Grant Report

The Development of Anxiety in Youth Study (DAYS): A Prospective Study of Trajectories of Brain Maturation among Youth at Risk for Anxiety†

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ABSTRACT

Anxiety disorders are common across development and are associated with significant functional impairment and distress. Despite neuroimaging advancements in uncovering key brain regions, including the amygdala and prefrontal regions, implicated in anxiety, there is a need to characterize the role of the ventral striatum given its well-documented link to several key anxiety processes. This study aims to characterize specific neural mechanisms that underlie the evolution of illness and impairment using a longitudinal design and to move beyond traditional case control designs to provide a more comprehensive view of the developmental psychopathology of pediatric anxiety.

KEYWORDS: anxiety; development; brain; reward

INTRODUCTION

Anxiety disorders occur commonly among children and adolescents [1], and they are associated with substantial distress and impairment [2]. When left untreated, these disorders typically run a chronic, fluctuating course, and they can place youth at risk for a host of subsequent difficulties, including substance use, depression, and educational/occupational underachievement [3–5]. Although evidence-based treatments exist and are helpful to many affected youth, few achieve full remission and relapse is unfortunately common over the long-term [6,7]. Against this backdrop, there remains a need to better understand factors that shape the course and persistence of anxiety and that might be inform novel treatment development.

As an emotion, anxiety captures a diffuse sense of unease or apprehension, often occurring in response to unknown or future-oriented events [8]. It is distinct from fear, which is an in-the-moment response to a known threat. As with all emotions, anxiety is conceptualized as a normal, natural, and necessary mood state. It occurs along a continuum,
and is cause for concern only at its more problematic extremes (i.e., when marked distress and impairment are present). Thus, the anxiety spectrum includes mild, transient, and normative symptoms at one end and pervasive, severe, and highly impairing symptoms at the other.

Longitudinal studies of youth anxiety reveal substantial heterogeneity in outcome, but with limited exception [9], rarely consider biological substrates that might account for these differences. By contrast efforts to understand the biological underpinnings of anxiety have been almost exclusively cross-sectional. This work pinpoints the amygdala (AMY) and ventrolateral prefrontal cortex (vlPFC) as central hubs in a fear circuit that also includes the anterior cingulate cortex (ACC) [10–12]. In both animal studies and human subject research, atypical responses to threat are reported in these regions both among adolescents with anxiety disorders and among those with a history of behavioral inhibition (BI) [11–15]. Previous studies [16,17] suggest that the vlPFC regulates arousal through its effects on attentional control. Human lesion [18] and brain imaging [19] work also implicate the ventromedial PFC (vmPFC) in regulating AMY activity in individuals with and without trait anxiety. Other research has focused on approach systems, specifically the ventral striatum, finding evidence for heightened striatal sensitivity among adolescents with a history of BI [20–22] and/or current anxiety disorder [23].

Despite these advances, the field lags in two key areas. First, although pediatric anxiety neuroimaging studies have proliferated over the past decade, there has been relatively less attention to the role of the ventral striatum in existing models. This is understandable in light of its central standing in the reward literature. At the same time, it is unfortunate given its well-documented link to several key anxiety processes (e.g., attention bias, fear conditioning, motivation) [24,25]. Indeed, emerging evidence suggests that atypical engagement of the ventral striatum is characteristic of youth with anxiety [26]. Second, the integration of approach and avoidance systems has received limited attention to date. Recent work suggests that both adolescents with generalized anxiety disorder (GAD) [10] and young adults with a childhood history of BI [27] exhibit altered frontostriatal/amygdaostriatal functional connectivity during threat processing. What remains unknown is the developmental trajectory of this unique connectivity phenotype and whether/how it explains worsening of anxiety symptoms and functional impairment as youth move through adolescence.

The Current Study

The Development of Anxiety in Youth Study (DAYS) is a prospective longitudinal study of youth across the anxiety spectrum. It aims to characterize specific neural mechanisms that underlie the evolution of illness and impairment and to move beyond traditional case control designs to provide a more comprehensive view of the developmental psychopathology of pediatric anxiety. Prior cross-sectional research has
been crucial for identifying circuitry that underlies pediatric anxiety. Yet, by design, it cannot answer questions about how these nodes develop. Equally important, it has overlooked the role of other systems with known links to anxiety, including the ventral striatum [24]. Finally, by relying on case control designs, it has sacrificed power and compromised the ability to understand individual differences in outcome. DAYS addresses these gaps by focusing on: (1) the interplay of a more complete suite of circuitry in contributing to youth anxiety and (2) the development of this network and its links to anxiety over time. Findings will illuminate the component/interactive processes by which approach, avoidance, and cognitive control circuitry contribute to anxiety. Study procedures for this study include the collection of multivariate and multi-informant data, including brain imaging, cognitive tests, computerized assessments, sleep assessments, clinical interviews and self-reports feelings and behaviors. Together, these rich data will permit a holistic examination of the underlying antecedents, mechanisms and behavioral patterns that will help guide treatment.

A Neurodevelopmental Framework

Age-expectant and adaptive changes in a distributed network of brain regions underlie behavioral sensitivity to risk and reward among typically-developing (TD) youth [28]. Our work has examined how the interplay of approach, avoidance, and cognitive control circuitry explains the propensity for increased risk-taking during adolescence, revealing that, among TD youth, subcortical regions underlying approach behaviors (e.g., ventral striatum; VS) show greater governance over behavior compared to the prefrontal regions that underlie regulation and inhibition [29–31]. These distinct developmental trajectories account for increases in exploration and risky behavior observed among TD adolescents [32–34]. Here, we use this model as a backdrop for understanding deviations from the TD trajectory among anxious youth. According to recent meta-analyses [35], epidemiological studies [36], and DSMV [37]. Anxiety peaks in adolescence and is characterized by behaviors at odds with normative development (risk-aversion), as well as neural perturbations associated with both approach and avoidance responses [10,12,16,20,23]. As noted, the role of the ventral striatum has been largely overlooked despite its role in processes central to anxiety (e.g., attention bias) [26]. Moreover, there is little understanding of the integrative relationships between approach and avoidant processes and the role that maturing cognitive control circuitry plays in modulating these limbic-based fear systems and influencing outcomes.

AIMS OF THE GRANT

**Aim 1:** To model connectivity among approach-, avoidance- and cognitive control circuitry during risky decision-making tasks across a continuum of anxious phenotypes cross-sectionally. We apply Dynamic
Causal Modeling (DCM) and novel functional connectivity methods [38] to advance current neurobiological models. Through this grant we aim to characterize the relationship between distinct neural nodes through the use of connectivity tools (dynamic causal modeling [DCM] and novel models of hemodynamic response/associations of response trajectories across regions). DCM is a powerful tool used to infer relational architecture of coupled or distributed systems [39]. It measures associations among physically disparate regions, and critically, the direction of those associations. DCM is used with fMRI data to create a simple model of neural dynamics in a network of interacting brain regions [40]. This model estimates how changes in neuronal activity in one node sequentially influence activity in other nodes. Since its inception, DCM has been refined to furnish an explicit generative model of relational linkages underlying observed data. Although it is a powerful tool, DCM is limited in its ability to examine several key attributes of functional connectivity (FC), including peak amplitude and latency and functional canonical correlations (FCC). Peak amplitude and latency correspond to the highest level of activity and shape of the hemodynamic response curve that contributes to connectivity parameters. FCC measures associations between entire activation trajectories for two regions, without focusing on particular features. Both of these classes of measurement are suitable for trial-based experiments, do not assume stationarity of the activation time series observed for each brain region and allow adjustments for other brain regions through partial correlations. These tools have been used with clinical populations [41] and anxious youth [38] can be used to determine whole brain network structure instead of simply doing FC analyses between ROIs, and are flexible, taking brain activity data as inputs but also accepting peripheral physiological measures into the FC function [38]. Specifically, these approaches will allow us to identify the precise contributions of known (AMY, PFC) and novel (VS) regions [39] by testing interactional and directional effects between prefrontal and limbic regions.

**Aim 2:** To track trajectories of symptoms, behavior and neural activation among youth who vary in anxiety longitudinally. Exploratory Aim: To examine trajectories of connectivity among approach-, avoidance- and cognitive control circuitry in youth who vary on anxiety symptomatology. We will fit DCMs at each time-point and use the resulting parameter estimates in longitudinal models to characterize changes in relational patterns at both the individual and group levels.

**PROCEDURES**

**Overall Structure.** This study includes a community sample ($n = 120$) of youth ages 9–13 years at baseline selected to capture the full range of anxiety with oversampling at the more severe end of the distribution. Efforts are made to oversample at the elevated end of the spectrum using the parent- and self-reported Screen for Child Anxiety Related Disorders
(SCARED) [42] as a screening tool. Importantly, our specified age range is not meant to capture first emergence of anxiety or, necessarily, the transition to disorder. Rather, it is chosen based on robust evidence documenting that symptoms are likely to worsen in this window. Although prior research in community samples suggests that for some youth, there will be attenuation of anxiety symptoms as they progress toward adolescence, it also highlights marked heterogeneity in outcomes with pathways of persistence and worsening for some [43]. Indeed, the average age of onset for several forms of anxiety disorder (a distinction made based on distress and impairment) is during adolescence, by definition suggesting a worsening of symptoms relative to childhood.

Participants are followed annually for three years to track trajectories of change in approach, avoidance, and cognitive control circuitry along with anxiety symptoms and functional impairment. Measurements are taken at year 1 and then twice more annually. At each time-point, participants perform computer tasks while undergoing fMRI designed to elicit engagement of the circuitry of interest, as well as completing self-report, behavioral, and psychophysiological measures. The computer tasks have been validated in our prior cross-sectional work [44] and have the distinct advantage of assessing unique and interactive contributions of approach-, avoidance-, and cognitive control circuitry. They position us to understand both the avoidance that characterizes the anxious phenotype and heterogeneity that may emerge over time with respect to risk-taking behavior (e.g., coping via risky behaviors such as drinking). This is particularly important given that a subset of anxious youth will exhibit increases in risk taking behavior over time, including substance use, distracted driving, and unprotected sex [45–51]. Study tasks are complemented by innovative neuroimaging models that specifically test the direction of influence among circuitry underlying these processes [40]. Uncovering the dynamics of this network will elucidate how regions previously studied in isolation interact to contribute to heterogeneity in symptom course and will identify targets for novel intervention.

Research Participants. This study enrolls participants who are (1) ages 9–13 at baseline; (2) right-handed; (3) free of metal; (4) have no medical or psychiatric conditions contraindicating study participation (e.g., suicidality); (5) have no current or lifetime history of treatment for anxiety, or history of taking medication for anxiety. Participants are ineligible for the study if they (1) use current psychotropic medication other than those that can be discontinued safely for brief washout prior to scanning; (2) have current major depressive disorder (MDD) as determined by semi-structured diagnostic interview; (3) present with other serious mental illness (i.e., schizophrenia, substance abuse) as assessed via semi-structured diagnostic interview. We exclude youth for whom naturalistic longitudinal study without intervention would pose medical or safety concerns. This includes youth with psychosis, eating disorder, and active self-injury and/or suicidal ideation. Youth with
medical conditions that may require ongoing intervention and/or medications that would interfere with imaging are also excluded, in consultation with our study physician.

**Assessment**

Symptoms are assessed both dimensionally and categorically using gold standard procedures. In line with our emphasis on capturing the full spectrum of anxiety symptom severity, participants complete the Screen for Child Anxiety Related Disorders (SCARED) [42], a 41-item questionnaire, which correlates strongly with clinician-based measures of symptom severity, provides a psychometrically-sound dimensional measure across the anxiety continuum, and enhances our ability to observe the evolution of symptoms over time.

To capture potential anxiety disorder diagnosis as well as relevant comorbidities, the Anxiety Disorders Interview Schedule for DSM-IV, Child Version (ADIS-C) [52] is also administered by trained evaluators. The ADIS assesses anxiety, mood, and externalizing behavior disorders in youth and screens for the presence of several additional disorders including developmental, psychotic, and somatoform disorders. Additionally, it provides information regarding age of onset, impairment, and avoidance [53]. The interview is both reliable and valid [54].

Additional domains of measurement capture potential risk and protective factors and include variables such as life stress, family functioning, peer relationships, puberty, and sleep.

**Brain Imaging Tasks**

Broadly, the neuroimaging tasks in this study are designed to measure risk-taking and striatal-based learning. The former is measured using the “Driving Game”. In this task, participants move a car along a computerized track with the goal of reaching the end as fast as possible to maximize earnings. Traffic lights positioned at intersections turn yellow as the car approaches. Drivers choose whether to make the cautious decision and stop at the light (adding a short delay) or make a risky decision and drive through the intersection to reach the finish line (gaining time and earnings). However, if the light turns red while the participant is crossing the intersection, the car crashes and there is a longer delay. There are two 12-min rounds, each using a track with 20 intersections, treated as separate trials with a jittered inter-trial interval (ITI). The latter is measured via a learning task called the “T-Shirt Game”. Participants are asked to learn associations between t-shirt patterns and universities. They will be presented with one t-shirt pattern (e.g., swirls) that is paired with a university (e.g., Northern University) on 80% of trials. They press a button when they see the correct pair.
Laboratory Tasks

Participants complete three computer tasks that capture information processing domains expected to interact with our risk taking measures of interest. These include measures of interpretation bias, decision-making, and frustration tolerance. Biased appraisals are captured via the Performance-Based Interpretation Bias Task [55]. This task is a lab measure of how youth attribute threat to environmental ambiguity, and it requires participants to watch a screen as a word appears (500 ms), with a sentence following the word and then indicate via button press whether the word and sentence are related \((n = 240 \text{ trials})\). The program provides the percentage of neutral/threat words endorsed as relevant to ambiguous sentences, and reaction time (RT). This task has established psychometric properties and predicts a significant proportion of variance in anxiety symptoms in our prior work. (~15 min). Participants also complete the Cups Task, which measures decision-making under conditions of potential gains and losses [56]. In both gain and loss domains, participants are asked to choose between a certain and uncertain option. Depending on the domain, the certain option is to win or lose $2 for sure, whereas the uncertain (risky) option consists of a probability (0.20, 0.33, or 0.50) of a larger win ($4, $6, or $10) or no win in the gain domain or of a greater loss ($4, $6, or $10) or no loss in the loss domain. This task uses images of overturned cups divided by a vertical line that demarcates which side of the line is associated with certain and uncertain monetary outcomes. Participants are asked to choose between the certain and uncertain option. After the choice is made, the gamble is resolved immediately, allowing participants to experience the consequences of the gains or losses. Outcome probabilities and the amount of money in this task are manipulated in such a way that the overall expected value of the certain and uncertain outcome is equal. Thus, this task examines whether or not participants’ decisions are influenced by who they’re making decisions for and/or whether the choice is presented as a gain or a loss. Participants perform 2 runs of this task, each run is approximately 7 min long. (~14 min). The final laboratory task is the Mirror-Tracing Persistence Task-Computerized Version (MTPC-C, 15 min). The computerized Mirror Tracing Persistence task has been shown to be difficult and frustrating [57] and has been used in the literature as a behavioral measure of distress tolerance in adolescents [58]. Participants are to move a red dot along lines of a star presented on a computer monitor with a computer mouse. The mouse is programmed to move the red dot in the opposite direction of physical movement of the mouse. In this way, the task simulates tracing an object that is viewed in a mirror. There are 3 levels used to increase stress and frustration, followed by a final level where participants can discontinue the task by pressing a key on the keyboard. Distress tolerance is measured as time to task termination on this final level. Using the Positive and Negative Affect Scale (PANAS), an established measure of
positive and negative affect, youth rate their levels of positive and negative affect before and after task-completion (~15 min).

**Biological Variables**

Physiological data is collected during the Mirror-Tracing and Cups tasks. These variables will be used as covariates in analyses to determine individual differences in physiological response as related to behavior and anxiety. The primary outcomes obtained during the MTPT-C include autonomic reactivity (galvanic skin response; GSR) and startle (electromyography; EMG). GSR is continuously recorded from two electrodes positioned on the distal phalanges of the fore- and middle fingers of the non-dominant hand. Startle is collected using orbicularis oculi EMG recorded continuously from two electrodes below each eyelid and a ground electrode behind the ear. Electrodes are filled with conduction gel as contact medium between skin and electrode.

**CONCLUSIONS**

We report on the DAYS Project, which is currently completing data collection. Findings from this study have the potential to inform our understanding of how anxiety develops over time and what contributes to risk of developing anxiety. In turn, the hope is that they might inform the development of novel interventions. Although speculative at this juncture, we see several potential applications. The longitudinal design will allow us to examine changes across a period of heightened plasticity to determine whether there are developmental windows during which we can leverage change to introduce positive remodeling (e.g., novel therapeutics). New interventions might directly target identified biomarkers (e.g., neurocognitive therapies to normalize aberrations in avoidance circuitry). Alternatively, findings may be used to make existing psychosocial interventions more potent and efficient. For example, given that cognitive behavior therapy (CBT) involves a collection of treatment techniques, awareness of where deficits lie (e.g., compromised cognitive control systems) may point to treatment components that require greater emphasis (e.g., cognitive coping skills). Finally, we note that while direct clinical translation remains steps away, the rich multivariate dataset that emerges from this project will allow testing of profiles at multiple levels of analysis and their role in anxiety at the individual level.

**AUTHOR CONTRIBUTIONS**

AG and TP wrote the manuscript.

**CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.
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