapid uncertainty-safety discrimination, a skill that is necessary for survival and disrupted in clinical anxiety (Ray et al., 2020), and optogenetics research has identified a specific fronto-striatal circuit that controls anxious avoidance behaviors in mice (Loewke et al., 2021). Therefore, it follows that striatal sensitivity and fronto-striatal plasticity in adolescence may contribute to both approach and avoidance behaviors in adolescents depending on factors such as anxiety symptoms.

In the current study, we find further evidence for the role of the striatum in anxiety and avoidance. First, change in anxiety over time tracked with striatal connectivity during risk

avoidance, highlighting the role of striatal communication in both risk avoidance and anxiety development in adolescence. Youth who reported worsening anxiety at Year 2 showed heightened striatal connectivity with a range of regions including the dACC and thalamus during risk avoidance, while risk-taking frequency was not associated with change in striatal connectivity. This may be similar to previous work showing that anxious youth show greater striatal response to low- rather than high-valued outcomes, perhaps due to the relative level of potential risk associated with each option (Benson et al., 2014); perhaps this is a similar scenario in which the lower risk associated with cautious choices is mirrored in striatal communication in anxious adolescents. Another hypothesis follows from the role of the striatum in avoidance. In Chapter 2, we showed that anxiety and risk-taking frequency interact to influence striatal communication with the rest of the brain during risk avoidance such that heightened striatal connectivity was associated with risk aversion in high anxiety and heightened risk taking in low anxiety, suggesting that the striatum may contribute to approach or avoidance depending on youth anxiety. In avoidance learning, an individual learns to avoid an aversive stimulus prior to the onset of the stimulus (Hofmann & Hay, 2018) which can become habitual and resistant to extinction, especially in adolescents. Connections from the dACC to the VS appear to support maladaptive avoidance independently of fear learning circuits (e.g., amygdala) (Diehl et al., 2019). Therefore, heightened connectivity between the VS and the dACC during risk avoidance in adolescents with anxiety may be indicative of a shift towards maladaptive avoidance that is more resistant to extinction.

Changes in risk taking did not show significant associations with striatal development during risk avoidance. However, interestingly, risk taking—but not anxiety—showed tight associations with amygdala connectivity during risk avoidance such that increases in risk taking

over time were paralleled by heightened amygdala connectivity with the superior parietal lobule (SPL) and pre- and postcentral gyri, and more negative coupling between the amygdala and the frontal pole. The increase in direct communication from the amygdala to regions involved in motor planning and action associated with increase in risky behavior may indicate a greater approach-oriented or impulse-driven system, while the increase in negative coupling between the amygdala and frontal pole may be indicative of a more adult-like phenotype of fear regulation (Gee, Humphreys, et al., 2013). Interestingly, activity in the SPL and premotor cortex has been linked to explorative decision-making, while activity in the ventromedial prefrontal cortex has been linked to exploitative decision-making (C.-W. Li, Lin, Chang, Yen, & Tan, 2021). Perhaps the shift towards greater risk taking in adolescence and its associations with amygdala connectivity were indicative of a shift in cognitive strategy from exploitation to exploration during risky decision-making. As anxiety development was linked to striatal connectivity and risk taking development was linked to amygdala connectivity during risk avoidance, these results again highlight the importance of considering both circuits in studies of adolescent development rather than a modular view of amygdala = avoid and striatum = approach.

Representational similarity analysis

It has been proposed that developmental changes in threat learning and threat generalization contribute to the development of anxiety in adolescence (Britton et al., 2013; Lau et al., 2011). On the other hand, developmental changes in reward learning and risk tolerance have been used to explain the development of risky decision-making in adolescence. While neuroimaging studies commonly employ univariate methods that are helpful for understanding mean differences in brain response to different stimuli, these methods are not well suited for addressing the question of how the brain distinguishes or generalizes across stimuli in

adolescence. Here, we use representational similarity analysis (RSA) (Kriegeskorte et al., 2008), a promising approach for tackling these types of question in which we leverage information contained in the *patterns* of activity across multiple voxels of the brain to characterize the unique neural representation of a stimulus. With this method, the similarity or dissimilarity of patterns is used to assess which representations of stimuli are alike and which diverge, allowing for a more nuanced examination of brain response across regions. This approach has proven useful for delineating how the brain distinguishes between threat and safety in youth with and without anxiety (Glenn et al., 2020); however, this method had yet to be used to examine how the adolescent brain distinguishes between approach and avoidance decisions involving risk and conflict. As the task used in this study involves approach and avoidance decisions across both risky decision-making and response inhibition conditions, we have a unique opportunity to test how whole-brain patterns of neural response show similarities or dissimilarities across decision scenarios.

Here, we find that adolescents who reported increases in anxiety from Year 1 to Year 2 showed more overlap between neural response during risk avoidance (cautious choices) and loss avoidance (response inhibition), suggesting that anxious adolescents may not distinguish between reasons for inhibiting behavior regardless of potential rewarding outcomes. In addition to showing more generalization across risk and loss avoidance, anxious youth showed more neural differentiation or dissimilarity between risk avoidance and risk taking, suggesting that risk avoidance may become more habitual, and less goal directed as anxiety worsens. Even further, the increase in generalization between risk and loss avoidance in anxious adolescents was associated with increases in decision panic and complacency and explained the link between anxiety and negative perceptions of decision-making, suggesting that neural generalization

across these conditions was directly tied to negative feelings about decision-making such as decision panic and avoidance. On the other hand, increases in risk-taking frequency between Year 1 and Year 2 were paralleled by increased generalization across risk avoidance and risk-taking decisions, suggesting that increases in risk taking in adolescence are associated with neural generalization across approach and avoidance decisions in conditions of risk and reward.

In addition to comparing neural representations across task conditions, we specifically targeted areas involved in approach-avoidance conflict by leveraging a meta-analysis of 337 studies on Neurosynth. To test the degree of conflict processing involved in risk avoidance across time points, we assessed the similarity between neural response during cautious choices and the Neurosynth association test map of brain regions preferentially activated in conflict processing. Interestingly, both change in anxiety and risk-taking frequency were related to the degree of similarity between neural response during risk avoidance and the Neurosynth conflict map over time such that increases in anxiety were associated with less overlap between conflict processing and risk avoidance, while increases in risk taking were associated with more overlap between conflict processing and risk avoidance. This suggests that increases in risk-taking frequency in adolescence may be tied to greater recruitment of areas involved in conflict processing during cautious behavior—even if the eventual decision is to avoid the risk, these adolescents were still engaging in a decision process involving conflicting motivations and weighing of potential outcomes. On the other hand, this once again suggests that anxiety may involve maladaptive avoidance and engaging neural systems involved in habitual avoidance rather than conflict processing during decision-making.

The dACC and approach-avoidance conflict

The regulatory brain area that is most frequently implicated in decision-making under conflict is the dorsal anterior cingulate cortex (dACC) (B. W. Smith et al., 2009), which also appeared as a key component of the Neurosynth conflict map. While the VS and amygdala track value and salience, the dACC governs conflict monitoring and regulates risk-related values and behavior (Christopoulos et al., 2009; Kolling et al., 2014) and is an important player in risky decision-making and anxiety development (Beard et al., 2022; Blair et al., 2012). Here, we find that dACC recruitment during risk avoidance was directly linked to both anxiety and risk-taking development over time, with increases in anxiety correlating with decreased dACC recruitment and increases in risk taking correlating with increased dACC recruitment during risk avoidance over time. Perhaps anxious adolescents showed increases in VS-dACC connectivity during risk avoidance as a compensatory measure to make up for decreased recruitment of the dACC. While VS-dACC connections have been implicated in habitual avoidance, engagement of the dACC is critical for the extinction of habitual avoidance (Diehl et al., 2019), suggesting that training aimed at increasing dACC engagement during risk avoidance may help adolescents shift away from maladaptive avoidance patterns. Amongst the 84 youth who had already returned for a third time point at the time of this dissertation, increased dACC recruitment during risk avoidance between Year 1 and Year 2 predicted lower anxiety at Year 3 over and above change in anxiety and risky behavior, suggesting that training aimed at increasing dACC conflict processing during risk avoidance and decision-making might prove useful for anxiety reduction.

Measuring latent change across constructs

For our final analysis, we used a multivariate latent change score model—a powerful and flexible type of structural equation model that can answer questions regarding how behavioral and neural measures change together over time and how starting values influence trajectories

(Kievit et al., 2018)—to characterize change in constructs over time and their associations with one another all in the same model. Results from this model indicate that negative perceptions of decision situations (e.g., panic, cop out, and complacency), greater dACC recruitment during risk avoidance, and longer deliberation time during decision-making at baseline were all predictive of worsening anxiety over time, while positive perceptions of decision situations at baseline predicted decreases in negative perceptions of decision-making over time. Correlations between the latent change scores indicated that change in anxiety was directly associated with change in perceptions to decision situations, increases in risk taking were directly associated with decreases in response time and increases in dACC recruitment over time, and greater dACC recruitment was directly linked to faster response time during decision-making. Anxiety was negatively correlated with dACC recruitment and positive perceptions of decision-making and positively correlated with negative perceptions of decision-making at baseline, highlighting the associations between these domains even in early adolescence. Overall, results from this model underscore the idea that anxiety and risk taking develop together through shared mechanisms—e.g., neural response and deliberation time during risk avoidance—rather than showing causal associations in this sample.

The COVID-19 pandemic

The COVID-19 pandemic was an unexpected interruption to data collection and to the lives of the adolescents participating in this study. However, as roughly half of the sample completed their second time point after the pandemic shutdown, we had the unique opportunity to examine differences in development between the two groups. This was not a well-controlled study, and of course there are confounding variables that may very well have impacted these results. However, it is still of interest to examine which variables showed differences, as well as

which direction those differences were pointed. Interestingly, there was only one measure of latent change that showed differences based on the pandemic, and that was change in negative perceptions of decision-making. Specifically, the pandemic group reported higher decision panic and complacency when they returned for their Year 2 visit. The pandemic shutdown not only took away many opportunities for adolescent decision-making, but also introduced an aspect of uncontrollability that may have negatively impacted adolescents' perceptions of their own decision-making abilities. Although we did not find significant differences in overall anxiety development between the pre- and post-pandemic shutdown groups, change in anxiety was tightly linked to change in negative decision perceptions, suggesting that the pandemic may have downstream negative effects on anxiety through its effect on decision perceptions. On a more hopeful note, positive perceptions of decision situations at baseline buffered against negative effects of the pandemic on negative perceptions of decision-making, suggesting that interventions aimed at building positive approaches to decision situations and increasing decision confidence might help foster resilience during times of great uncertainty such as the COVID-19 pandemic.

Limitations

The findings discussed in this chapter should be interpreted in the context of several limitations. First, as the bulk of these analyses include only 2 timepoints, we were not able to examine growth curves or shape of growth patterns over time. Future work with more time points is needed to ascertain true developmental patterns, as these facets of adolescent development may not demonstrate simple linear trajectories. Additionally, participants in this sample showed average decreases in anxiety over time, limiting our ability to make inferences about the factors driving clinical levels of anxiety at this time. The COVID-19 pandemic was an

unexpected interruption to this study that posed very real challenges for adolescent mental health and introduced a huge life change that included changes such as attending school virtually and decreased in-person social interactions. While these changes were stressful for many, they also may have ameliorated some school and social-based anxieties in certain adolescents. For example, while recent research on the pandemic has documented increases in anxiety and depression amongst adolescents (Magson et al., 2021), findings suggest that pandemic-related effects were dependent adolescent mental health prior to the pandemic (Rothe, Buse, Uhlmann, Bluschke, & Roessner, 2021). In a longitudinal study of adolescents during the pandemic, pre-pandemic generalized anxiety predicted higher initial levels and maintenance of anxiety and stress during the pandemic, while pre-pandemic social anxiety predicted lower initial levels of anxiety and stress (Morales et al., 2022), perhaps due to the differing stressors associated with each disorder. As the shutdown interrupted the study and shifted the intervals between visits, future work will be needed ascertain how much of the variability was caused by this interruption to regular procedures. Additionally, while we did uncover effects of task on brain functional connectivity, we did not measure effective connectivity and therefore cannot speak to the direction or causality of these effects. Future research will be important for identifying how the dynamics of these neural circuits relate to anxiety and approach motivations in adolescents.

Nonetheless, this study provides valuable information regarding the concurrent development of anxiety and risky decision-making in adolescents and suggests potential avenues for intervention that might be especially fruitful during this period of development. Due to the importance of agency and self-identity in adolescence, fostering positive perceptions of decision-making that encourage confidence and vigilance in one's decisions might have an especially important impact on trajectories at this time. While greater positive perceptions of decision-

making predicted decreases in negative approaches to decision situations over time, changes in positive perceptions were not predicted by baseline negative perceptions, suggesting that interventions aimed at fostering positive perceptions of decision situations might have downstream effects on negative perceptions, in turn decreasing anxiety symptoms. As neural decision-making circuits are especially sensitized and still developing through this period, learning methods for conflict processing that encourage critical thinking and agency in one's decisions might be especially useful and resistant to extinction during this time. Furthermore, as faster deliberation time during decision-making at baseline predicted decreased anxiety, increased neural conflict processing, and (marginally) greater positive perceptions of decision situations over time, improving decision confidence and focusing on the rewarding aspects of action and learning rather than rumination and avoidance may be an especially useful strategy for adolescents who struggle with anxiety.

CHAPTER 5

General Discussion to the Dissertation

Pediatric anxiety disorders often emerge in adolescence, are marked by behavioral avoidance, and prove difficult to effectively diagnose and treat (Kessler et al., 2007; Merikangas et al., 2010). Although avoidance conflicts with the typical adolescent propensity for approach behavior, research suggests that shared neural mechanisms—namely, the combination of subcortical sensitivity in the striatum and amygdala and ongoing regulatory development in the prefrontal cortex—contribute to both the rise of sensation seeking and the emergence of clinical anxiety during this time. Prior to this dissertation, anxiety and risk-taking in adolescents have primarily been studied in isolation, precluding the opportunity to understand how brain and behavioral development contributes to *both* phenotypes during this period and identifying factors that promote healthy development across decision making and mental health domains. The studies contained in this dissertation help to fill this gap in the literature by conducting a thorough examination of both neural and behavioral markers of risky decision-making and anxiety symptoms in a group of 100+ diverse adolescents over a period of 1-3 years.

Learning to avoid situations that trigger fear is a cardinal symptom of anxiety disorders that conflicts with the normative adolescent propensity for heightened approach behavior (Galván, 2013) and can be especially resistant to extinction during this period of development (Klein et al., 2020). In both human and animal models, adolescents show impairments in fear extinction and demonstrate increased fear generalization and elevated fear responses to safety during avoidance learning (K. D. Baker et al., 2016, 2014; Klein et al., 2021, 2020), leaving adolescents especially vulnerable to persistent or habitual avoidance. The consequences of overly

avoidant behavior may be particularly insidious for adolescents, who are in a critical period of development during which approach-motivated behavior serves to promote exploration, learning, and goal-directed behavior (Casey et al., 2008). Therefore, an understanding of how adolescent brain development contributes to vulnerability for both maladaptive approach (e.g., substance abuse or criminal offending) and maladaptive avoidance (e.g., anxiety and fear-related disorders) trajectories is a crucial next step for combatting and ameliorating anxiety in adolescents.

According to the Triadic Model of adolescent motivated behavior, heightened sensitivity of the ventral striatum (VS) coupled with still-developing regulatory systems in adolescence will bias behavior towards approach responses in the face of an approach-avoidance conflict (Ernst et al., 2009). However, the striatum and its connections are also crucial for avoidance learning (Delgado et al., 2008) and play a critical role in adolescent anxiety (Bar-Haim et al., 2009; Benson et al., 2014; Guyer et al., 2012, 2006). While overly avoidant behavior is often attributed to over reactivity of the threat-sensitive amygdala, animal models have demonstrated that habitual or persistent avoidance forgoes the amygdala and instead correlates with activity in the striatum and prelimbic cortex—or dorsal anterior cingulate cortex (dACC) in humans (Bravo-Rivera et al., 2015). Therefore, heightened striatal sensitivity and neuroplasticity of dACC-VS circuits may also contribute to a different phenotype in anxious adolescents that is not captured by the current model. Understanding how the competing influences of anxiety and approach motivations influence adolescent behavior and neural decision-making circuits is an important next step for delineating the shift from normative to pathological anxiety from a neurobiological perspective.

In Study 1, we made a first foray at answering these questions by examining the neural mechanisms underlying avoidance behaviors in situations involving risky decision-making and

response inhibition in a group of early adolescents ages 9-13. The adolescents studied in this dissertation were across a continuum of normative anxiety levels with the intent of examining factors contributing to adolescent-onset anxiety *prior to* the development of full-blown clinical anxiety. Adolescents with higher anxiety in the current sample did not show associations with task risk aversion, highlighting the nuanced association between anxiety and risk-taking behaviors in adolescence. Although there was no association between anxiety and frequency of risks, this study did uncover an interesting pattern: anxious youth were faster at inhibiting their behavior when instructed on response inhibition trials, but they took longer to respond when voluntarily avoiding a risk, suggesting that the approach-avoidance conflict inherent in decision-making involving uncertain outcomes interfered with their decision-making efficiency. Even further, anxious adolescents reported significantly higher negative perceptions of decision situations such as panicking when and putting off making decisions and significantly lower positive perceptions of decision situations such as confidence in and vigilance when making decisions, suggesting that even subclinical anxiety symptoms show strong associations with self-perceptions of one's own decision-making abilities. Of note, these negative perceptions of decision situations were not related to accuracy or risk-taking frequency on the task, suggesting that they were driven by anxiety rather than reflecting their personal abilities.

The Triadic model posits that reward sensitivity and regulatory systems will bias behavior towards approach responses in adolescents compared to adults, while the emergence of anxiety in adolescence has been attributed to developmental changes in threat sensitivity and threat generalization that bias behavior towards avoidance responses (Britton et al., 2013; Lau et al., 2011). As the neural circuits involved in approach and avoidance decisions overlap, a nuanced analytic approach that considers the patterns of brain response across regions can be

especially useful for gleaning insight into how the adolescent brain distinguishes between or generalizes across decision situations. The studies in this dissertation utilize representational similarity analysis (RSA) (Kriegeskorte et al., 2008), a promising approach for tackling these types of questions in which we leverage information contained in the *patterns* of activity across multiple voxels of the brain to characterize the unique neural representation of a stimulus. Using this approach, we find that adolescents with higher anxiety show greater neural generalization across voluntary risk avoidance and instructed loss avoidance conditions, and this overgeneralization across conditions involving inhibition explained the link between anxiety and negative perceptions to decision situations. Therefore, their longer response time during risky decision-making was paralleled by generalization across risk avoidance and loss avoidance in the brain, suggesting an impairment in conflict processing perhaps driven by or contributing to their negative perceptions of decision situations.

While anxiety was not linked to risk-taking frequency, the neural mechanisms driving risk taking differed by anxiety such that greater left inferior frontal gyrus (IFG) recruitment during risk avoidance was associated with greater risk taking in high anxiety and greater risk aversion in low anxiety. We also identified a circuit between the VS and the right IFG that promoted risk avoidance regardless of anxiety levels. This suggests that while VS-IFG connections promote risk avoidance in non-anxious adolescents, anxious youth might demonstrate a different phenotype in which the usual regulatory function of the left IFG is repurposed to promote risky behavior in anxious youth, perhaps due to amygdala down-regulation. VS connectivity during risk avoidance was negatively associated with risk-taking frequency in youth with high anxiety and positively associated with risk taking in youth with low anxiety, highlighting the role of the VS in both adolescent approach and avoidance phenotypes.

Overall, these findings suggest that cautious behavior, or risk avoidance, plays an important role in adolescent decision-making and shows fundamental differences from instructed inhibition (e.g., loss avoidance) that may be important when considering anxiety. Figure 5.1. shows a theoretical model adapted from (Diehl et al., 2019) that lays out the hypothesized differences between the neural circuits involved in voluntary risk avoidance versus instructed loss avoidance. During avoidance of ambiguous or conflicting (e.g., due to potential reward) threat, the dACC (or prelimbic cortex in rodents) is necessary for active avoidant behavior. However, when threat becomes imminent or clear (e.g., response inhibition), the amygdala to VS pathway takes over, bypassing the inhibitory influence of the dACC on the VS (Diehl et al., 2019). This model helps explain the findings involving response time and dACC recruitment that show up repeatedly across chapters: youth with higher anxiety demonstrated reduced dACC recruitment paralleled by increased deliberation time on risky decision-making trials but not on response inhibition trials. This suggests that the dACC plays a crucial role in avoidance involving uncertainty or conflict but is not as necessary for the avoidance of clear and imminent threat, suggesting that the dACC may be a promising region to target in interventions for adolescent anxiety.

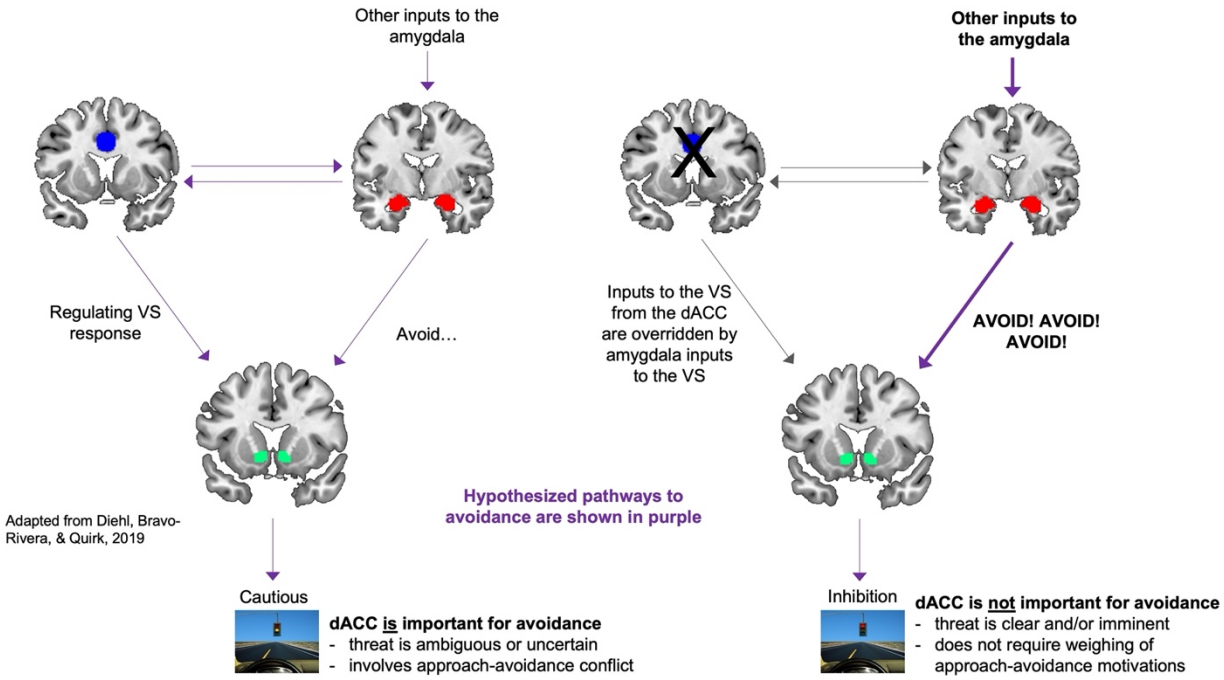

Figure 5.1. Proposed model of the brain regions involved in voluntary risk avoidance (cautious choice) versus instructed loss avoidance (response inhibition). In situations involving conflict or uncertainty, the dACC and its projections to the VS and amygdala are crucial for avoidance. However, in situations where threat is clear and imminent, amygdala signals to the VS override input from the dACC, triggering urgent avoidance. As youth with higher anxiety showed reduced dACC recruitment paralleled by longer response time on risky decision-making trials, this may signify impairments in conflict processing in the dACC. Adapted from Diehl, Bravo-Rivera, and Quirk, 2019 (Diehl et al., 2019).

Although anxiety can impact decision-making, it is far from the only important factor influencing brain and behavioral functioning in adolescence and may interact with other facets of adolescent development to impact approach and avoidance behaviors. In Study 2, we probed further into the mechanisms underlying risk taking in anxious youth by examining how anxiety

and approach motivations relate to adolescent risk-taking behaviors and amygdala-striatal-dACC circuitry during risky decision-making. Approach motivations, measured through sensitivity of the behavioral activation system (BAS), were positively correlated with positive perceptions of decision situations but unrelated to anxiety levels, suggesting that confidence and vigilance in decision-making are intertwined with adolescent approach motivations such as drive to achieve goals and fun seeking. As hypothesized, BAS sensitivity moderated the association between anxiety and task risk taking such that youth with high anxiety and low BAS were risk-averse, while youth with high anxiety and high BAS were high risk-takers, providing further evidence for the idea that anxious adolescents may demonstrate excessive risk taking or excessive risk avoidance depending on factors such as approach motivations.

In the brain, BAS sensitivity was negatively associated with dACC-amygdala and dACC-VS communication during risk taking versus risk avoidance, while anxiety severity was associated with heightened dACC-amygdala and reduced amygdala-VS communication during risk taking. Youth with higher anxiety also showed reduced dACC recruitment during risk avoidance, and dACC recruitment during risk avoidance was positively associated with risk-taking frequency and positive perceptions to decision situations. Study 2 also extends the task-based findings to the resting adolescent brain, finding that BAS correlated positively with dACC-VS and amygdala-VS connectivity at rest, while youth with higher anxiety did not show age-related decreases in dACC-amygdala coupling. Overall, the findings presented in Study 2 provide a mechanistic explanation regarding how anxiety and approach motivations might interact to influence adolescent risk taking through their influence on shared neural circuits during risky decision-making.

In Study 3, we shed light on the mechanisms contributing to the development of anxiety and risk taking in adolescence by examining longitudinal change in anxiety symptoms and neural and behavioral correlates of risk avoidance in the same sample of adolescents over a period of approximately 1.3 years. Changes in anxiety over time were directly associated with changes in the way in which adolescents approach decision situations, with worsening anxiety predicting decreased decision confidence and increased decision panic and complacency over time. Increases in anxiety were reflected in reduced dACC activation and increases in striatal connectivity with the dACC during risk avoidance, while increases in risk taking were reflected in heightened dACC and VS activation during risk avoidance. Even further, changes in risk taking were paralleled by changes in amygdala (but not striatal) connectivity during risk avoidance, highlighting the importance of the amygdala in studies of adolescent risk taking. Taken together, results from this chapter help to delineate the shared behavioral and neural mechanisms that contribute to anxiety and risky decision-making in adolescents and highlight the potential of leveraging these shared mechanisms to promote positive approaches to decision-making amongst developing youth.

A key finding that emerged across the chapters in this dissertation was that increases in anxiety correlated with reduced dACC activation paralleled by heightened communication between the VS and the dACC during risk avoidance. On the other hand, increases in adolescent risk taking correlated with increased activation in both the dACC and the VS during risk avoidance. The combination of low dACC activation and heightened dACC-VS communication observed in anxious adolescents may indicate habitual or persistent avoidance as shown in Figure 5.2. While the reduced dACC activation might indicate impaired conflict processing or lack of approach-avoidance conflict during decision-making, dACC-VS circuits are important

for habitual avoidance and may indicate a shift towards maladaptive avoidance from goal-directed decision-making. This also helps explain how VS sensitivity in adolescence could function to promote both approach and avoidance responses and offers additional insight on the results from Study 1 in which striatal connectivity during risky decision-making was related to risk taking in youth with low anxiety but risk avoidance in youth with high anxiety.

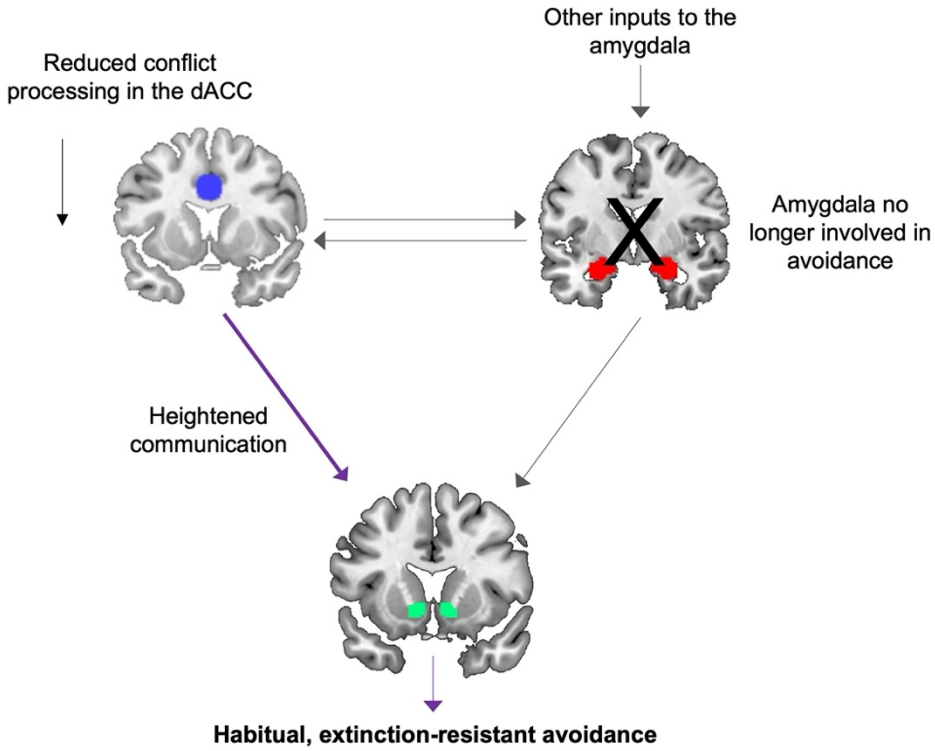

Figure 5.2. Proposed model of the brain regions involved in habitual or persistent avoidance. When avoidance becomes persistent or habitual, the amygdala is no longer involved in shaping avoidance action selection processes, with avoidance instead relying on the dACC and VS (Bravo-Rivera et al., 2015). While anxious adolescents in this study demonstrated reduced dACC activation during risk avoidance, they also showed heightened dACC-VS communication during risk avoidance, suggesting a shift towards habitual avoidance that no longer requires conflict processing or threat signaling from the amygdala.

Interestingly, it has been hypothesized that a more general role for the dACC is a center that is responsible for determining the optimal allocation of control by calculating expected value of control in a given situation (Shenhav, Cohen, & Botvinick, 2016). Research suggests that in adaptive aversive learning, the dACC receives information regarding absolute errors from regions such as the amygdala, which it then evaluates and turns into signed errors before sending them back to the amygdala and related regions (e.g., ventral striatum) for implementation (Klavir, Genud-Gabai, & Paz, 2013). According to this theory, the dACC evaluates the situation and determines the cost and benefit of control-based effort for a given task. Although control in a situation is valuable, it requires effort as compared to automatic responding. dACC signals during demanding tasks have been shown to correlate with avoidant preferences and task-related negative affective reactions, as well as with decreased reward-related responses in the VS following task completion (Shenhav et al., 2016). Lesions to the dACC have been linked to slower response time and difficulty overcoming effortful obstacles, while dACC stimulation has been linked to willingness to persevere (Shenhav et al., 2016). The results discussed in this dissertation align with this theory, as we repeatedly find associations between worsening anxiety, slower response time during approach-avoidance conflict, and reduced dACC recruitment during risk avoidance. Even further, dACC recruitment during risk avoidance was positively associated with positive perceptions of decision situations in the current sample, suggesting that the dACC and its connections could be a promising target for intervention.

The COVID-19 pandemic

The COVID-19 pandemic was an unexpected interruption to data collection and to the lives of the adolescents participating in this study. However, as roughly half of the sample completed their second time point after the pandemic shutdown, this study provided the unique

opportunity to examine differences in development between the two groups. Interestingly, only one measure of change showed differences based on the pandemic, and that was change in negative perceptions of decision-making—the pandemic group reported higher decision panic and complacency when they returned for their Year 2 visit.

The pandemic shutdown not only took away many opportunities for adolescent decision-making, but also introduced an aspect of uncontrollability that may have negatively impacted adolescents' perceptions of their own decision-making abilities. On a more hopeful note, positive perceptions of decision situations at baseline buffered against negative effects of the pandemic on negative perceptions of decision-making, suggesting that interventions aimed at building positive approaches to decision situations and increasing decision confidence might help foster resilience during times of great uncertainty such as the COVID-19 pandemic.

Limitations

The findings discussed in this dissertation should be interpreted in the context of several limitations. First, as the bulk of these analyses include only 1 or 2 timepoints, we were not able to examine growth curves or shape of growth patterns over time. Future work with more time points is needed to ascertain true developmental patterns, as these facets of adolescent development may not demonstrate simple linear trajectories. Additionally, participants in this sample showed average decreases in anxiety over time, limiting our ability to make inferences about the factors driving clinical levels of anxiety at this time. The COVID-19 pandemic was an unexpected interruption to this study that posed very real challenges for adolescent mental health and introduced a huge life change that included changes such as attending school virtually and decreased in-person social interactions. While these changes were stressful for many, they also may have ameliorated some school and social-based anxieties in certain adolescents. For

example, in a longitudinal study of adolescents during the pandemic, pre-pandemic generalized anxiety predicted higher initial levels and maintenance of anxiety and stress during the pandemic, while pre-pandemic social anxiety predicted lower initial levels of anxiety and stress (Morales et al., 2022), perhaps due to the differing stressors associated with each disorder. As the shutdown interrupted the study and shifted the intervals between visits, future work will be needed ascertain how much of the variability was caused by this interruption to regular procedures. Additionally, while we did uncover effects of task on brain functional connectivity, we did not measure effective connectivity and therefore cannot speak to the direction or causality of these effects. Future research will be important for identifying how the dynamics of these neural circuits relate to anxiety and approach motivations in adolescents.

Finally, although the fMRI task employed in the studies in this dissertation had valuable assets such as measuring risky decision-making and cognitive control in the same design, there were downsides to including more conditions—most notably in the number of trials per condition. Although each participant encountered hundreds of "go" trials, they encountered only about 35 risky decision-making trials and 35 response inhibition trials at each time point. To examine differences between successful inhibition and false alarms, or between risky and cautious trials, divides these numbers even further and introduces unavoidable confounds for study inclusion whereby one of the key variables of interest (e.g., number of risks taken) affects whether the participant can be included in an analysis. For example, if a certain group of participants never takes risks, they cannot be included in a group analysis examining the neural correlates of risky trials. Having more trials offers a higher degree of reliability, which is an important factor in longitudinal designs. Therefore, future analyses with the same task may want to utilize an approach such as group independent components analysis (ICA) that uses all trials

across all subjects to identify meaningful components of neural response that can then be related back to individual differences in task behavior and anxiety.

Future directions: How do we encourage positive risk taking?

When discussing adolescent risk taking and avoidance, the matter of safety always comes into play. It is undeniable that risky behaviors can have negative consequences, and those negative consequences are often unfairly distributed amongst adolescents. For example, we (amongst others) have previously shown that Black adolescents have a significantly lower barrier to entry into the criminal justice system than white adolescents: white adolescents committed significantly more risky criminal behaviors prior to justice system involvement, while Black adolescents were arrested after fewer risky behaviors (Padgaonkar et al., 2021). While this is a critical issue that needs addressing going forward, this dissertation emphasizes the value of cautious decision-making—even in the absence of risks themselves. In fact, most adolescents across the ages of 9-16 in this sample made significantly more cautious than risky choices. However, where the anxiety-based differences emerged was not in the amount of risky behavior, but rather in the deliberation time and brain response during risk avoidance. Neural response during risk avoidance showed associations with anxiety and with number of risks taken during the task, highlighting its use for understanding the neural computations that go into building up to take a risk without requiring risky behavior in and of itself. It is possible that the deliberation and conflict processing involved in cautious decision-making serves to bolster decision confidence and vigilance that works adolescents up for eventual exploration and risk taking. Studying cautious decision-making in adolescents could prove useful for understanding cases of excessive risk taking (e.g., substance abuse or criminal offending) as well as cases of excessive risk aversion (e.g., anxiety or fear-related disorders).

Due to the importance of agency and self-identity in adolescence, fostering positive perceptions of decision-making that encourage confidence and vigilance in one's decisions might have an especially important impact on anxiety trajectories at this time. As neural decision-making circuits are especially sensitized and still developing through this period, learning methods for conflict processing that encourage critical thinking and agency in one's decisions might be especially useful and resistant to extinction. It has been hypothesized that developmental studies involving early-life enriched experiences (as opposed to early-life stress) would be a useful model for understanding whether pleasurable experiences during childhood promote neuroplasticity and lead to better top-down inhibition and more "balanced" adolescent responses to environmental demands (Fernández-Teruel, 2021). Here, we argue for a similar idea: perhaps interventions aimed at increasing positive perceptions about and approaches to decision situations through a focus on learning and problem solving could help train regulatory systems in the dACC and allow for more flexible responding to environmental demands, thereby giving adolescents a sense of control, safety, and confidence in their ability to approach decisions. Encouraging positive approaches to decision-making could bolster adolescent agency and perhaps reduce the urge to "act out" through criminal offending or internalize and start a pattern of habitual avoidance which keeps one from learning and exploring in adolescence. Taken together, the findings presented in this dissertation provide valuable information regarding the concurrent development of anxiety and risky decision-making in adolescents and highlight potential avenues for intervention that might be especially fruitful during this period of development.

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