

ABSTRACT

Title of Thesis: PREADOLESCENT REWARD PROCESSING
DIFFERENTIATES IRRITABILITY
TRAJECTORIES ACROSS EARLY
ADOLESCENCE

Annika J. Quam, Master of Science
2025

Thesis Directed By: Professor Lea Rose Dougherty
Department of Psychology

Aberrations in reward processing are associated with youth irritability, a top psychiatric concern. Some youth show chronically high or increasing levels of irritability across development, which are associated with psychiatric problems in adulthood. The current study examines whether preadolescent reward processing differentiates high-risk irritability trajectories across the transition to early adolescence. This study used participants from the Adolescent Brain Cognitive Development (ABCD) study (n = 5794, 49.67% female) and caregiver-reported youth irritability scores using the Child Behavior Checklist (CBCL) from ages 9-10 to 13-14. Preadolescent reward-related brain function was used to predict four irritability trajectories: high chronic (n=307, 5.29%), high decreasing (n=498, 8.60%), low increasing (n=689, 11.89%), and low stable (n=4300, 74.20%). Reward-related brain function was measured using the Monetary Incentive Delay (MID) task during reward anticipation and reward feedback. Findings demonstrated that youth in the high chronic and high decreasing trajectory groups had less

activation and weakened right ventral striatum and right amygdala connectivity during reward and loss anticipation compared to the low stable and low increasing groups. During the feedback period, youth in the high chronic trajectory group had greater right amygdala connectivity during hit versus miss trials and increased right ventral striatum connectivity in the missed trial during the loss condition. Preadolescent reward processing differentiated youth who showed high irritability levels across the transition to early adolescence. These neural patterns may identify high-risk youth and serve as potential targets to intervene and alter the course of irritability.

PREADOLESCENT REWARD PROCESSING DIFFERENTIATES IRRITABILITY
TRAJECTORIES ACROSS EARLY ADOLESCENCE

by

Annika Quam

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, College Park in partial fulfillment
of the requirements for the degree of
Masters of Science in Psychology
2025

Advisory Committee:
Chair: Dr. Lea R. Dougherty
Dr. Alexander J. Shackman
Dr. Alyssa Parker

© Copyright by
Annika J. Quam
2025

Introduction

Youth irritability, characterized as proneness to frustration and anger, is a top presenting problem in youth seeking psychiatric care (Copeland, Brotman, & Costello, 2015; Evans et al., 2023; Leibenluft et al., 2024). Irritability is a transdiagnostic symptom associated with both youth internalizing and externalizing psychopathology (Leibenluft et al., 2024; Vidal-Ribas & Stringaris, 2021) and prospectively predicts adult depression, anxiety, suicide, and impaired functioning (Brotman et al., 2006; Silver et al., 2024; Stringaris et al., 2009). Moreover, there are individual differences in how youth irritability levels change across development with approximately 5-18% of youth experiencing chronically high or increasing irritability levels over time (Ezpeleta et al., 2016; Orri et al., 2019; Pagliaccio et al., 2018; Riglin et al., 2019; Wiggins et al. 2014). These high risk irritability trajectories incur risk for psychiatric disorders and impairment later in development (Ezpeleta et al., 2016; Pagliaccio et al., 2018). Identifying neural predictors that differentiate high risk irritability trajectories can potentially aid in developing targeted mechanistic treatments that can alter the course of irritability.

Longitudinal research including youth from early childhood through adolescence has identified distinct developmental trajectories of irritability. Across development, the majority of youth in community samples experience low and stable irritability levels with normative increases occurring around early childhood and adolescence (Boylan et al. 2017; Ezpeleta et al., 2016; Orri et al., 2019; Pagliaccio et al., 2018; Riglin et al., 2019; Wiggins et al. 2014; Yu et al., 2023; Zhang et al., 2024). Using data from the Adolescent Brain Cognitive Development (ABCD) study, we previously identified four distinct irritability trajectories spanning from preadolescence (ages 9-10) to early adolescence (ages 12-13) using annual caregiver-report youth irritability scores from the Child Behavior Checklist (Jordan et al., *in prep*). Consistent with previous literature, the

majority of youth had low stable irritability across early adolescence ($n= 8692$, 73.28%), while low but increasing ($n=1449$, 12.22%), high and decreasing ($n=1083$, 9.13%), and high and chronic irritability trajectories ($n=638$, 5.38%) made up about a quarter of the sample. The changes in irritability across this developmental period may be particularly important as Yu et al. reported that during preadolescence (around age 9), irritability levels show an inflection point from which irritability levels begin to increase or decrease as they enter adolescence (Yu et al., 2023). These findings suggest that preadolescence may be a pivotal time in changing irritability between childhood and adolescence, particularly as irritability levels during adolescence do not show the same decline as earlier in development (Silver et al., 2024). Thus, an important next step is to identify preadolescent predictors, particularly mechanism-based neural predictors, of high risk irritability trajectories. These predictors could then potentially serve as intervention targets to alter the course of irritability and related psychiatric problems in adolescence.

As irritability results from a frustrative non-reward response, aberrant neural responses to reward are hypothesized to contribute to chronic and severe youth irritability (Leibenluft et al., 2024). When an individual does not receive an expected reward, individuals with higher levels of irritability demonstrate altered neurobiological circuitry in the regions involving the ventromedial prefrontal cortex, amygdala, and ventral striatum (for a review see Leibenluft, 2017 and Brotman et al., 2017). Recent studies have also shown that irritability impacts other facets of reward processing than frustrative non-reward, including altered neural activation and connectivity during reward anticipation and performance feedback (Dougherty et al., 2018; Krzya-Lacombe et al., 2021; Nielsen, Wakschlag, & Norton, 2021; Parker et al., 2025). However, there has not been a clear pattern of results across studies, possibly due to small sample sizes, different developmental ages included, and the use of different fMRI tasks to measure reward processing (Lee et al., 2023). Importantly, the current literature is limited to cross-sectional studies of youth irritability and

reward processing. No study, to our knowledge, has examined whether reward-related brain function predicts changes in youth irritability over time. Distinct neurobiological activation and connectivity patterns during reward processing, especially in reward-related regions such as the ventral striatum and amygdala, may differentiate youth who go on to exhibit high and increasing levels of irritability from youth who show low, stable levels of irritability or decreasing levels during critical periods of development.

The goal of this study is to determine preadolescent reward-based neurobiological predictors of high-risk irritability trajectories across the transition to early adolescence. We used the four trajectories previously derived from the ABCD study spanning ages 9-10 to ages 12-13 in a sample of 11,874 youth: high chronic, high decreasing, low increasing, and low stable (Jordan et al., *in prep*). To measure baseline reward-related brain function, the ABCD study uses the monetary incentive delay (MID) task, which assesses both reward anticipation and reward feedback to reward and loss. We hypothesize that neural responses to anticipated and received reward and loss will differentially predict high-risk irritability trajectories from low-risk trajectories above and beyond baseline irritability. As previous literature has highlighted the role of the amygdala and ventral striatum in both irritability and reward processing, we hypothesize that there will be aberrant whole brain activation and connectivity in these regions in youth with high-risk irritability trajectories during reward and loss anticipation and performance feedback compared to low-risk trajectories (Kryza-Lacombe et al., 2021; Liuzzi et al., 2023; Perlman et al., 2015).

Methods

Participants

This study used data from the ABCD study Release 4.0 (baseline fMRI and demographic

data; DOI: 10.15154/1523041) and 5.1 (irritability data; DOI: 10.15154/z563-zd24). Participants were excluded if they did not have complete basic demographic information or MRI data files (n=5600). Additionally, participants were excluded if they had poor task performance (n=436), a history of brain trauma or seizures (n=57), or failed to pass fMRI quality checks, which includes ABCD study's quality checks and author checks of collinearity, coverage, motion, and censored TR checks (n=388). For more detailed information regarding the exclusion criteria, see Parker et al., 2025.

Irritability Trajectories

To assess irritability levels at each time point, the irritability scores were summed from three questions on the Child Behavioral Checklist on a scale from 0, not at all, to 2, very true/often true (Achenbach & Edelbrock, 1991). This assessment of irritability has been validated and used in previous research (Roberson-Nay et al., 2015; Stringaris et al., 2012; Wiggins et al., 2014). The questions include, item 85- stubborn sullen, or irritable, item 86- sudden changes in mood or feelings, and item 95- temper tantrums or hot temper. The total irritability score is from 0 to 6, with higher scores indicating higher irritability. The trajectories were derived using Latent Class Growth Modeling. The 4-class model rendering the best model fit with four different irritability trajectories between preadolescence into early adolescence. The groups include: low stable irritability (n= 8692, 73.28%), low increasing irritability (n=1449, 12.22%), high decreasing irritability (n=1083, 9.13%), and high chronic irritability (n=638, 5.38%), see Figure 1. For more information about the trajectory development, see Jordan et al., *in prep*. For the demographic information of each trajectory included in the final analyses, see Table 1.

Irritability trajectories differed significantly by parental education [$\chi^2(3)=31.19, p<.001$]. Individuals in the high chronic group are significantly more likely to have no parent with a college degree than individuals in the low increasing ($p < 0.001$) or low stable ($p < 0.001$) groups.

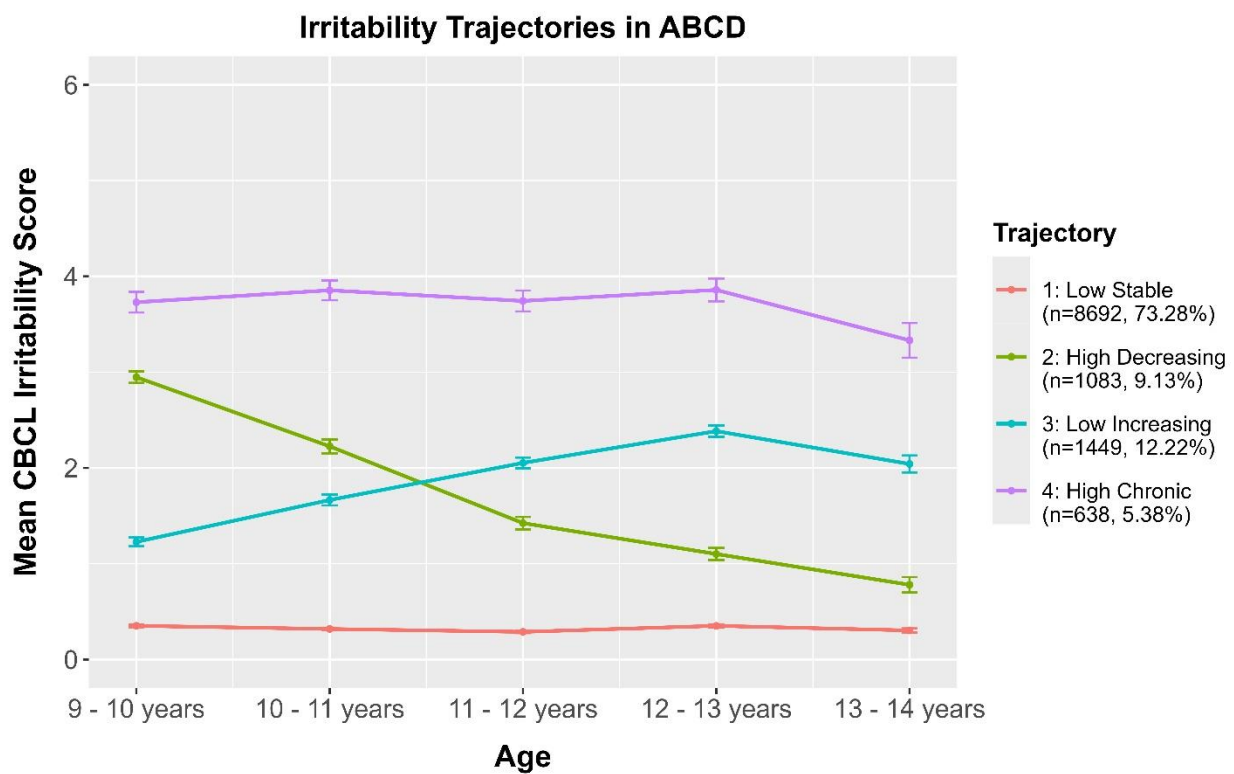
Individuals in the low increasing group are significantly more likely to have a parent with a college degree than individuals in the high decreasing group ($p = 0.002$). Irritability trajectories also significantly differed by sex assigned at birth [$\chi^2(3)=10.93, p=0.012$], with the high chronic group having a greater percentage of males than the low increasing ($p = 0.034$) or low stable ($p = 0.018$) groups. Irritability trajectories did not differ significantly by age or race/ethnicity.

Table 1: Demographic Information

Trajectory Group		High Chronic	High Decreasing	Low Increasing	Low Stable
Participants (%)		307 (5.29%)	498 (8.60%)	689 (11.89%)	4300 (74.20%)
Youth age (SD)		9.95 (0.62)	9.90 (0.63)	10.00 (0.62)	9.96 (0.63)
Sex	Male	180 (58.63%)	263 (52.81%)	337 (48.91%)	2137 (49.70%)
	Female	127 (41.37%)	235 (47.19%)	352 (51.09%)	2163 (50.30%)
Race/Ethnicity	White	186 (60.59%)	295 (59.24%)	424 (61.54%)	2381 (55.37%)
	Black	28 (9.12%)	46 (9.24%)	58 (8.42%)	519 (12.07%)
	Asian	3 (0.98%)	8 (1.61%)	13 (1.89%)	91 (2.12%)
	Multiracial	26 (8.47%)	46 (9.24%)	70 (10.16%)	385 (8.95%)
	Hispanic or Latine/a/o	62 (20.20%)	95 (19.08%)	114 (16.55%)	871 (20.26%)
	Indigenous/Other	1 (0.33%)	7 (14.06%)	7 (10.16%)	45 (1.05%)
	Refused/Missing/Don't Know	1 (0.33%)	1 (0.20%)	3 (0.44%)	8 (0.19%)
Parental Education	No parent with a 4-year college degree	146 (47.56%)	205 (41.16%)	215 (31.20%)	1524 (35.44%)
	At least one parent with a 4-year college degree	161 (52.44%)	291 (58.43%)	474 (71.70%)	2770 (64.42%)
Irritability Index M(SD)					
Baseline	N = 5,794	3.79 (1.31)	2.92 (1.01)	1.25 (0.91)	0.35 (0.63)

1-Year Follow-Up	N = 5,497	3.70 (1.32)	2.20 (1.19)	1.64 (1.08)	0.32 (0.62)
2-Year Follow-Up	N = 5,397	3.64 (1.33)	1.45 (1.02)	2.07 (1.05)	0.28 (1.02)
3-Year Follow-Up	N = 5,096	3.87 (1.38)	1.09 (0.98)	2.43 (1.10)	0.35 (0.67)
4-Year Follow-Up	N = 2,702	3.23 (1.48)	0.77 (0.85)	1.99 (1.03)	0.29 (0.60)

Figure 1. Irritability trajectories of the ABCD sample (N = 11862)



Reproduced with permission from *Jordan et al. (in prep)*.

Monetary Incentive Delay (MID) Task

To assess reward processing, the ABCD study uses the MID task. To perform this task, participants were asked to quickly press a button in response to a stimulus while in a fMRI scanner. Based on the speed of pressing the button, participants could either win an amount of money

(reward condition), lose that same amount of money (loss condition), or neither win nor lose money (neutral condition). The task analysis is divided into two parts: anticipation and feedback. Anticipation is the period prior to pushing the button during which participants are informed of the trial's condition (reward, loss, neutral), and feedback is the period following the button pressing, during which participants are informed of their performance (i.e., whether they “hit” or “miss”). The task difficulty changes throughout the task in response to participant performance to ensure an accuracy rate of 60%. Participants who failed to respond to 30 or more trials or had <4 events for any trial type were excluded (n = 433).

Neuroimaging Analysis

Scans took place at 21 sites across the country using 3T scanners, either General Electric, Phillips, or Siemens, with a 32-channel head coil. The Functional MRI (fMRI) data was originally processed by DCAN (Developmental Cognition and Neuroimaging; Feczko et al., 2021). After DCAN's preprocessing, functional MRI data were downloaded from Release 4.0. Additional preprocessing steps and quality control measures were applied after download, including smoothing using a 6 mm kernel, censoring TR pairs with a framewise displacement exceeding 0.5mm, and adding nuisance regressors for head motion in the x, y, z, roll, pitch, yaw directions and their first derivatives to individual level analyses. dmBLOCK was used to model the data, with a variable anticipation period of 2-6s and feedback period of 1.5-1.8s. Each of the anticipation and feedback images were created on an individual level.

In order to build a comprehensive neurobiological understanding of the relationship between irritability trajectories and reward processing, we completed both activation and connectivity analyses. The activation analyses use voxel-wise whole brain activation to evaluate significant regions across the entire brain. Whole brain connectivity analysis investigation applied generalized psychophysiology interaction (gPPI) analyses (McLaren et al., 2012). gPPI analyses

are a method of functional connectivity that measure the connectivity between a designated seed region and the rest of the brain as a function of task conditions. Because the ventral striatum and amygdala have been associated with irritability and aberrant reward processing, we used the left and right ventral striatum and the left and right amygdala as the seed regions, or regions of interest (ROIs), for the analysis (Bell et al., 2021; Kryza-Lacombe et al., 2022). These seed regions were anatomically mapped using Talairach atlas-derived masks and transformed into MNI space through AFNI's 3dWarp tool. These seed regions were then used in whole brain analyses to determine clusters with significant connectivity with each region.

Data Analysis Plan

Whole brain analyses were conducted using 3dMVM in AFNI (Version 22.3.05; Cox, 1996) to examine the interaction of irritability trajectories and MID condition and/or performance on activation and connectivity. Irritability trajectories were coded as factors in the analysis. gPPI and whole brain activation analyses were performed for each period (anticipation, feedback). For the anticipation period, the independent variables in the analysis were irritability trajectory and condition (neutral, reward, loss). For the feedback period, the independent variables were irritability trajectory, condition (neutral, reward, loss), and performance (miss, hit). To account for potential differences among scanners, scanner serial number was used as a covariate in this initial analysis. A minimum cluster size of 87 voxels was determined through AFNI's ClustSim tool with a significant p -threshold of 0.005, which corrects for multiple comparisons through family-wise error rate.

As the ABCD study is a complicated dataset nested within various sites and families, follow up analyses were completed in R (R Core Team, 2025) using multilevel mixed effects linear models in package lme4 (Bates et al., 2015) and lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017) to account for these structural dependencies. These models controlled for youth age, parental

education, as measured by whether at least one parent received a college degree, and baseline parent-reported youth pubertal development, as measured with the parent report Pubertal Development Scale (PDS; Petersen et al., 1988), and nested within family and site scanner. For those with missing parent-reported pubertal development, youth reports on the PDS were used (n=96). Participants were excluded for corresponding analyses if they had zero voxels in the gPPI seed mask (n= 0-86) or if they had outliers in their activation or connectivity (>2.5 standard deviations from the mean; n = 5-115). Irritability trajectories and condition and/or performance were used as independent variables, and activation or connectivity within the significant cluster was used as the dependent variable. Tukey’s HSD test was used within each cluster to correct for multiple comparisons.

To ensure that the change in activation and connectivity are due to the relationship between the irritability trajectory and not the participants’ baseline level of irritability, baseline irritability and the interaction of baseline irritability and condition and/or performance were included as covariates.

Results

Significant whole brain results are presented in Table 2. Below we report results for significant interactions during anticipation and feedback periods.

Table 2.					
<i>Significant clusters resulting from whole brain analyses</i>					
<u>Anticipation</u>					
<i>Irritability Trajectory</i>					
<u>Left Ventral Striatum Connectivity</u>					
<u>k</u>	<u>F(3,5563)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
224	11.8	-44	-62	48	Left Inferior Parietal Lobe
150	8.5	-36	-82	8	Middle Occipital Gyrus
<i>Irritability Trajectory x Condition</i>					

Activation					
<u>k</u>	<u>F(6,11354)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
150	5.4	-38	-62	-10	Left Fusiform Gyrus
142	6	-58	-44	-14	Left Inferior Temporal Gyrus
115	5.2	-28	-76	50	Left Middle Occipital Gyrus
109	5.7	-6	44	-44	Left Cerebellum
89	5.4	14	-66	-44	Right Cerebellum
87	5.4	-32	14	32	Left Middle Frontal Gyrus
Right Ventral Striatum Connectivity					
<u>k</u>	<u>F (df=6,11174)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
204	5.2	-26	-62	-32	Left Cerebellum
178	5.5	42	-38	34	Right Postcentral Gyrus
129	5.8	0	-66	48	Left Precuneus
111	5.3	12	-40	30	Right Middle Cingulate Cortex
111	5.1	-24	-56	40	Left Precuneus
102	4.8	16	60	18	Right Superior Frontal Gyrus
100	4.9	-44	-74	0	Left Middle Occipital Gyrus
Right Amygdala Connectivity					
<u>k</u>	<u>F (df=6,11186)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
101	7.3	-42	-24	36	Left Postcentral Gyrus
Feedback					
<i>Irritability Trajectory</i>					
Activation					
<u>k</u>	<u>F (df=3,5705)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
101	9.5	-10	2	72	Left Superior Frontal Gyrus
Right Ventral Striatum Connectivity					
<u>k</u>	<u>F (df=3,5687)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
232	8.2	-18	40	44	Left Superior Frontal Gyrus
135	6.9	-42	-72	32	Left Angular Gyrus
96	8.9	-34	52	-6	Left Middle Orbital Gyrus
<i>Irritability Trajectory x Performance</i>					
Right Amygdala Connectivity					
<u>k</u>	<u>F (df=3,5681)</u>	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
397	10.7	-32	-70	54	Left Inferior Parietal Lobe
241	8.2	42	-60	52	Right Angular Gyrus
99	7.7	0	-60	42	Right Precuneus

<i>Irritability Trajectory x Performance x Condition</i>					
Right Ventral Striatum Connectivity					
<u>k</u>	<u>F</u> (df=6,11374)	<u>x</u>	<u>y</u>	<u>z</u>	<u>Region</u>
126	5.3	6	44	30	Right Superior Medial Gyrus

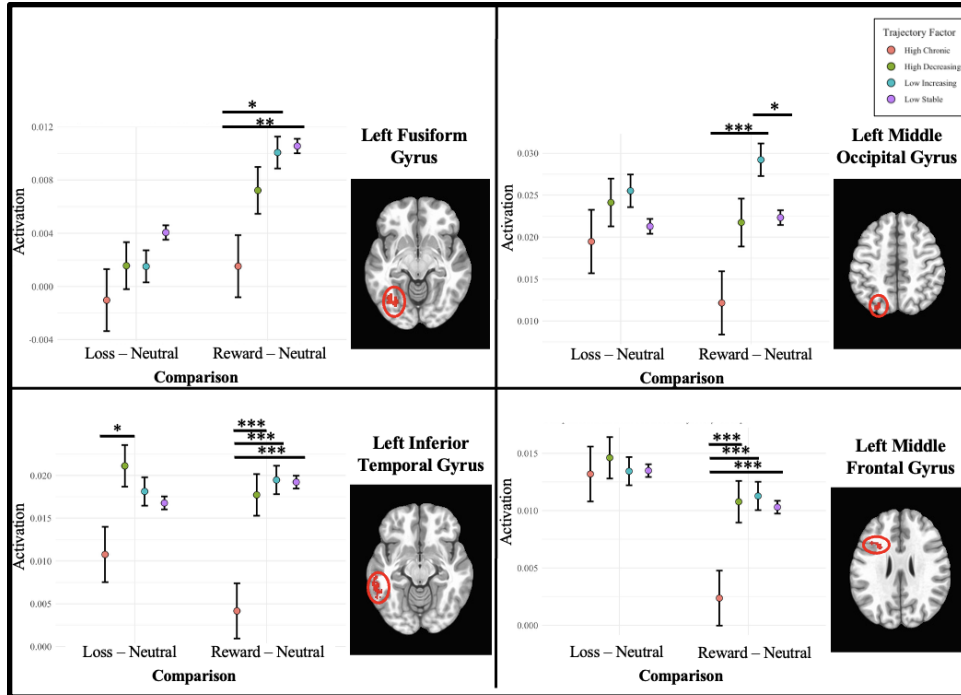
Anticipation Period

Irritability x Condition

Linear mixed effects models revealed significant interactions between irritability trajectory and condition on cluster activation and connectivity during the anticipation phase of the task. For each significant cluster, activation or connectivity differences in reward anticipation (reward condition minus neutral condition) and loss anticipation (loss condition minus neutral condition) were compared among trajectory groups.

Activation. Analyses showed a significant interaction of irritability trajectory and condition on activation during the anticipation phase in six clusters (Figure 1). The high chronic group had significantly lower activation during reward anticipation in the left inferior temporal and middle frontal gyri than the low stable, low increasing, and high decreasing groups, and in the left fusiform gyrus than the low increasing and low stable groups. The high chronic and low stable groups had significantly lower activation in the left middle occipital gyrus during reward anticipation than the low increasing group. The high decreasing group had significantly lower activation in the left and right cerebellum than the low stable and low increasing groups during reward anticipation. During loss anticipation, the high chronic group had significantly lower activation in the left inferior temporal gyrus compared to the high decreasing group.

Figure 2. Associations between whole brain activation and irritability trajectories during anticipation period.



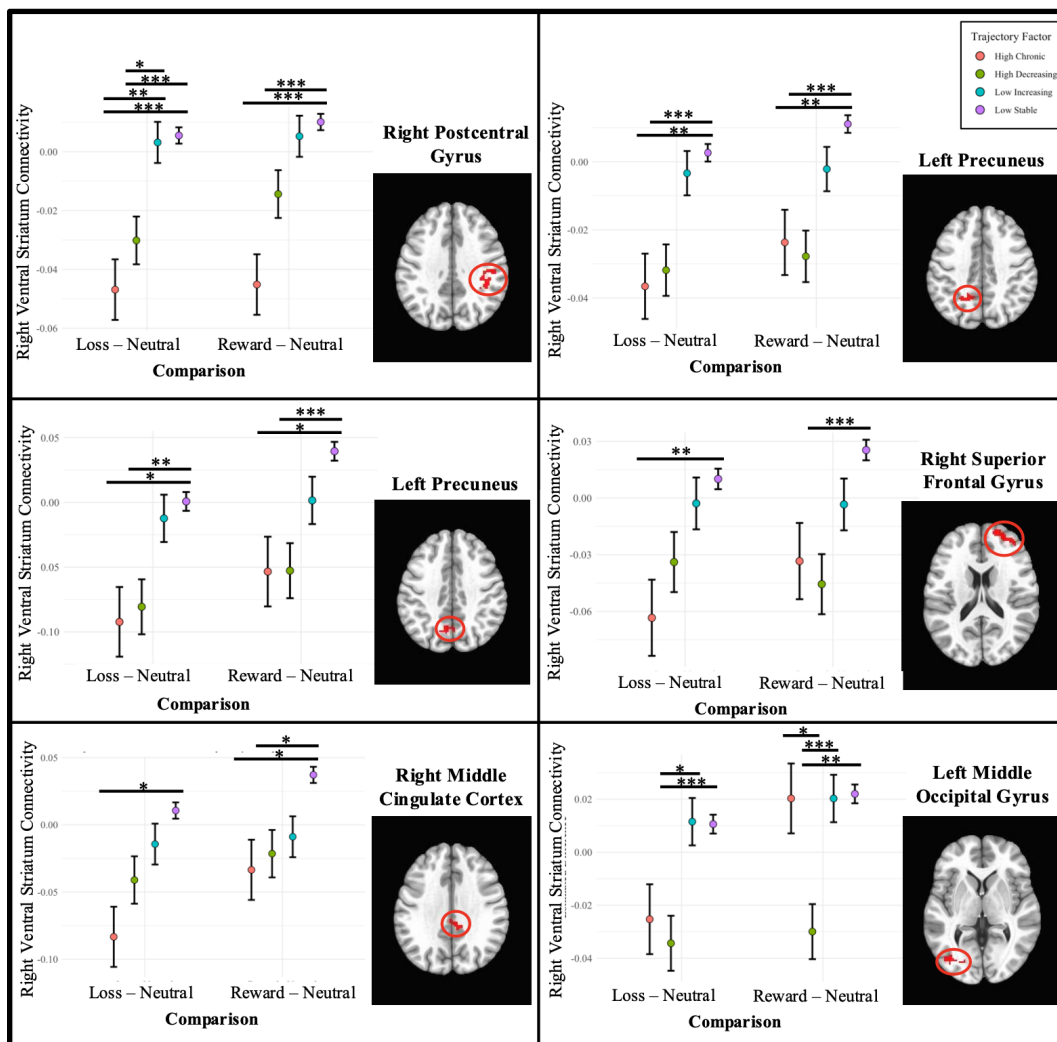
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Right Ventral Striatum Connectivity. Linear mixed effects models revealed a significant interaction between irritability trajectory and condition on the connectivity between the right ventral striatum and seven whole brain clusters (Figure 2). During reward anticipation, the high chronic group had significantly weaker right ventral striatum connectivity with the right postcentral gyrus than the low stable and low increasing groups and with the left precuneus than the low stable group. The high decreasing group had significantly weaker right ventral striatum connectivity with the left cerebellum, left precuneus, right superior frontal gyrus, and left middle occipital gyrus than the low stable group and with the left middle occipital gyrus than the low increasing group during reward anticipation.

During loss anticipation, the high chronic group had significantly weaker right ventral striatum connectivity with the left cerebellum, right postcentral gyrus, left precuneus, right middle cingulate cortex, and left middle occipital gyrus than the low stable group, and with the left

cerebellum, right postcentral gyrus, and left precuneus than the low increasing group. During loss anticipation, the high decreasing group had significantly weaker right ventral striatum connectivity with the left cerebellum, right postcentral gyrus, and left precuneus than the low stable group, and with the right postcentral gyrus, left middle occipital gyrus, and left precuneus than the low increasing group.

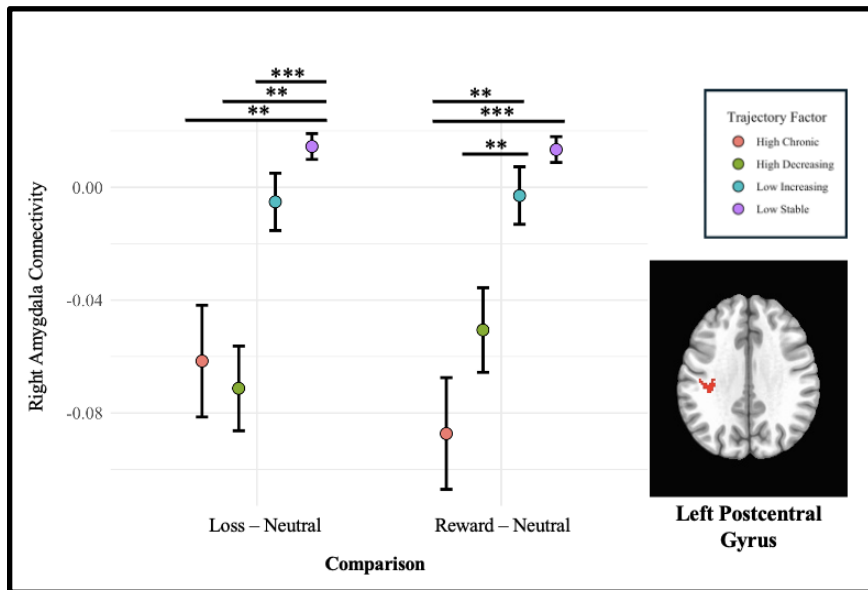
Figure 3. Associations between right ventral striatum connectivity and irritability trajectories during anticipation period.



* p < 0.05; ** p < 0.01; *** p < 0.001

Right Amygdala Connectivity. Linear mixed effects models revealed a significant interaction between irritability trajectory and condition on the connectivity between the right amygdala and the left postcentral gyrus. The high chronic group had significantly weaker connectivity during reward anticipation than the low increasing and low stable groups and significantly weaker connectivity during loss anticipation than the low stable group. The high decreasing group had significantly weaker connectivity during reward anticipation than the low stable group and significantly weaker connectivity during loss anticipation than the low increasing and low stable groups.

Figure 4. Associations between right amygdala connectivity and irritability trajectories during anticipation period.



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Performance Feedback Period

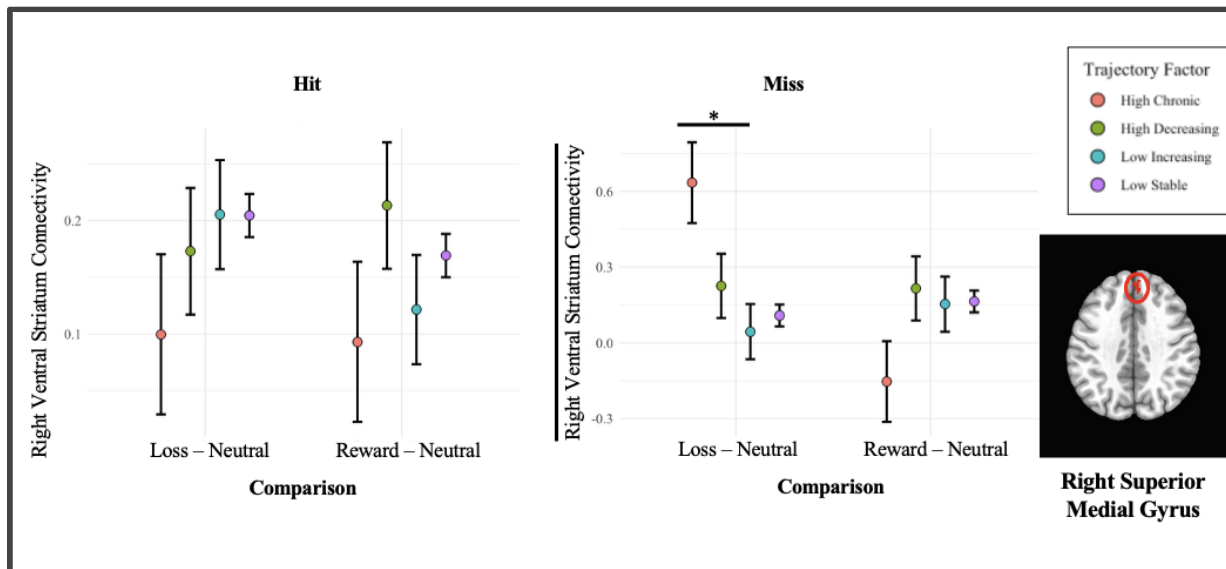
Irritability Trajectory x Condition x Performance

There was no significant interaction of irritability trajectory, condition, and performance

on cluster activation during the feedback period. Linear mixed effects models revealed a significant three-way interaction between irritability trajectory, condition, and performance on cluster connectivity.

Right Ventral Striatum Connectivity. Linear mixed effects models revealed a significant three-way interaction among irritability trajectory, condition, and performance on the connectivity between the right ventral striatum and the right superior medial gyrus. During miss trials, the high chronic group had significantly greater connectivity during the loss compared to the neutral condition than the low increasing group.

Figure 5. Associations between right ventral striatum connectivity and irritability trajectory during performance feedback.



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

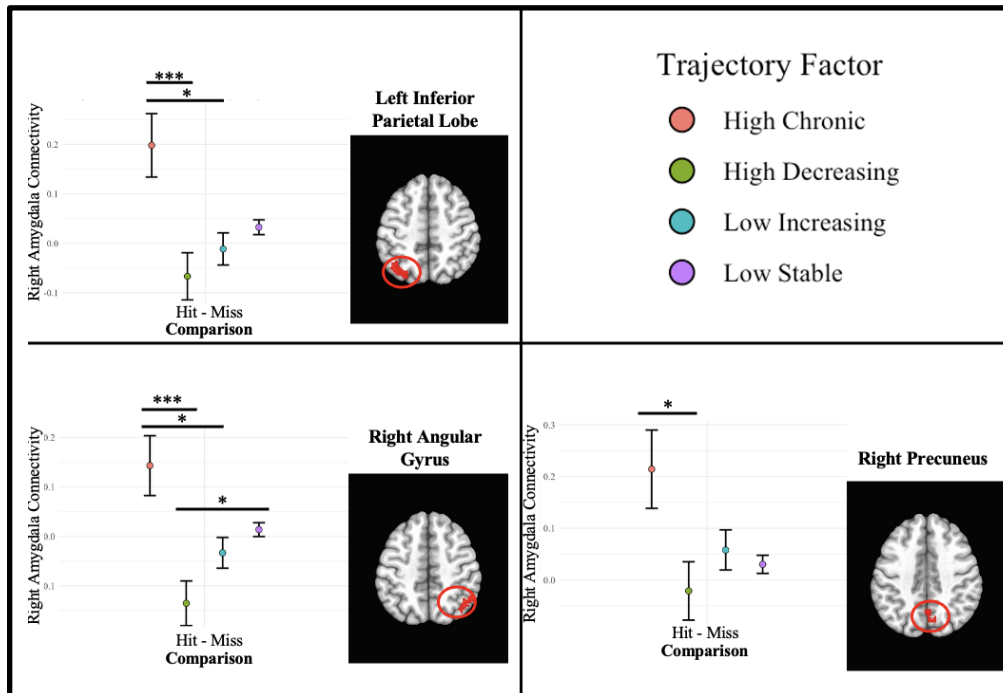
Irritability Trajectory x Performance

There was no significant interaction of irritability trajectory and performance on cluster activation during the feedback period. Linear mixed effects models revealed significant interactions between irritability trajectory and performance on cluster connectivity during the

feedback phase of the task. For each significant cluster, the difference in connectivity between hit and miss conditions were compared among trajectory groups.

Right Amygdala Connectivity. Linear mixed effects models revealed a significant interaction between irritability trajectory and performance on the connectivity between the right amygdala and three clusters: the left inferior parietal lobe, right angular gyrus, and right precuneus. In response to hit compared to missed feedback, the high chronic trajectory group had significantly greater right amygdala connectivity with the left inferior parietal lobe and right angular gyrus than the high decreasing and low increasing groups and with the right precuneus than the high decreasing group. The high decreasing group had significantly weaker right amygdala connectivity with the right angular gyrus than the low stable group in response to hit compared to miss.

Figure 6. Associations between right amygdala connectivity and irritability trajectories during performance feedback period



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Discussion

The present study identified preadolescent reward-related neural markers that predict the course of irritability across the transition to early adolescence above and beyond baseline irritability. During the reward and loss anticipation periods, youth characterized by high and chronic or high and decreasing levels of irritability exhibited both shared and distinct patterns of activation and connectivity compared to youth characterized by low and stable or low and increasing levels of irritability. Furthermore, youth with persistently high irritability showed aberrant connectivity during the feedback period compared to youth characterized by initially low and stable or low and increasing levels of irritability, underscoring the importance of both phases of reward processing in distinguishing the course of irritability. These reward-related neural patterns during preadolescence may contribute to these changes in irritability and may serve as neural targets to alter the course of early adolescent irritability.

During the anticipation phase, unique activation and neural connectivity patterns differentiated the high chronic group from the other trajectory groups. The high chronic group had decreased activation during reward anticipation in the left inferior temporal gyrus and left middle frontal gyrus compared to the other three trajectory groups. Moreover, the high chronic group exhibited uniquely weaker right ventral striatum connectivity with the right middle cingulate cortex and right superior frontal gyrus during loss anticipation compared to the low stable group. This relative blunted activation in regions involved in reinforcement learning, affect, and decision-making during reward anticipation, as well as weaker connectivity between subcortical and frontal regions during loss anticipation, may suggest less cognitive and emotional control during anticipation of a potential reward or loss (Dadario & Sughrue, 2023; Shackman et al., 2011; Zhuang et al., 2021). Neural connectivity during anticipation also identified shared neural responses between the high chronic and high decreasing groups compared to the low stable and

low increasing groups. During both reward and loss anticipation, the high chronic and high decreasing groups exhibited weaker right ventral striatum and amygdala connectivity with regions involved in self-referential, social, and emotional processing (Dadario & Sughrue 2023; Kropt et al., 2018; Rolls 2019). This weakened connectivity during reward anticipation across these regions aligns with neurological responses to reward anticipation in individuals with major depressive disorder, attention-deficit/hyperactivity disorder (ADHD), and high levels of concurrent irritability (Geugies et al., 2022; Kryza-Lacombe, et al., 2021; Plichta & Scheres, 2014). The blunted neural responses to reward and loss anticipation in both high chronic and high decreasing trajectory groups may be due to shared factors associated with high preadolescent irritability, including genetics, parental factors, life stress, and co-occurring psychopathology (Evans et al., 2017; Grasser et al., 2024; Vidal-Ribas et al., 2016; Wiggins et al., 2014).

Neural patterns during the feedback period demonstrated both sensitivity to loss and performance that may contribute to persistently high levels of irritability in youth. For instance, there was significantly greater connectivity between the right ventral striatum and the right superior medial gyrus in the high chronic group compared to the low increasing group during *loss*, i.e., a miss trial in a loss condition. This highlights a unique neurological response in the high chronic group in response to a lost reward in regions involved in decision making and emotion regulation, potentially contributing to persistent negative emotional responses to loss (Bratec et al., 2017). Consistent with this finding, studies have reported greater connectivity between the ventral striatum and the medial frontal gyrus during missed trials and more pronounced aberrant connectivity during miss trials between the amygdala and the superior frontal gyrus in youth with high compared to low irritability (Dougherty et al 2018; Kryza-Lacombe et al., 2021). Moreover, across conditions, there was significantly greater right amygdala connectivity with three clusters involved in the default mode network and fronto-parietal control network in the high chronic group

compared to the high decreasing and low increasing groups when they receive positive versus negative performance feedback. Previous studies have found greater differences in activation in the default mode network between positive and negative feedback in youth with chronic irritability, and our findings extend this to neural connectivity (Deveney et al., 2012; Perlman et al., 2015). Youth with chronically high irritability may be more sensitive to their own performance, either a success or failure.

Strengths of this study include a large, longitudinal, nationwide sample of youth and an examination of irritability trajectories and whole brain activation and connectivity during multiple phases of reward processing. This study also has its limitations. The irritability measure is limited to parent-report only and is a unidimensional three-item measure that does not differentiate distinct features of irritability (e.g. phasic and tonic) that have unique prognostic and mechanistic properties (Moore et al., 2019; Silver et al., 2023; Sorcher et al., 2024). Thus, future research should incorporate youth-reports of irritability and include multidimensional measures of irritability. Additionally, there was substantial exclusion of participants due to elevated movement and incomplete fMRI data, which limits the generalizability of the results. Moreover, the connectivity analyses focused on four seed regions; however, additional neural connections with other seed regions are likely implicated in irritability and warrant further investigation. Future work should also examine potential moderators of the relations between irritability trajectories and reward processing, such as parenting or parent psychopathology, or other comorbid forms of youth psychopathology, to identify risk and resilience factors that contribute to chronic vs. decreasing levels of irritability over time (Evans et al., 2017; Vidal-Ribas et al., 2016; Wiggins et al., 2014). This can further disentangle the longitudinal relationships between the brain, behavior, and environment on the mechanisms contributing to youth irritability. Additionally, future work is needed to examine associations between changes in reward processing and irritability across

development, given the robust developmental changes taking place in the cortical-amygdala circuitry and cognitive control networks through adolescence (Swartz et al., 2014).

This study highlights the predictive power of preadolescent reward processing on the course of irritability and contributes to our knowledge of the pathophysiology of youth irritability. We identified shared and unique neural patterns associated with the course of irritability which may provide insight into risk and resilience across this vulnerable developmental transition. Moreover, this work informs our search for biomarkers for youth irritability that identify high risk groups and can serve as potential targets for early intervention. It is imperative to unpack the neural processes contributing to chronic irritability given the long term negative consequences of chronic and severe irritability on youth's development.

Bibliography/References

- Achenbach, T. M., & Edelbrock, C. (1991). Child behavior checklist. *Burlington (Vt)*, 7, 371–392.
- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, 67(1), 1–48.
<https://doi.org/10.18637/jss.v067.i01>
- Bell, E., Boyce, P., Porter, R. J., Bryant, R. A., & Malhi, G. S. (2021). Irritability in mood disorders: neurobiological underpinnings and implications for pharmacological intervention. *CNS drugs*, 35(6), 619-641.
- Boylan, K., Rowe, R., Duku, E., Waldman, I., Stepp, S., Hipwell, A., & Burke, J. (2017). Longitudinal profiles of girls' irritable, defiant and antagonistic oppositional symptoms: Evidence for group based differences in symptom severity. *Journal of abnormal child psychology*, 45(6), 1133-1145.
- Bratec, S. M., Xie, X., Wang, Y., Schilbach, L., Zimmer, C., Wohlschläger, A. M., ... & Sorg, C. (2017). Cognitive emotion regulation modulates the balance of competing influences on ventral striatal aversive prediction error signals. *Neuroimage*, 147, 650-657.
- Brotman, M. A., Kircanski, K., Stringaris, A., Pine, D. S., & Leibenluft, E. (2017). Irritability in youths: A translational model. *American Journal of Psychiatry*, 174(6), 520-532.
- Brotman, M. A., Schmajuk, M., Rich, B. A., Dickstein, D. P., Guyer, A. E., Costello, E. J., ... & Leibenluft, E. (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biological psychiatry*, 60(9), 991-997.

- Copeland, W. E., Brotman, M. A., & Costello, E. J. (2015). Normative irritability in youth: developmental findings from the Great Smoky Mountains Study. *Journal of the American Academy of Child & Adolescent Psychiatry, 54*(8), 635-642.
- Cox, R. W. (1996). AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Computers and Biomedical Research, 29*(3), 162–173. <https://doi.org/10.1006/cbmr.1996.0014>
- Dadario, N. B., & Sughrue, M. E. (2023). The functional role of the precuneus. *Brain, 146*(9), 3598-3607.
- Deveney, C. M., Connolly, M. E., Jenkins, S. E., Kim, P., Fromm, S. J., Pine, D. S., & Leibenluft, E. (2012). Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biological psychology, 89*(1), 148-155.
- Dougherty, L. R., Schwartz, K. T. G., Kryza-Lacombe, M., Weisberg, J., Spechler, P. A., & Wiggins, J. L. (2018). Preschool- and school-age irritability predict reward-related brain function. *Journal of the American Academy of Child and Adolescent Psychiatry, 57*(6), 407–417.e2. <https://doi.org/10.1016/j.jaac.2018.03.012>
- Evans, S. C., Burke, J. D., Roberts, M. C., Fite, P. J., Lochman, J. E., de la Peña, F. R., & Reed, G. M. (2017). Irritability in child and adolescent psychopathology: An integrative review for ICD-11. *Clinical psychology review, 53*, 29-45.
- Evans, S. C., Corteselli, K. A., Edelman, A., Scott, H., & Weisz, J. R. (2023). Is Irritability a Top Problem in Youth Mental Health Care? A Multi-informant, Multi-method Investigation. *Child psychiatry and human development, 54*(4), 1027–1041. <https://doi.org/10.1007/s10578-021-01301-8>
- Ezpeleta, L., Granero, R., de la Osa, N., Trepato, E., & Domènech, J. M. (2016). Trajectories of

oppositional defiant disorder irritability symptoms in preschool children. *Journal of Abnormal Child Psychology*, 44(1), 115–128. <https://doi.org/10.1007/s10802-015-9972-3>

Feczko, E., Conan, G., Marek, S., Tervo-Clemmens, B., Cordova, M., Doyle, O., Earl, E., Perrone, A., Sturgeon, D., & Klein, R. (2021). Adolescent brain cognitive development (ABCD) community MRI collection and utilities. *BioRxiv*, 2021–07.

Geugies, H., Groenewold, N. A., Meurs, M., Doornbos, B., de Klerk-Sluis, J. M., van Eijndhoven, P., ... & Ruhé, H. G. (2022). Decreased reward circuit connectivity during reward anticipation in major depression. *NeuroImage: Clinical*, 36, 103226.

Grasser, L. R., Yang, R., Brotman, M. A., & Wiggins, J. L. (2024). The contribution of childhood trauma to irritability symptoms. *JCPP Advances*, 5(1), e12260. <https://doi.org/10.1002/jcv2.12260>

Jordan, L.S., Quam, A.J., Parker, A.J., Wiggins, J.L., & Dougherty, L.R. (*in prep*). A Machine Learning Approach to Predicting High-Risk Irritability Trajectories Across the Transition to Adolescence

Kryza-Lacombe, M., Hernandez, B., Owen, C., Reynolds, R. C., Wakschlag, L. S., Dougherty, L. R., & Wiggins, J. L. (2021). Neural mechanisms of reward processing in adolescent irritability. *Developmental Psychobiology*, 63(5), 1241–1254.

Kryza-Lacombe, M., Palumbo, D., Wakschlag, L. S., Dougherty, L. R., & Wiggins, J. L. (2022). Executive functioning moderates neural mechanisms of irritability during reward processing in youth. *Psychiatry Research: Neuroimaging*, 323, 111483.

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*,

82(13), 1–26. <https://doi.org/10.18637/jss.v082.i13>

- Lee, K. S., Hagan, C. N., Hughes, M., Cotter, G., Freud, E. M., Kircanski, K., Leibenluft, E., Brotman, M. A., & Tseng, W.-L. (2023). Systematic review and meta-analysis: Task-based fMRI studies in youths with irritability. *Journal of the American Academy of Child & Adolescent Psychiatry, 62*(2), 208–229.
- Leibenluft, E. (2017). Pediatric irritability: A systems neuroscience approach. *Trends in Cognitive Sciences, 21*(4), 277–289.
- Leibenluft, E., Allen, L. E., Althoff, R. R., Brotman, M. A., Burke, J. D., Carlson, G. A., Dickstein, D. P., Dougherty, L. R., Evans, S. C., & Kircanski, K. (2024). Irritability in youths: A critical integrative review. *American Journal of Psychiatry, 181*(4), 275–290.
- Liuzzi, M. T., Kryza-Lacombe, M., Christian, I. R., Owen, C., Redcay, E., Riggins, T., ... & Wiggins, J. L. (2023). Irritability in early to middle childhood: Cross-sectional and longitudinal associations with resting state amygdala and ventral striatum connectivity. *Developmental Cognitive Neuroscience, 60*, 101206.
- McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. *Neuroimage, 61*(4), 1277–1286.
- Moore, A. A., Lapato, D. M., Brotman, M. A., Leibenluft, E., Aggen, S. H., Hettema, J. M., ... & Roberson-Nay, R. (2019). Heritability, stability, and prevalence of tonic and phasic irritability as indicators of disruptive mood dysregulation disorder. *Journal of Child Psychology and Psychiatry, 60*(9), 1032-1041.
- Nielsen, A. N., Wakschlag, L. S., & Norton, E. S. (2021). Linking irritability and functional brain networks: A transdiagnostic case for expanding consideration of

development and environment in RDoC. *Neuroscience and biobehavioral reviews*, 129, 231–244. <https://doi.org/10.1016/j.neubiorev.2021.07.022>

Orri, M., Galera, C., Turecki, G., Boivin, M., Tremblay, R. E., Geoffroy, M.-C., & Côté, S. M. (2019). Pathways of association between childhood irritability and adolescent suicidality. *Journal of the American Academy of Child & Adolescent Psychiatry*, 58(1), 99–107.

Parker, A. J., Walker, J. C., Takarae, Y., Dougherty, L. R., & Wiggins, J. L. (2025). Neural mechanisms of reward processing in preadolescent irritability: Insights from the ABCD study. *Journal of Affective Disorders*, 370, 286–298.

Pagliaccio, D., Pine, D. S., Barch, D. M., Luby, J. L., & Leibenluft, E. (2018). Irritability trajectories, cortical thickness, and clinical outcomes in a sample enriched for preschool depression. *Journal of the American Academy of Child and Adolescent Psychiatry*, 57(5), 336–342.e6. <https://doi.org/10.1016/j.jaac.2018.02.010>

Perlman, S. B., Jones, B. M., Wakschlag, L. S., Axelson, D., Birmaher, B., & Phillips, M. L. (2015). Neural substrates of child irritability in typically developing and psychiatric populations. *Developmental cognitive neuroscience*, 14, 71-80.

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, 17(2), 117-133.

Plichta, M. M., & Scheres, A. (2014). Ventral–striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: A meta-analytic review of the fMRI literature. *Neuroscience & Biobehavioral Reviews*, 38, 125-134.

- R Core Team. (2025). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. <https://www.R-project.org/>
- Riglin, L., Eyre, O., Thapar, A. K., Stringaris, A., Leibenluft, E., Pine, D. S., Tilling, K., Davey Smith, G., O'Donovan, M. C., & Thapar, A. (2019). Identifying Novel Types of Irritability Using a Developmental Genetic Approach. *The American journal of psychiatry*, *176*(8), 635–642. <https://doi.org/10.1176/appi.ajp.2019.18101134>
- Roberson-Nay, R., Leibenluft, E., Brotman, M. A., Myers, J., Larsson, H., Lichtenstein, P., & Kendler, K. S. (2015). Longitudinal stability of genetic and environmental influences on irritability: From childhood to young adulthood. *American Journal of Psychiatry*, *172*(7), 657–664.
- Shackman, A., Salomons, T., Slagter, H. *et al.* The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* *12*, 154–167 (2011). <https://doi.org/10.1038/nrn2994>
- Silver, J., Mackin, D. M., Bufferd, S. J., Dougherty, L. R., Goldstein, B. L., Carlson, G. A., & Klein, D. N. (2023). Tonic and phasic irritability in 6-year-old children: differential correlates and outcomes. *Journal of child psychology and psychiatry, and allied disciplines*, *64*(2), 234–243. <https://doi.org/10.1111/jcpp.13688>
- Silver, J., Sorcher, L., Carlson, G. A., Dougherty, L. R., & Klein, D. N. (2024). Irritability across adolescence: Examining longitudinal trajectory, stability, and associations with psychopathology and functioning at age 18. *Journal of Affective Disorders*, *354*, 611–618.
- Sorcher, L. K., Silver, J., Chad-Friedman, E., Carlson, G. A., Klein, D. N., & Dougherty, L. R. (2024). Early predictors and concurrent correlates of tonic and phasic irritability in adolescence. *Research on Child and Adolescent Psychopathology*, *52*(7), 1105-

1117.

- Stringaris, A., Cohen, P., Pine, D. S., & Leibenluft, E. (2009). Adult outcomes of youth irritability: A 20-year prospective community-based study. *American Journal of Psychiatry, 166*(9), 1048–1054.
- Stringaris, A., Zavos, H., Leibenluft, E., Maughan, B., & Eley, T. C. (2012). Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *American Journal of Psychiatry, 169*(1), 47–54.
- Swartz, J. R., Carrasco, M., Wiggins, J. L., Thomason, M. E., & Monk, C. S. (2014). Age-related changes in the structure and function of prefrontal cortex–amygdala circuitry in children and adolescents: A multi-modal imaging approach. *Neuroimage, 86*, 212–220.
- Vidal-Ribas, P., Brotman, M. A., Valdivieso, I., Leibenluft, E., & Stringaris, A. (2016). The status of irritability in psychiatry: a conceptual and quantitative review. *Journal of the American Academy of Child & Adolescent Psychiatry, 55*(7), 556–570.
- Vidal-Ribas, P., & Stringaris, A. (2021). How and why are irritability and depression linked? *Child and Adolescent Psychiatric Clinics, 30*(2), 401–414.
- Wiggins, J. L., Mitchell, C., Stringaris, A., & Leibenluft, E. (2014). Developmental trajectories of irritability and bidirectional associations with maternal depression. *Journal of the American Academy of Child & Adolescent Psychiatry, 53*(11), 1191–1205.
- Yu, Q., Hodgdon, E. A., Kryza-Lacombe, M., Osuna, L., Bozzetto, L. E., Ciro, D., Wakschlag, L. S., & Wiggins, J. L. (2023). Roads diverged: Developmental trajectories of irritability from toddlerhood through adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 62*(4), 457–471.
- Zhang, Y., MacNeill, L. A., Edwards, R. C., Burns, J. L., Zola, A. R., Poleon, R. B., Nili, A. N.,

Giase, G. M., Ahrenholtz, R. M., & Wiggins, J. L. (2024). Developmental trajectories of irritability across the transition to toddlerhood: Associations with effortful control and psychopathology. *Research on Child and Adolescent Psychopathology*, 52(1), 125–139.

Zhuang, Q., Xu, L., Zhou, F., Yao, S., Zheng, X., Zhou, X., ... & Becker, B. (2021). Segregating domain-general from emotional context-specific inhibitory control systems-ventral striatum and orbitofrontal cortex serve as emotion-cognition integration hubs. *Neuroimage*, 238, 118269.