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Feedback-Related Negativity, Reward-Based Learning, and ADHD Symptoms: Preliminary Findings in a Pediatric Sample with Prominent Mood Symptoms

Giulia C. Salgari
University of Central Florida

FEEDBACK-RELATED NEGATIVITY, REWARD-BASED LEARNING, AND ADHD SYMPTOMS: PRELIMINARY FINDINGS IN A PEDIATRIC SAMPLE WITH PROMINENT MOOD SYMPTOMS

by

GIULIA C. SALGARI
M.S., Università Vita-Salute San Raffaele, 2012

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ABSTRACT

Reward-based learning is the ability to alter our future behavior following a novel reward. Dysregulation in this system has been linked to different forms of adult and pediatric psychopathologies such as mood disorders, for which it has proved to be an important treatment target given its link to broader health outcomes for these disorders. However, more research is needed to better understand its underlying mechanisms in the pediatric population. The current study examined how probabilistic reward learning, feedback-related negativity (FRN; an event-related potential from EEG), and dimensional ADHD symptom severity relate in adolescents with prominent mood symptoms. The final sample included 36 adolescents (72.2% female; aged 13 to 17) who completed a Probabilistic Reward Task (PRT) during EEG recording. Results revealed an inverse relationship between FRN mean amplitude and the reward learning score, independent of mood and ADHD symptoms. We also found that teens with increased overall ADHD symptom severity showed a larger (i.e., more negative voltage) FRN amplitude and a lower reward learning score. Exploratory analyses also showed that as ADHD inattentive symptom severity increased, FRN mean amplitude became more negative and reward learning score decreased. No significant relationship was found with ADHD hyperactive/impulsive symptom severity. In conclusion, our results showed that a poor modulation of behavior based on prior reward contingencies was related to an increase in dimensional ADHD symptom severity in a sample of adolescents with prominent mood difficulties. This behavioral dysfunction was also reflected by a blunted neural habituation to reward feedback as evidenced by a larger FRN mean amplitude. Additionally, exploratory analyses highlighted how the relationship between overall ADHD symptom severity and FRN may be driven especially by symptoms of inattention vs.

hyperactivity/impulsivity. Results suggest deficits in reward learning that could impact response to behavioral therapies in youth with mood disorders and comorbid inattentive ADHD.

For my son, Leonardo: All my work is for you.

For my parents, Naty and Roberto, and my husband, Federico, who always believed in me.

None of this would have been possible without your support.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER ONE: INTRODUCTION

Reward-Based Learning

The National Institute of Mental Health's Research Domain Criteria (RDoC) approach was created to characterize symptoms based on "dimensions of observable behaviors and brain functions" with a particular focus on biomarkers and behaviors associated with domains of basic human neurobehavioral functioning (Insel, 2010). One of these domains, "positive valence systems," includes different constructs of the reward system such as reward responsiveness (i.e., ability to experience pleasure in anticipation or presence of a possible reward), reward learning (i.e., learning to alter future behavior following receipt of reward), and reward valuation (i.e., evaluation of the probability and benefits of a possible outcome based on different elements such as external information and past experiences).

Dysregulation in reward-based learning has been linked to different forms of adult psychopathology, such as mood disorders (Vrieze et al., 2013), anxiety disorders (Reilly et al., 2020), and externalizing disorders (e.g., attention-deficit/hyperactivity disorder; Aster et al., 2024). In addition, it has been hypothesized that blunted reward learning may also reflect a deficit in the approach-related system and may lead to low motivational drive, reduced goal-directed behavior, inattention, diminished engagement in pleasurable behaviors, and/or anhedonia (Vrieze et al., 2013), which are presumed to be possible risk factors for different forms of psychopathology. However, while various aspects of hedonic functioning, such as reward-seeking, and anticipatory and consummatory reward, have been researched in pediatric populations (Forbes and Dahl, 2012), only a few studies have focused on reward-based learning (Morris et al., 2015). Therefore, more research is needed to better understand the underlying

mechanisms of reward-based learning in pediatric populations to inform the development of more efficacious treatments and potential prevention strategies.

Neurobiological Basis of Reward-Based Learning

Reinforcement learning is thought to be reflected by the reward prediction error signal (RPE; i.e., the difference between expectations and outcome) conveyed by the mesocortical dopamine system (Schultz, 2009), as evidenced by hemodynamic activity in the ventral striatum and other brain regions (Pine et al., 2018). Although dopamine neurotransmission has been involved in reward-related processes, its exact role is still equivocal (Glimcher, 2011; Wise, 2004). In general, it is thought that when a reward received deviates from what is expected, dopaminergic neurons in the midbrain change their baseline phasic firing rate in proportion to the magnitude of the deviation, leading to learning or extinction of a learned contingency. In particular, the phasic firing rate tends to increase to better than expected outcomes and slow down to worse than expected outcomes (Holroyd and Coles, 2008; Martin et al., 2009; Bech et al., 2023).

In support of the role of dopamine in reward-based learning, individuals who were administered a single dose of a dopamine agonist showed impaired reward learning, an enhanced amplitude (i.e., more negative voltage) in the EEG event-related potential called feedback related negativity (FRN) and decreased dorsal anterior cingulate cortex (dACC) activity (Santesso et al., 2009). On the contrary, individuals who received a placebo showed better reward learning, smaller (i.e., more positive voltage) FRN amplitude, and greater dACC activity. These results provide additional support for the role of dopamine in reward-based learning and support that disruption of phasic DA responses negatively impacts prediction error and, thus, reduces reinforcement learning.

Functional neuroimaging studies suggest that different brain regions are implicated in reward-based learning, such as the anterior cingulate cortex, the basal ganglia, the ventral striatum, and the orbitofrontal cortex (OFC), among others (Haber and Behrens, 2014). In particular, both human (Rogers et al., 2004) and non-human primate (Chudasama et al., 2013) studies show that the dACC plays an important role in integrating reinforcement history over time. In general, the role of the ACC can be understood in terms of its role within the mesocortical dopamine system (Holroyd and Coles, 2002), which, as previously mentioned, codes errors in reward prediction by phasic changes in the activity of midbrain dopamine neurons depending on the outcome being better or worse than expected (Maia and Frank, 2011). Indeed, the dACC was implicated in guiding choices based on the history of actions and outcomes whereby monkeys with dACC lesions did not perform worse than those without lesions immediately after errors but had marked difficulties integrating reinforcement history over time, thus supporting the central role of the dACC in reward learning and goal-directed behaviors (Kennerley et al. 2006). Similarly, monkeys with a bilateral lesion of the ACC, compared to those without, had impairments in their ability to use reward information to guide their actions or switch their responses after a series of errors (Chudasama et al., 2013). The ACC seems to play a central role in relating behaviors to their consequences and guiding decisions about which actions are worth taking (Rushworth et al., 2004).

Event Related Potentials: Feedback Related Negativity (FRN)

Event-related potentials (ERPs), extracted from electroencephalography (EEG), have been extensively used and are well-suited for measuring individual differences in aspects of reward, including reward learning. In particular, the feedback related negativity (FRN; also referred to as medial frontal negativity, feedback negativity, or feedback error-related negativity),

a frontocentral negative voltage deflection that occurs between 200 ms to 400 ms after presentation of a feedback stimulus, has been linked to reward-based learning. A related ERP, feedback-related positivity (FRP; also referred to as P2a or reward positivity), is a positive voltage deflection following rewarding outcomes over the same electrode sites and time course (Proudfit, 2015). For clarity, similarly to other researchers, we will refer to a larger FRN amplitude to positive feedback to reflect what others refer to as a reduction in the FRP in relation to reduced learning in probabilistic reward paradigms.

The FRN has been commonly used to study performance feedback and it is believed to be larger in negative voltage amplitude for negative feedback (e.g., when the individual is told that their response is incorrect) than for positive feedback (e.g., when the individual is told that their response is correct), due to the slowing down of the phasic dopamine response. However, studies conducted in the last two decades suggest that the FRN is also reliably elicited by positive feedback or settings in which the outcome is better than expected and appears as a relatively more positive voltage ERP deflection (compared to that elicited by negative feedback; Bellebaum et al., 2010; Hajcak et al., 2005; Oliveira et al., 2007), which is thought to reflect the speeding up of the phasic response. Some studies also suggest that the degree to which feedback is unexpected vs. expected produces an overall larger voltage change independently of the feedback valence (Ferdinand et al., 2012; Hajcak et al., 2007), and, since it appears to be modulated by expectancy, that the FRN tends also to become more positive in voltage over the time-course of learning (Müller et al., 2005; Holroyd and Coles, 2002). Additionally, when looking at the FRN across development some research has found that the FRN amplitude tends also to be larger in adolescents than adults and to discriminate less strongly between gains and losses in teens (e.g., Zottoli and Grose-Fifer, 2012; Hämmerer et al., 2011), thus suggesting that

the brain processing that generate the FRN may still be developing in adolescence. Finally, other studies suggest that the FRN might covary with the subjective relative value of rewarding options (e.g., Goyer et al., 2008; Gehring and Willoughby, 2002;). Using simultaneously recorded EEG and functional magnetic resonance imaging (fMRI) data from 15 healthy controls while completing a probabilistic reversal learning task, results suggested that the FRN originates in the dACC. Employing a single-trial analysis approach, results also suggested that the FRN may indeed reflect "surprise" signals which, in turn, are projected to the dACC, directly from the dopamine neurons of the mesencephalon, further supporting the FRN's role as a possible biomarker to study reward-based learning (Hauser et al. 2014a). This finding contradicts earlier theories which assumed that the surprise signals are projected to the dACC via the striatum (Holroyd and Coles, 2002) but is in line with a recent theory stating that dopamine neurons also encode surprise-like saliency signals (Bromberg-Martin et al., 2010a; 2010b).

Interestingly, in healthy controls (N = 30) during a probabilistic reward learning task, during which fMRI and EEG data were recorded, results indicated that non-learners vs. learners generated a greater FRN amplitude (i.e., more negative/less positive voltage) and lower dACC fMRI activation in response to reward feedback following correct identification of the more frequent reward stimulus. In addition, both FRN amplitude (i.e., less negative/more positive voltage) and dACC activity were positively correlated with reward learning, thus providing additional support for the role of the FRN as an indicator of reward learning (Santesso et al., 2008a). Similar results were obtained in a more recent study (Frank et al., 2019) on a sample of psychiatrically healthy adolescents and young adults. In particular, the results showed that individuals who did not develop a response bias had less cortical positivity at Fz from 224 ms to 316 ms post feedback onset compared to those that developed a response bias during the task.

Taken together, there is robust support to suggest that FRN can be considered a valid indicator of ACC activity and reward-based learning, where individuals with blunted reward learning display a larger FRN, due to reduced positive deflection, to unexpected positive feedback.

Attention Deficit/Hyperactivity Disorder and Mood Disorders

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, impulsivity, and/or hyperactivity present across multiple contexts. ADHD has been associated with educational, clinical, and interpersonal-emotional impairments (Erskine et al., 2016; Faraone et al., 2015; Sun et al., 2019), as well as a high economic burden (Barkley, 2020). The prevalence of ADHD in the United States in children aged 3-17, according to a recent study (Bitsko et al., 2022), is estimated at around 9.8%, with boys (13%) more likely to be diagnosed with ADHD than girls (6%). Comorbidities, which may exacerbate the above-mentioned negative outcomes, are highly prevalent in children and teens with ADHD. In support of this, previous studies estimated that about 60% of children aged 3-17 with ADHD have at least one other psychiatric disorder, such as conduct problems (27% to 52%), anxiety (18% to 33%), and mood disorders (14% to 17%), among others (Bitsko et al., 2022; Larson et al., 2011). In particular, mood disorders occur at significantly higher rates (approximately 1.5x) in youths with ADHD, and youths with both disorders tend to be at higher risk for a more severe course of psychopathology, long-term impairments, and suicide than youths with either disorder alone (Daviss, 2008). Additionally, a number of studies have shown that cognitive dysfunctions, including attention and concentration impairments, are not only a hallmark of ADHD but also of mood disorders in which they have been associated with poorer clinical outcome (for a review see Keller et al., 2019). Although different factors likely

contribute to the high rates of co-occurrence between the two disorders, including attention dysfunction as a shared mechanism, one possible explanation is also similar neurobiology.

In individuals with mood disorders, dysfunctions in the prefrontal and ACC regions are one of the most replicated findings (Alexander et al., 2021; Yucel et al., 2008) and one that has also been consistently reported in both adults and children with ADHD (Cubillo et al., 2012; Vogt, 2019). In addition, emerging evidence suggests that disruptions in dopamine systems may underlie the pathophysiology of several psychiatric disorders, including ADHD and depression. Consistent with this idea, studies have highlighted the role of the dopamine systems in the pathophysiology and treatment of ADHD (Del Campo et al., 2011) with a particular focus on the dopamine transporter (DAT) and D4 and D5 receptors (Klein et al., 2019). Similarly, dysfunctions in the dopamine system have been consistently associated with symptoms such as anhedonia and lack of motivation which are characteristic of mood disorders (Grace, 2016).

This neurobiological evidence is intriguing, particularly when considering that, as reviewed above, dysfunctions in the dopamine system and the frontal (e.g., dACC) and cingulate regions are also involved in reward-based learning. This suggests the possibility that both disorders are characterized by an impaired ability to modulate behavior as a function of prior reinforcements, which may contribute to their high comorbidity.

Reward Learning and Feedback Related Negativity in ADHD and Mood Disorders

Reward learning during a probabilistic reward task has been less studied in ADHD in comparison to mood disorders. Nevertheless, both adults and children with ADHD, reward learning seems to lack modulation by motivational factors such as frequency and magnitude of reward and an impaired ability to use feedback in the context of learning (Marx et al., 2013; Luman et al., 2009; Tripp and Alsop, 1999). Although preliminary, some recent studies also

suggest that during reward-based learning tasks, individuals with ADHD tend to switch their choices more often, regardless of the previous feedback. This behavior may be adaptive in changing environments; however, it is dysfunctional when the environment is stable. Additionally, it is proposed that the "choice switching" could be related to a blunted sensitivity to both negative and positive rewards, which would result in weaker ability to discern values for the available options (Hauser et al., 2014b; Aster et al., 2024). For example, during a reinforcement-learning task, children with ADHD showed minimal problems with feedback learning when feedback was given in a consistent and immediate way. However, when feedback was infrequent, children with ADHD vs control group showed difficulties in keeping track of the history of reinforcement, focusing instead only on the "last reward received," thus supporting the presence of difficulties when presented with a stimulus-response learning task such as the PRT (Luman et al., 2009).

A number of studies have evaluated the FRN in ADHD samples with contrasting results (Rosch et al., 2013; van Meel et al., 2005, 2011). However, none of these studies focused specifically on probabilistic reward learning, as feedback was not used to guide learning/optimize behavior. More recently an EEG study (Thoma et al., 2015) was conducted comparing 14 adults with ADHD combined type and 14 healthy controls while performing both an active (i.e., the participant performed the task) and an observational (i.e., the participant observed another person completing the task) probabilistic reward-based learning task. These results were the first to demonstrate a general FRN enhancement, independent of feedback valence, and a reduced learning performance during both active and observational reward learning in adults with ADHD of the combined subtype. These results suggest that an enhanced

FRN could reflect a larger prediction error in ADHD indicating impaired reward prediction/learning performance.

Several studies reported alteration in the reward system, including reward-based learning, as a possible endophenotype for mood disorders. Impaired reward learning has been demonstrated in both medicated and unmedicated adults with mood disorders and individuals at risk and remitted from major depressive disorder (MDD) while completing a probabilistic reward task (PRT; Admon and Pizzagalli, 2015), as well as in youth samples (Morris et al., 2015).

In general, these studies suggest that individuals with mood disorders tend to use feedback less efficiently than healthy controls. A recent study conducted by Reilly et al. (2020), using the same type of task, also suggested that deficits in reward-based learning may be associated with anhedonia and not necessarily MDD as a diagnosis, further supporting the use of transdiagnostic approaches. Similar results have been obtained in a study conducted by Luking et al. (2017) with children aged 7-10. The results showed that children with lower hedonic capacity/approach motivation had a reduced responsivity to gains during a modified version of the PRT, thus suggesting consistency with the pediatric and adult literature. In addition, studies have suggested that the amplitude of the FRN correlates with higher levels of anhedonia (Santesso et al., 2008a) and tends to be enhanced (i.e., more negative) for individuals with major depressive disorder compared to controls (Mueller et al., 2015; Santesso et al., 2008b). Relative to control subjects, individuals with mood symptoms display larger FRN due to bunted reward learning resulting in greater reward expectancy violation and a reduced positive prediction error (Pizzagalli, 2008). Interestingly, some studies have found a link between RPE signals and changes in symptoms and functioning in individual with psychological distress. In particular, it was found that stronger RPE signals predicted improvements in psychological functioning over

six months, and that this improvement was mediated by improvements in anhedonia (Eckstrand et al., 2019). These results suggest that reward learning and the underlying neurocircuitry may be an important target for treatment in mood disorders. Additionally, some recent findings also indicate that anhedonia and its reward-related neural correlates are linked to variability in quality of life over time in individuals with mood disorders. This suggests that treatments capable of improving anhedonia and normalizing brain reward function may be necessary for improving broader health outcomes for at least a subset of individuals seeking treatment for mood disorders (Whitton et al., 2023). In conclusion, this recent evidence highlights the importance of studying reward-based learning in this population.

Aims and Hypotheses

ADHD and mood disorders are highly comorbid and one possible explanation is similar neurobiology and impairments in probabilistic reward learning. However, to date, few studies have focused on reward-based learning in pediatric populations. Therefore, more research is needed to better understand the underlying mechanisms of reward-based learning in pediatric populations to inform the development of more efficacious treatments and potential prevention strategies. As the research was conducted in a pediatric mood disorder clinic, the current study will focus on dimensional ADHD symptom severity in youths with prominent mood symptoms.

The goal of the present study is to evaluate the relationship between probabilistic reward learning, feedback-related negativity, and dimensional ADHD symptom severity in a sample of adolescents (aged 13-17) with prominent mood symptoms. In particular, by looking at the relationship between reward-based learning and dimensional overall ADHD symptom severity within a sample of youths with prominent mood symptoms and controlling for current mood

symptom severity, we aim to examine the independent, unique effects of ADHD symptoms above and beyond the comorbidity of mood symptoms.

We hypothesize (hypothesis 1) that, across the entire sample, the presence of a larger FRN in response to unexpected positive feedback will be associated with lower learning during a Probabilistic Reward Task, thus suggesting that FRN may represent a reliable index of reward-based learning. Frank et al., 2019; Santesso et al., 2008a; Thoma et al., 2015)

In addition, we hypothesize (hypothesis 2) that, across the entire sample and after covarying for severity of mood symptoms, greater overall ADHD symptom severity will relate to both a larger FRN to unexpected positive feedback and reduced performance on a Probabilistic Reward Task (PRT), thus suggesting impaired reward-based learning.

In conclusion, hypotheses suggest that during a reward probability task, an inability to develop a response bias toward the rich stimulus, represented by an enhanced FRN, will be associated with more severe symptoms of ADHD while controlling for the severity of mood symptoms.

CHAPTER TWO: METHODS & MATERIALS

Participants

The present study will be utilizing data that I collected during my employment as a Research Assistant at the University of California Los Angeles (UCLA), under the supervision of Dr. Alissa Ellis, Ph.D., from 2015 to 2019, as part of a larger study.

In line with the dimensional approaches to the study of psychopathology, recruited youths who varied in type and severity of mood symptoms. Adolescents were recruited from the UCLA Child and Adolescent Mood Disorder Program (CHAMP) and Youth Stress and Mood (YSAM) clinics. To guarantee variability in the type, state, and severity of symptoms, we recruited both individuals who were new intakes into the clinics and previously established patients. Additionally, to ensure variability in symptom presentation, we stratified recruitment efforts based on frequency of clinic visits, under the assumption that the frequency of visits is related to symptom severity, as follows: monthly visits: severe; visits every 1 - 6 months: moderate; visits every 6 - 12 months: mild. The inclusion criteria to participate in the study included a current age of 13 to 17, an estimated IQ above 80 (assessed as part of the intake process at CHAMP and YSAM clinics), and the ability to speak, read, and understand in English sufficiently well (child and parent). Furthermore, to increase ecological validity, we did not exclude participants who were currently medicated. However, if they were currently consuming psychostimulants, we asked participants to refrain from taking them on the day of the assessment. The following were all exclusion criteria: current use of illicit psychoactive drugs (e.g., cocaine, marijuana), history autism spectrum disorder, serious medical complications (e.g., epilepsy, head trauma, multiple concussion with loss of consciousness), and presence of sensory impairments which could impact behavioral measures. Participants received a monetary stipend for their participation ($60

for the initial session and an additional $35 (3-months) and $50 (6-months) after each follow-up telephone interview). The study received approval from the Institutional Review Board (IRB) of the host university where the data was collected (UCLA) and the IRB of the University of Central Florida for analyses and use of the de-identified data for this dissertation.

Following recruitment attempts and limitations due to the Covid-19 pandemic, we recruited 57 participants. All participants had mood symptoms that were of sufficient severity that they were being treated in a mood disorders clinic, but only 51 met full diagnostic criteria for a mood disorder at the time of assessment for the study. Of the initial 57, 21 were not included in the final analysis: 1 did not complete the Probabilistic Reward Task (PRT), 16 did not pass the PRT quality control criteria (see below for details), and 4 had problems with EEG recording. Following these exclusions, 36 participants were included in the analyses. As expected with depression during adolescence, which was the most prominent diagnosis in the current sample, 72% (n = 26) of the final sample was composed of females. For demographics, including diagnostic frequencies, see Table 1.

Table 1: Demographic and Clinical Characteristics

N		36
Sex (% Male)		27.80
Age		14.64 (1.78)
Race (%)		
	Caucasian	77.80
	African American	5.60
	Asian	5.60
	More Than One Race	11.10
Ethnicity (% Hispanic/Latinx)		27.80
Diagnoses (%)		
	Unspecified Bipolar & Related Disorders	11.10
	Bipolar Disorder - I	8.30
	Disruptive Mood Dysregulation Disorder	5.60
	Major Depressive Disorder (MDD)	58.30
	Unspecified Depressive Disorder	5.60
	None	11.10
SNAP-IV Total		16.53 (1.78)
SNAP-IV Inattentive		11.53 (5.52)
SNAP-IV Impulsive/Hyperactive		5.00 (4.85)
Depression Rating Scale#		33.97 (10.39)
Mania Rating Scale#		21.72 (4.23)

Represent summary score clinically derived from the responses using best estimate consensus ratings to reconcile parent and child differences.
SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale
Values for age, SNAP-IV, Depression Rating Scale, and Mania Rating Scale are mean (standard deviation)

Diagnostic and Symptoms Assessment

The *Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime* (K-SADS-PL; Kaufman and Schweder, 2004) was administered via separate clinical interviews to the youth and the accompanying parent. The K-SADS-PL is a semi-structured diagnostic interview used to assess current and past psychopathology for children ages 6 to 18. It is administered by interviewing the parent and the child and finally achieving summary ratings which include all sources of information. The K-SADS-PL has well-

established psychometric properties (Birmaher et al., 2009; Kaufman et al., 1997). All diagnoses in the study were based on consensus ratings across the parent and youth. A licensed psychologist (Dr. Ellis) determined the final primary diagnoses following case presentations with student research assistants who contributed to the collection of the information.

Depression Rating Scale (DRS) & Mania Rating Scale (MRS) from the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; Geller et al., 1996; 2001*)* were administered via separate clinical interviews to both the the accompanying parent and youth. The DRS and MRS are semi-structured diagnostic interviews to assess symptoms of depression (e.g., depressed mood, irritability and anger, excessive and inappropriate guilt, negative self-image) and mania (e.g., elation and expansive mood, mood lability, decreased need for sleep, racing thoughts) for children ages 6 to 18. The scales are administered by interviewing the parent and the child and finally a summary score is clinically derived from the responses using best estimate consensus ratings to reconcile parent and child differences. The DRS and MRS allow for calculation of individual total scores representing severity and number of symptoms. These measures provided data on the worst symptomatic period in the youth's life, as well as information on current mood state (over the past two weeks). Only the current mood state ratings are used in the present study. The DRS and MRS have well-established psychometric properties, with a coefficient alpha for MRS of .94 (Axelson et al., 2003) and for DRS of .82 (Ambrosini et al., 2000).

Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale (SNAP- IV; Swanson et al., 2001) was completed by the parent at the time of the meeting as part of a predetermined set of questionnaires that were administered via an online platform. The SNAP-IV is a widely used scale to assess symptoms of ADHD in children and adolescents ages 6 to 18.

The short form has 18 items and measures the core ADHD symptoms of impulsivity, hyperactivity, and inattention. As such, three scores are produced: ADHD Predominantly Inattentive (n = 9 items), ADHD Predominantly Hyperactive/Impulsive (n = 9 items), and ADHD Combined (i.e., sum of all items endorsed). Ratings (0 to 3) are based on frequency (e.g., does not experience the symptoms at all, just a little, quite a bit, or very much). The scale asks the parent to check the column that best describes the child/adolescent. No specific time period is provided.

The SNAP-IV has good psychometric properties. In a large longitudinal ADHD detection study (Bussing et al., 2008), coefficient alpha for overall parent ratings was .94, with alphas coefficients of .90 and .79 for the inattentive and hyperactive/impulsive subdomains. Finally, there was no significant variation in internal consistency by gender or race for parents SNAP-IV ratings.

Procedure

The study consisted of one meeting with a typical duration of two to three hours. Following informed consent and assent with parent and youth, the K-SADS-PLwas administered via separate clinical interviews to the parent and youth to assess current and past psychopathology. Medication use and adherence was also assessed during the clinical interview. Both the youth and the parent then completed a wide battery of questionnaires as part of a larger study, which included demographic data and the SNAP- IV, which were used in the current project.

Subsequently, youths were fitted with electroencephalogram (EEG) electrodes and completed several computer tasks as part of a larger study, including the Probabilistic Reward Task (PRT), while continuous EEG data were collected. All EEGs were recorded in a

comfortable, electrically shielded, soundproof room with an isolated power supply to minimize A/C noise. Locally-networked computers were used for stimulus presentation and electrophysiological data collection.

Behavioral Task

The *Probabilistic Reward Task* (PRT; Pizzagalli et al., 2005) is a signal-detection task that uses a reinforcement schedule with monetary reward to study reward responsiveness and reward-based learning. On each trial, individuals are asked to choose between two difficult-to-differentiate stimuli. Following a practice of 20 trials, the task was presented in 3 blocks consisting of 100 trials. Each trial began with the presentation of a fixation cross in the center of the screen for a randomly selected duration from the interval of 250 – 600 ms. The cross was then replaced by a schematic mouthless face (diameter 25 mm; eyes: 7 mm) in the center of the screen for 500 ms. After, either a straight mouth of 10.0 mm (little mouth) or 11.0 mm (big mouth) appeared briefly (100 ms) and then disappeared, leaving the mouthless face on the screen (1400 ms or until participant response). Participants were instructed to press a specific key on the computer keyboard to decide whether a big or little mouth was presented.

Little and big stimuli were presented equally often (50 trials each per 100-trial block) in a quasi-randomized order (i.e., neither size was presented more than 3 trials in a row). Participants were also instructed that not all correct identifications would be followed by a reward. Indeed, only 40 correct identifications per each 100trial block were scheduled to receive a reward and, without knowledge of the participant, correct identification of one of the stimuli (“rich stimulus”) was rewarded three times (30 trials) more frequently than the other (“lean stimulus”; 10 trials). Only when correct identification was rewarded, feedback (“Great! You win 10 cents!”) was presented for 1200 ms followed by a black screen for 150 ms. All other trials (incorrect and

correct, non-rewarded) offered no feedback and a blank screen (1350 ms). Figure 1 displays a schematic of a representative trial.

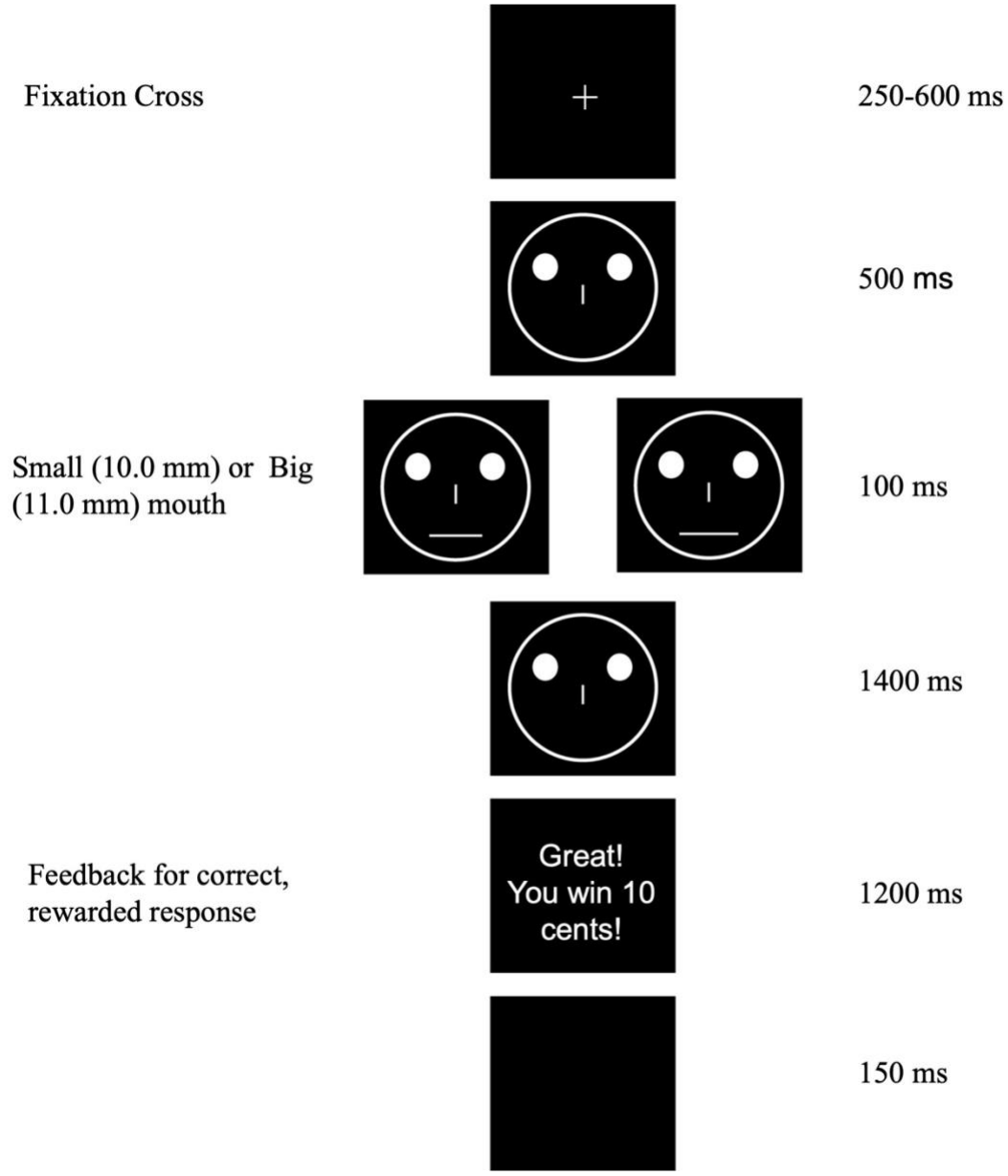

Figure 1: Trial Schematic. This figure represents a schematic of a representative trial for a correct, rewarded response
Note: All other trials (incorrect and/or correct, non-rewarded) offered no feedback and a blank screen for 1350ms.

PRT Data Collection & Reduction

The PRT data were subjected to a quality control assessment (Pizzagalli et al., 2005). The PRT task performance was then analyzed with respect to discriminability, response bias, accuracy (% correct), and reaction time. Discriminability (*d*) gives us information about task performance by assessing the participants' ability to discriminate between the two stimuli. In line with previous studies (e.g., Morris et al., 2015), it was computed as follows:

$$\log d = \tfrac{1}{2} \log [(\mathrm{H} * \mathrm{C}) / (\mathrm{M} * \mathrm{F})] \quad (1)$$

- H = Hits = Correct identification of the rich stimulus
- C = Correct Rejections = Correct identification of the lean stimulus
- M = Misses = Choosing the lean stimulus when the rich one was presented
- F = False Alarms = Choosing the rich stimulus when the lean one was presented

Response bias (*b*) refers instead to the tendency to systematically prefer the rich stimulus over the lean one. In line with previous studies (e.g., Morris et al., 2015), it was computed as follows:

$$\log b = \tfrac{1}{2} \log [(\mathrm{H} * \mathrm{F}) / (\mathrm{M} * \mathrm{C})] \quad (2)$$

Following prior recommendations, 0.5 was added to every cell of the detection matrix to allow calculation of the response bias and discriminability in cases with zero in one cell of the formula (Hautus, 1995).Finally, to assess the overall development of response bias across the task, consistent with previous studies, *Reward Learning* (i.e., ΔResponse Bias) was computed as the response bias score from block 3 minus block 1 (Pizzagalli et al., 2005; Santesso et al., 2008a; Vrieze et al., 2013; Whitton et al., 2016). Negative values represent poor reward learning.

In addition, consistent with past studies from the author of the task (Pizzagalli et al., 2005; Bogdan and Pizzagalli, 2006), trials with reaction times less than 150 ms or longer than 1500 ms were excluded, to help ensure that only trials in which the participant paid attention

were included. Participants with < 75 valid trials in any block were excluded from the final analyses. In addition, participants who received either < 20 rich rewards, or < 6 lean rewards, and/or had a rich/lean reward ration < 2.0 in any block were excluded to ensure that included participants received a sufficient number of rewards to create the 3:1 ratio (n = 16 were excluded). According to the task manual, subjects unable to perform the task and/or follow instructions tend to have several of the above-mentioned problems.

EEG Recording and Processing

Continuous EEG activity was recorded using the ActiveTwo BioSemi system (BioSemi, Amsterdam, The Netherlands) sampled at 512 Hz. An elastic Active Two Lycra head cap was placed on the youth's head and 64 Ag/AgCl-tipped electrodes were attached to the cap based on the 10/20 system. In addition, two electrodes were placed approximately 1 cm above and below the right eye to monitor vertical eye movements and blinking and two on the side (1 cm) of the left and right eyes to monitor horizontal eye movements. Two electrodes were also placed on the bilateral mastoids and one on the tip of the nose. As designed by BioSemi, the reference electrode during acquisition was formed by the Common Mode Sense (CMS) active electrode and the Driven Right Leg (DRL) passive electrode. All the signals were digitized on a laboratory microcomputer using ActiView software (BioSemi, Amsterdam, The Netherlands). Key head landmarks (nasion, inion, preauricular notches) and 3-D electrode locations were recorded (Zebris Electrode Positioning System (ELPOS), Medical GmBH) to allow three-dimensional reconstruction of scalp electrode positions.

EEG processing followed previously used procedures from the laboratory (for more details see Lenartowicz et al., 2024). EEG data were analyzed off-line within Matlab (Mathworks) utilizing EEGLAB (Delorme and Makeig, 2004, Psychology Software Tools,

2019). Offline EEG data were pre-processed using a high-pass filter at 0.1 Hz and re-referenced to the channel average. Noisy electrodes were removed using visual inspection. Artifact rejection used a semi-automated procedure. The data was segmented into 0.5-second time bins, and any segment outside of 5 standard deviations of the overall data was removed, up to a maximum of 10% of the data. These "bad" segments were visually confirmed as "noise" (i.e., major movement and muscle artifacts). Following, Independent Component Analysis (ICA) was performed on each participant's data to further separate neural from artifact signals (Makeig et al., 1996) using parameters set by binica in EEGLAB (1000 maximum learning steps; a stopping weight change of 1e-7). Clusters representing artifacts (e.g., ocular activity, EMG, EKG, and line noise) were then removed. Data was epoched from 2000 ms before and after reward feedback following correct identification of the rich stimulus. To allow participants to be exposed to the differential reinforcement schedule, FRN was initially computed by averaging artifact-free EEG epochs time-locked to reward feedback for the rich stimuli from blocks 2 and 3, as traditionally computed in previous studies (e.g., Santesso et al., 2008a). However, since our manipulation check, looking at the relationship between FRN and reward learning behavior was not significant (see Table 1), we instead used a ΔFRN amplitude score (FRN amplitude from Block 3 minus Block 1).

Table 2: Summary of Hierarchical Regression Analysis for Variables Predicting Reward Learning Score (N = 36) - FRN Block 2 and 3 Combined

Variable	B	Std. Error	Beta	Sig.	R2	ΔR2	f^2
Step 1					.10	.10	.11
Constant	.102	.171		.557			
Sex	-.099	.082	-.250	.235			
DRS Total	.003	.003	.182	.371			
MRS Total	.002	.008	.046	.815			
SNAP-IV Combined	-.106	.004	-.323	.117			
Step 2					.117	.017	.13
Constant	.076	.176		.669			
Sex	-.085	.084	-.215	.320			
DRS Total	.003	.003	.180	.378			
MRS Total	.002	.008	.055	.785			
SNAP-IV Combined	-.006	.004	-.317	.127			
FRN Blocks 2&3	-.011	.014	-.136	.448			

SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale; DRS: Depression Rating Scale; MRS: Mania Rating Scale

This was chosen as it mirrors what was done on the reward learning behavioral score and is consistent with existing research suggesting that the FRN changes over the course of blocks (e.g., Müller et al., 2005). Following a statistically significant manipulation check with ΔFRN, we used this new difference waveform for the remaining analyses. A baseline correction of –200 ms to 0 ms was applied. In line with Santesso et al. (2008a, 2009), the amplitude of the ERP of interest was derived from each individual's average waveform for the Fz and FCz channels (separately), where it is typically larger. As in previous papers (Santesso et al 2008a), for each participant, the FRN mean amplitude was computed as the area around the most negative voltage peak in the 250 – 400 ms timeframe after feedback presentation, using a 20 ms window before and after the peak.

Data Analysis

Statistical Analyses

Data were analyzed using SPSS Statistics for Windows (v. 28.0). Descriptive statistics, correlations, and graphical summaries were obtained for the neurophysiological and behavioral measures to check for outliers and violations of model assumptions. If one or more outliers were detected in a particular analysis, it was conducted again without those participants and the change in results was examined. In case of model assumptions violation, non-parametric statistics were used. Pearson correlations were used to screen for potential confounding variables (i.e. age, sex, race, ethnicity, and diagnosis), which were added as covariates in the analyses of interest if they significantly related to either the overall ADHD severity, mood severity, FRN amplitude, or behavioral PRT change score.

Behavioral Data (PRT): to assess the presence of differences between blocks, Response Bias and Discriminability were analyzed across the entire sample using one-way repeated measures ANOVAs. Accuracy and Reaction Time were analyzed using two-way repeated measures ANOVAs (block x stimulus type: lean vs rich).

ERP Data: First, a paired sampled t-test was run to estimate whether the ΔFRN amplitude differed between electrodes FCz and Fz. If significant, the electrode that showed the larger ΔFRN was then retained for subsequent analyses. To assess the overall effect of task manipulation (hypothesis 1), a hierarchical linear regression was used across the entire sample to determine if the dependent variable of Reward Learning related to the ERP of interest, independent of mood and ADHD symptoms. Potential confounding variables of sex, participants total scores from the MRS and DRS (based on severity over the past two weeks), and ADHD combined score of the SNAP-IV were added to Step 1 of the regression. In Step 2, we added the

ΔFRN mean amplitude scores. To examine hypothesis 2, a second regression analysis was run across the entire sample to test if reward learning and ΔFRN amplitude predicted greater overall ADHD symptom severity, as measured by the ADHD combined score of the SNAP-IV, after controlling for recent mood symptom severity. The total scores from the MRS and DRS, and sex were entered in Step 1 of the regression as potential confounding variables. In Step 2, we added the reward leaning and ΔFRN mean amplitude scores. Additional exploratory regression analyses were conducted in relation to the ADHD Predominantly Inattentive and ADHD Predominantly Hyperactive/Impulsive subscales.

Multicollinearity of regression predictors was defined by a Variance Inflation Factor > 4.00 or Condition Index > 30.00. Statistical outliers were defined by a combination of Studentized residual > 3.00 and Cook's d > .03, who were then removed from the respective regression. Any deviation from these parameters is reported in the results.

Power Analyses

Post-hoc power analyses were conducted using G*Power- Statistical Power Analyses 3.1 for Windows and Mac (Faul et al., 2007). In relation to the regression analyses, the final sample size of 36 provides sufficient power (> .80) for our study to be sensitive to detect $f^2 > .26$, an effect size that Cohen (1988) described as medium ($.15 < f^2 < .35$). However, as suggested by Boudewyn et al. (2017), several factors have an impact on statistical power in ERP studies, including number of trials, sample size, and effect magnitude, as well as interactions among these factors. As the authors suggested, “the field needs a power calculator that can indicate the expected power for a given study when given the number of trials, number of participants, anticipated difference in amplitude between conditions or groups, and the noise level of the raw EEG” (Boudewyn et al., 2017).

CHAPTER THREE: RESULTS

See Table 1 for demographics and Table 3 for main correlations.

Table 3: Zero-Order Pearson Correlation r Values of Main Variables of Interest

Variable name	1	2	3	4	5	6	7	8	9
1. Age	—								
2. Sex	.051	—							
3. Diagnosis	.266	-.023	—						
4. Race	.020	.205	-.173	—					
5. Ethnicity	-.321	.108	-.147	-.329	—				
6. DRS	.324	.350*	.025	.295	-.111	—			
7. MRS	.192	.123	-.103	.291	-.003	.395*	—		
8. SNAP-IV#	-.038	-.374*	-.009	.044	-.215	-.025	.153	—	
9. ΔFRN	.263	-.137	-.008	-.007	.096	.127	.055	-.213*	—
10. Reward Learning	-.300	-.078	-.120	.012	.012	.226	-.105	-.157	-.279

* $p < .05$, $n = 36$ for all cells
DRS: Depression Rating Scale; MRS: Mania Rating Scale; SNAP-IV: Swanson, Nolan, and Pelham Questionnaire - 18 Items Parent Rating Scale
#Overall ADHD Symptom Severity

PRT Behavioral Data

See Figure 2 for a depiction of how the behavioral variables of interest changed over the three blocks of the task. See Table 1 and 3 for descriptive statistics and zero-order correlations involving the behavioral variables of interest.

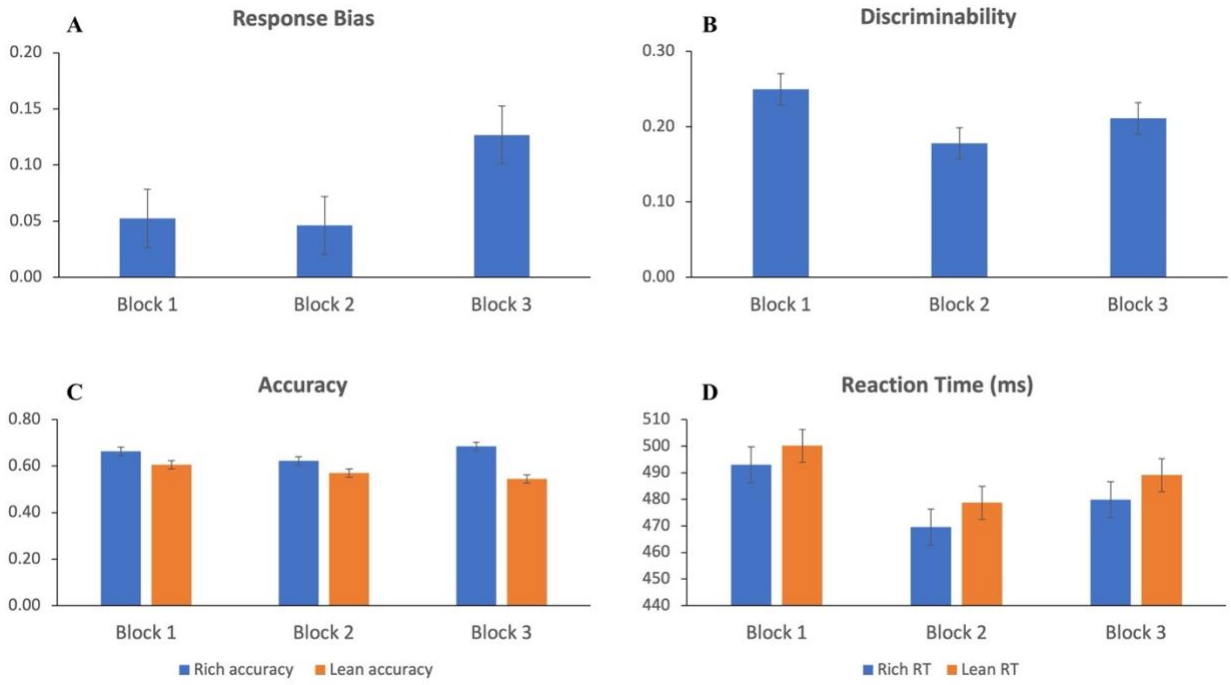

Figure 2: Depiction of how Response Bias (A), Discriminability (B), Accuracy (C), and Reaction Time (D) changed over the three blocks of the Probabilistic Reward Task

Response Bias (RB)

The repeated measures ANOVA showed that RB differed statistically significantly across the three blocks of the task ($F(2,70) = 4.123$, $p = .020$, $\eta_p^2 = .105$). Fisher's Least Significant Difference (LSD) test revealed that RB in Block 3 ($M = .127$, $SD = .151$) was significantly larger than the RB from both Block 1 ($M = .052$, $SD = .133$) and Block 2 ($M = .046$, $SD = .148$). No significant difference was present between Block 1 and Block 2). This suggests that, across the entire sample, RB increased from Block 1 and 2 to Block 3. Mauchly's Test of Sphericity indicated that the assumption of sphericity was not violated in this ANOVA, $\chi^2(2) = 0.326$, $p = .850$.

Discriminability

The repeated measures ANOVA showed that there was a significant difference in Discriminability across blocks ($F(2,70) = 3.359$, $p = .040$, $\eta_p^2 = .088$). Fisher's Least Significant

Difference (LSD) test revealed that Discriminability from Block 1 (M = .250, SD = .182) was statistically significantly different from Block 2 (M = .178, SD = .183). No other significant differences were present. This suggests that, across the entire sample, participants' ability to discriminate between lean and rich stimuli was lower in Block 2 vs Block 1, however, by Block 3, no difference was present. Mauchly's Test of Sphericity indicated that the assumption of sphericity was not violated in this ANOVA, χ^2 (2) = 1.055, p = .590.

Accuracy

The two-way repeated measures ANOVA showed that there was a significant block number*stimulus type (i.e., rich vs. lean) interaction (F(2,70) = 4.386, p = .016, η_p^2 = .111). We then looked at the simple effects of the interaction. In relation to stimulus type, results from paired t-tests showed a significantly higher accuracy for the rich, compared to lean, stimuli in Block 1 (t(35) = 2.640, p = .012) and Block 3 (t(35) = 5.157, p < .001), and a trend toward significance for higher accuracy for rich stimuli for Block 2 (t(35) = 1.954, p = .059). A one-way repeated measure ANOVA was run in relation to block differences. Regarding the rich stimuli, Mauchly's Test of Sphericity indicated that the assumption of sphericity had not been violated, χ2(2) = 2.782, p = .249. The repeated measures ANOVA showed that there was a significant difference in accuracy across blocks (F(2,70) = 5.587, p = .006, η_p^2 = .138). Fisher's Least Significant Difference (LSD) test revealed a significant difference for accuracy for the rich stimuli for Block 1 (M = .664, SD = .093) vs Block 2 (M = .622, SD = .114) and Block 2 vs Block 3 (M = .685, SD = .074). Regarding the lean stimuli, Mauchly's Test of Sphericity indicated that the assumption of sphericity had not been violated, χ2(2) = 1.285, p = .526. The repeated measures ANOVA showed a trend toward significance in accuracy across blocks for the lean stimuli (F(2,70) = 3.102, p = .051, η_p^2 = .081). Fisher's Least Significant Difference (LSD)

test revealed a significant difference for accuracy for the lean stimuli for Block 1 (M = .605, SD = .133) vs Block 3 (M = .544, SD = .158). In general, accuracy was greater for the rich stimuli across blocks. In particular, by block 3, accuracy for the lean stimuli tended to decrease while the one for rich stimuli increased.

Reaction Time (RT)

The two-way repeated measures ANOVA showed that there was a significant main effect for stimulus type (rich vs lean) on RT ($F(1,35) = 4.906$, $p = .033$, $\eta_p^2 = .123$). A Fisher's Least Significant Difference (LSD) test revealed that RT to the rich stimulus (M = 480.80, SD = 116.13) was statistically significantly shorter compared the lean RT (M = 489.34, SD = 118.10). This suggests that, across the task, participants tended to respond faster to the rich vs lean stimulus.

ERP Data

Paired Sample t-Test

The results indicated that, across the task, the ΔFRN amplitude mean score at the electrode Fz was significantly larger (i.e., more negative in voltage; M = -1.183, SD = 1.846) than the FCz electrode (M = - 0.410, SD = 2.149), $t(35) = -3.090$, $p = .004$. As such, for the following analyses, only electrode Fz was used.

Task Manipulation Check: Regression Analysis of Reward Leaning and ΔFRN amplitude mean score (Block 3 minus Block 1) Independent of Mood and ADHD Symptoms

See Table 4 for regression analysis results.

Table 4: Summary of Hierarchical Regression Analysis for Variables Predicting Reward Learning Score (N = 36)

Variable	B	Std. Error	Beta	Sig.	R2	ΔR2	f^2
Step 1					.10	.10	.11
Constant	.102	.171		.557			
Sex	-.099	.082	-.250	.235			
DRS Total	.003	.003	.182	.371			
MRS Total	.002	.008	.046	.815			
SNAP-IV Combined	-.106	.004	-.323	.117			
Step 2					.294	.195**	.24
Constant	.110	.154		.481			
Sex	-.158	.076	-.400	.047			
DRS Total	.004	.003	.255	.171			
MRS Total	.001	.007	.034	.849			
SNAP-IV Combined	-.009	.004	-.479	.016*			
ΔFRN	-.046	.016	-.468	.007**			

* $p < 0.05$; ** $p < 0.01$
SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale; DRS: Depression Rating Scale; MRS: Mania Rating Scale
ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1

In Step 1, sex, participants' total scores from the MRS and DRS, and the ADHD combined severity score accounted for 10.0% of the variance in Reward Learning (p = .502). Adding ΔFRN amplitude in Step 2 resulted in significantly more explanatory power in our model, new model R^2 = .294 and ΔR^2 = .195, and this change in R^2 was significant, $F(1,30)$ = 8.300, p = .007. In particular, the results showed that as Reward Learning increased over the blocks of the task, there was an increase (i.e., less positive/more negative voltage) in ΔFRN mean amplitude (p = 007; see Figure 3).

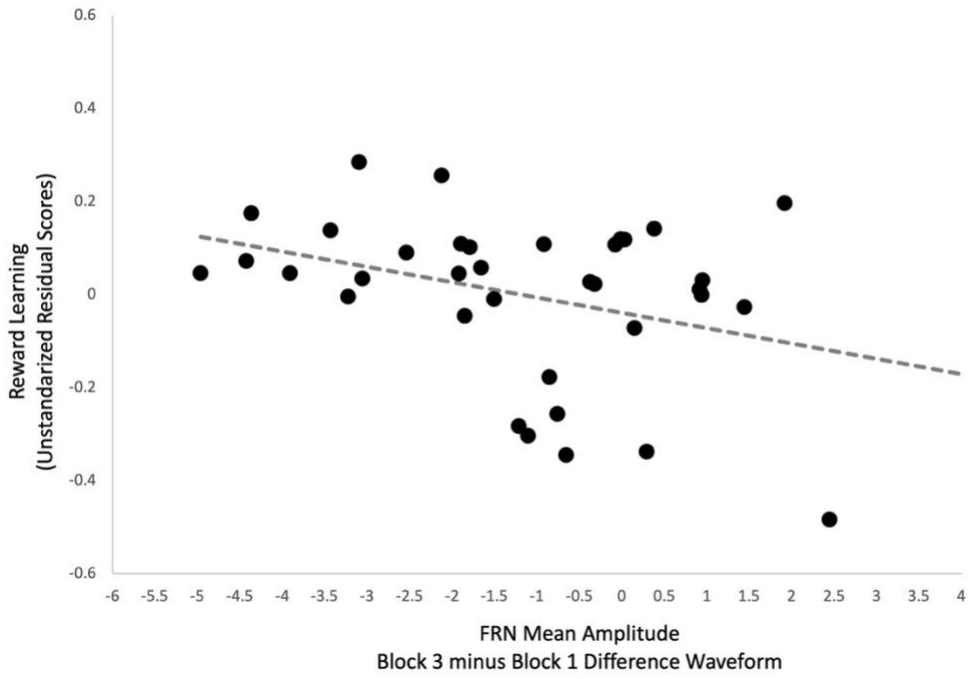

Figure 3: Scatterplot of the relationship between Reward Learning and ΔFRN mean amplitude
Note: ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1

Regression Analysis of Overall ADHD Symptom Severity, ΔFRN amplitude mean score (Block 3 minus Block 1), and Reward Learning scores

See Table 5 for regression analysis results.

Table 5: Summary of Hierarchical Regression Analysis for Variables Predicting Overall ADHD Symptom Severity (N = 36)

Variable	B	Std. Error	Beta	Sig.	R2	ΔR2	f^2
Step 1					.278	.278*	.38
Constant	12.201	7.348		.107			
Sex	-10.185	3.169	-.509	.003**			
DRS Total	.036	.154	.042	.815			
MRS Total	.481	.362	.224	.194			
Step 2					.455	.177*	.83
Constant	11.451	6.607		.093			
Sex	-11.957	2.901	-.597	.000**			
DRS Total	.138	.142	.158	.340			
MRS Total	.378	.327	.176	.256			
ΔFRN	-1.861	.720	-.378	.015*			
Reward Learning	-18.765	7.379	-.370	.016*			

* $p < 0.05$; ** $p < 0.01$
SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale; DRS: Depression Rating Scale; MRS: Mania Rating Scale
ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1

In Step 1, sex and MRS and DRS scores accounted for 28% of the variance in Overall ADHD Symptom Severity scores ($p = .014$). Adding ΔFRN mean amplitude and Reward Learning in Step 2 resulted in significantly more explanatory power in our model, model $R^2 = .455$ and $\Delta R^2 = .177$, and this change in R^2 was significant, $F(2,30) = 4.877$, $p = .015$. In particular, the results showed that as Overall ADHD Symptom Severity increased there was a reduction in Reward Learning ($p = .016$) and an increase in ΔFRN mean amplitude (i.e., less positive/more negative voltage change over blocks; $p = 015$; see Figure 4).

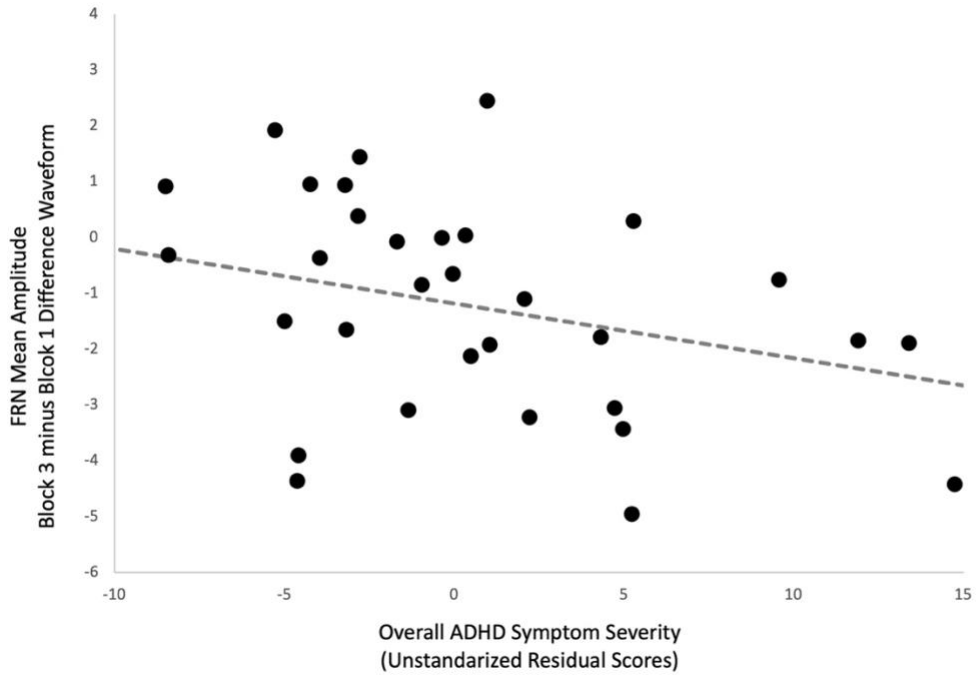

Figure 4: Scatterplot of the relationship between ΔFRN amplitude mean score and Overall Attention Deficit Hyperactivity Disorder Symptom Severity as measured by the SNAP-IV
Note: ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1; SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale

Exploratory Regression Analysis of ADHD Predominantly Inattentive Subtype, ΔFRN amplitude mean score (Block 3 minus Block 1), and Reward Learning scores

See Table 6 for regression analysis results.

Table 6: Summary of Hierarchical Regression Analysis for Variables Predicting ADHD Predominantly Inattentive Subtype (N = 36)

Variable	B	Std. Error	Beta	Sig.	R2	ΔR2	f^2
Step 1					.255	.255*	.34
Constant	6.423	4.530		.166			
Sex	-5.701	1.954	-.469	.006**			
DRS Total	.128	.095	.240	.189			
MRS Total	.225	.223	-.173	.321			
Step 2					.461	.206**	.85
Constant	5.907	3.987		.149			
Sex	-6.867	1.751	-.565	.000**			
DRS Total	.194	.086	.365	.031*			
MRS Total	.157	.197	.120	.432			
ΔFRN	-.1.247	.434	-.417	.007**			
Reward Learning	-.11.981	4.453	-.389	.012*			

* $p < 0.05$; ** $p < 0.01$
SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale; DRS: Depression Rating Scale; MRS: Mania Rating Scale
ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1

In Step 1, sex and MRS and DRS scores accounted for 25% of the variance in ADHD Predominantly Inattentive Subtype scores (p = .023). Adding ΔFRN mean amplitude and Reward Learning in Step 2 resulted in significantly more explanatory power in our model, model R^2 = .461 and ΔR^2 = .206, and this change in R^2 was significant, F (2, 30) = 5.746, p = .008. In particular, the results showed that as ADHD Predominantly Inattentive Subtype symptom severity increased there was a reduction in Reward Learning (p = .012) and an increase in ΔFRN mean amplitude (i.e., less positive/more negative voltage; p = 007; see Figure 5).

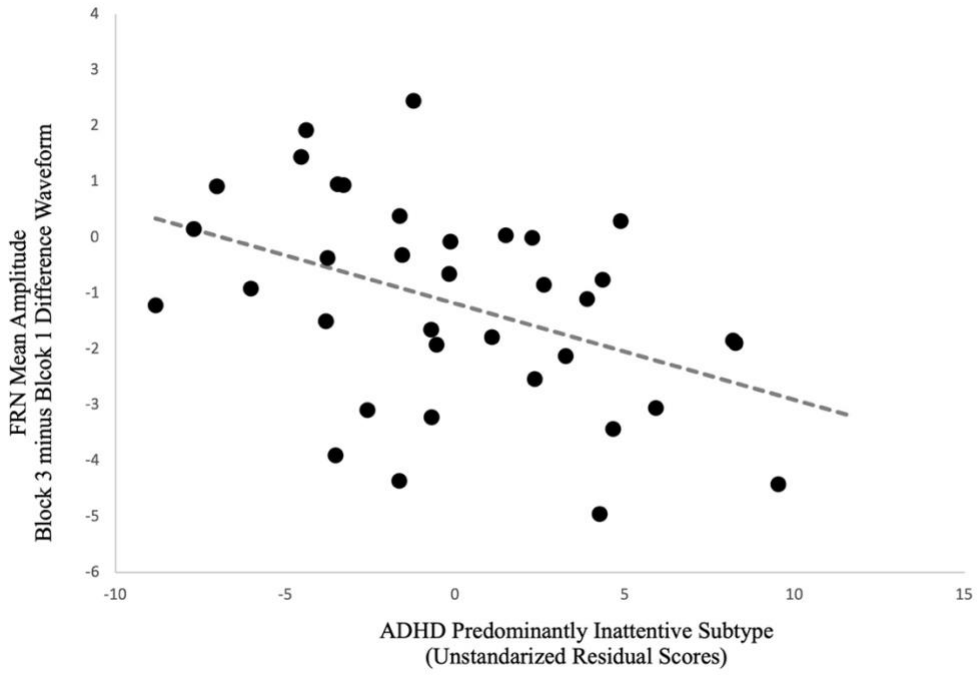

Figure 5: Scatterplot of the relationship between ΔFRN amplitude mean score and Attention Deficit Hyperactivity Disorder Predominantly Inattention Subtype Severity as measured by the SNAP-IV
Note: ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1; SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale

Exploratory Regression Analysis of ADHD Predominantly Hyperactive/Impulsive Subtype, ΔFRN amplitude mean (Block 3 minus Block 1), and Reward Learning scores.

See Table 7 for regression analysis results.

Table 7: Summary of Hierarchical Regression Analysis for Variables Predicting ADHD Predominantly Hyperactive/Impulsive Subtype (N = 36)

Variable	B	Std. Error	Beta	Sig.	R2	ΔR2	f^2
Step 1					.253	.253*	.34
Constant	5.778	3.985		.157			
Sex	-4.485	1.719	-.420	.014*			
DRS Total	-.091	.084	-.195	.284			
MRS Total	.256	.196	.223	.202			
Step 2					.328	.075	.49
Constant	5.545	3.913		.167			
Sex	-5.090	1.718	-.476	.006**			
DRS Total	-.056	.084	-.120	.512			
MRS Total	.221	.194	.193	.262			
ΔFRN	-.614	.426	-.234	.160			
Reward Learning	-6.784	4.371	-.251	.131			

* $p < 0.05$; ** $p < 0.01$
SNAP-IV: Swanson, Nolan, and Pelham Questionnaire -18 Items Parent Rating Scale; DRS: Depression Rating Scale; MRS: Mania Rating Scale
ΔFRN: Feedback Related Negativity Mean Amplitude Derived from Block 3 minus Block 1

In Step 1, sex and MRS and DRS scores accounted for 25% of the variance in ADHD Predominantly Hyperactive/Impulsive Subtype scores (p = .024). Adding ΔFRN mean amplitude and Reward Learning scores in Step 2 did not result in significantly more explanatory power in our model, model R^2 = .328 and ΔR^2 = .075, and this change in R^2 was not significant, $F(2,30)$ = 1.665, p = .206. In particular, the results showed that ADHD Predominantly Hyperactive/Impulsive Subtype symptom severity was not related to either Reward Learning (p = .131) or ΔFRN mean amplitude (p = .160).

CHAPTER FOUR: DISCUSSION

The focus of the current study was to examine the relationship between behavioral reward-based learning, the scalp-recorded ERP Feedback Related Negativity, and dimensional ADHD symptom severity during a well-validated probabilistic reward task. Although dysfunctions in various aspects of hedonic functioning have been reported in the pediatric literature (e.g., Forbes and Dahl, 2012; Morris et al., 2015), more research is needed to better understand the underlying mechanisms of reward-based learning in this population. In general, our results showed that in teens with prominent mood difficulties, dimensional ADHD symptom severity was related with a propensity toward a poor modulation of behavior as a function of prior reward contingencies. In addition, this behavioral dysfunction was mirrored by a blunted neural response to reward feedback as evidenced by a reduction in the typical expected dampening of the FRN amplitude over the course of learning during the task. Consistent with prior work (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005; Whitton et al., 2015), PRT behavioral analyses revealed that, by block 3, participants showed an increase in response bias toward the rich stimuli that did not appear to be driven by task difficulty (i.e., ability to discriminate between the two stimuli). In addition, as expected based on prior literature (e.g., Pizzagalli et al., 2008; Pechtel et al., 2013), a shorter reaction time and greater accuracy was found for the rich vs. lean stimuli across blocks. Overall, as the behavioral changes expected in PRT performance across the task occurred in the overall sample, this suggests that the task "worked" as intended.

Contrary to our hypothesis, we found an increase (i.e., less positive/more negative voltage) in the ΔFRN mean amplitude as the reward learning score increased, independent of mood and ADHD symptoms. An explanation of our results could be found in studies suggesting

that the FRN may reflect not only the early judgment of feedback based on a binary classification of good vs bad outcomes (Hajcak et al., 2006; Yeung & Sanfey, 2004), but that it could also be affected by top-down processes, such as motivation, level of interest, and subjective relative value of the reward received (Goyer et al., 2008; Gehring and Willoughby, 2002). Some studies have also suggested that the FRN tends to be larger when there is a mismatch between the outcome (e.g., reward received) and subjective expectations, independent of whether the outcome was better or worse than expected (Walentowska et al., 2019). On the contrary, it seems that in healthy controls, the FRN habituates (e.g., smaller amplitude over time) to reward when it becomes more expected or predictable (Santesso et al., 2008a; Frank et al., 2019). In addition, from a neural point of view, some have theorized that the dopamine feedback signal may be less effective in differentiating between good and bad outcomes during adolescence as compared to adulthood (Zottoli & Grose-Fifer, 2012). If confirmed, this suggests that rewards of larger magnitude may be needed in studies on youth to elicit similarly effective dopaminergic responses seen in adults. Consistent with this theory, research has shown that the major components of the reward system undergo significant changes and reorganization during adolescence, including changes in projections from DA neurons deep in the base of the brain (e.g., ventral tegmental area, substantia nigra) to subcortical and cortical regions including the hippocampus, amygdala, striatum, and prefrontal cortex, among others (for a review see: Telzer, 2016).

In conclusion, we could speculate that, while participants showed an ability to learn based on the reinforcement schedule (i.e., an increase in Response Bias over blocks), there may have been a mismatch between the participants' subjective expectations and the outcome. In particular, the small monetary value of the reward (i.e., 10 cents) may have been processed, as the task progressed, as neutral (vs positive) and thus did not elicit the typical reward pattern (i.e.,

a smaller/more positive FRN). However, this hypothesis requires further evaluation such as examining probabilistic reward-based learning in the context of different magnitudes of reward across blocks. This would help us, for example, to better understand how lower versus larger magnitude rewards are processed.

Consistent with our hypotheses (hypothesis 2), we found that teens with increased overall ADHD symptom severity showed a larger (i.e., more negative voltage) ΔFRN amplitude and lower Reward Learning during the probabilistic reward learning task. This result is consistent with a previous study that evaluated the FRN in the context of probabilistic reward learning (Thoma et al., 2015) and found altered learning and enhanced FRN in participants with ADHD. Similarly, our result appears consistent with previous studies that showed alternations in individuals with ADHD in reward learning and its neural underpinning (Aster et al., 2024). In particular, some studies found altered dopamine neurotransmission in the reward pathway (Jucaite et al., 2005; Véronneau-Veilleux et al., 2022). For example, some reported lower striatal dopamine transporter density in drug-naïve participants with ADHD (Fusar-Poli et al., 2011) as well as lower D2 and D3 receptors and dopamine transporter (DAT) availability in midbrain regions and the nucleus accumbens, areas that are involved in reward and motivation (Volkow et al., 2009). Interestingly, a study on youth with ADHD (Hauser et al., 2014b) utilized Reward Prediction Error (RPE)-based reinforcement learning models paired with multimodal imaging techniques (EEG and fMRI) to better understand the mechanisms underlining the learning dysfunctions often reported in this population. Results showed impaired RPE processing in the medial prefrontal cortex and a reduced FRN in that region. The study also revealed that teens with ADHD seem to be characterized by a suboptimal choice selection as reflected by excessive exploratory behavior. This behavioral strategy could be beneficial under uncertainty but when

paired with an inability to adjust the exploratory behavior based on the feedback received, as seen in healthy controls, it may instead be detrimental.

Although exploratory, our results regarding ADHD symptoms subtypes seem to suggest that the above-mentioned relationship may be driven especially by symptoms of inattention vs hyperactivity/impulsivity. These findings are similar to a study that found that the relationship between ADHD symptom severity, as measured by the SNAP-IV, and decreased-reward-based learning was mostly driven by symptoms of inattention (vs impulsivity) in teens and adults (Portengen et al., 2021). More generally, the exploratory results are in line with studies suggesting that not only reward but also attention have a strong impact on learning and that attention is an additional factor that gates plasticity in the context on reward learning (i.e., changes specific connections in the brain; for more details, Vartak et al., 2017).

While the current study is correlational and cannot establish causality, it provides preliminary information about specific relationships that can inform future studies that can directly test tentative causality theories. Finally, although the current results may not directly translate into immediate practical implications, if further replicated, they could inform treatment approaches. In particular, given strong ties between reward-based learning and operant conditioning, a treatment often used with pediatric mood disorders, the results could help to better understand the presence of possible comorbid deficits in reward learning that could impact response to behavioral therapies**.** For example, the use of clear and predictable reinforcements that hold high subjective value may be more effective in facilitating response acquisition in youth with mood disorders with comorbid inattentive ADHD.

A limitation of the current study can be found in the use of a different approach to calculate the FRN during the PRT. In particular, we scored the FRN as the difference between

Block 3 and Block 1 instead of the more traditional method of averaging it across Block 2 and Block 3. Additionally, when employed the more traditional method to score the FRN to look at its relationship with reward learning behavior, the results did not show the expected pattern across the sample. However, the ΔFRN used in the current study mirrors the approach used to calculate the Reward Learning score and gives us the possibility to look at how participants learned over the task. Nonetheless this approach is novel and should be replicated. A similar limitation is the absence of negative feedback in the PRT task that does not allow the assessment of ERP difference waves that capture processing of reward versus non-reward. The study is also limited by the relatively small sample size which could inflate effect sizes (Button et al., 2013).

In conclusion, our results showed that a poor modulation of behavior based on prior reward contingencies was related to an increase in dimensional ADHD symptom severity in a sample of adolescents with prominent mood difficulties. This behavioral dysfunction was also reflected by a blunted neural habituation to reward feedback as evidenced by a larger FRN mean amplitude. Additionally, exploratory analyses highlighted how the relationship between overall ADHD symptom severity and ΔFRN may be driven especially by symptoms of inattention vs. hyperactivity/impulsivity. Future research should assess reward-based learning in the context of both different magnitudes of reward and non-reward feedback across blocks to better clarify the results of the current study. In addition, it could be interesting to assess potential mediating/moderating factors influencing the observed relationship, such as the presence of low approach motivation. A prior study using a probabilistic reward task similar to the PRT, found that children with low approach motivation tended to display a blunted response to feedback signaling either gains or losses (Luking et al.,2017). This would allow us not only to better

understand the results of the present study but, from a practical perspective, it could also provide support for a novel treatment target within this population.

CHAPTER FIVE: DIVERSITY CONSIDERATIONS

Efforts were made to recruit an adequate number of subjects from different racial and ethnic groups. The UCLA CHAMP and YSAM clinics, that provided the sample, usually receive referrals from diverse outlets, which helped ensure that rates of ethnic and racial backgrounds were somewhat similar to rates found in the greater Los Angeles area. No exclusionary criteria were made regarding ethnic or racial groups. Additionally, no subject was excluded on the basis of gender, sex, SES, and/or family structure. In conclusion, the ethnic/racial composition of the study sample was based on the characteristics of similar local patient samples as well as the demographics of the population from which most referrals were generated.

Regarding sex-related differences, previous research yielded inconsistent findings with respect to the FRN during monetary-reward tasks. Although some studies reported that adolescent boys (vs girls) showed larger amplitudes (Crowley et al., 2013; Yi et al., 2012), findings from other studies contradict these results (e.g., Greimel et al., 2018; Santesso et al., 2011). In the present study, we added sex as a covariate of no interest to identify results independent of sex differences.

When discussing diversity, an important aspect, barely discussed in the literature, is the unintended racial biases that impact neuroscience, particularly research using EEG. EEG requires electrodes to adhere to the scalp to measure brain activity and, to obtain high-quality data, various factors are considered, such as hair type and length, that often cause challenges in recruiting and retaining African American participants due to their common hairstyles and hair characteristics. However, the lack of data on African American participants reduces the generalizability of research findings and results in disparities in theoretical knowledge (Choy et al., 2021). Although no clear solution is currently available, as suggested by Choy et al. (2021):

"It is our hope that by acknowledging the current systemic biases and unintended exclusions, we can advance the field towards practicing and utilizing innovative ideas that may be more inclusive in the recruitment and retention of minority populations."

CHAPTER SIX: ETHICAL CONSIDERATIONS

Consent to participate in the study was thoroughly discussed with parents and children, including the general purpose of the study, potential benefits, risks and discomforts, confidentiality and limits to confidentiality, participants' rights if they decided to take part in the study, and contact information in case of questions, comments, or concerns related to the study/researchers. Possible potential risks and discomfort included the following: (1) embarrassment and anxiety due to discussion of personal information, (2) mild frustration during computer tasks which may be challenging, and/or (3) slight discomfort during due to electrodes application. Youth were provided with assent to participate in the research study.

During the interviews, subjects were informed that they could refuse to answer questions and were encouraged to discuss concerns of any nature. Precautions and safeguards were followed during and after EEG recording to minimize discomfort and to guarantee that adequate hygiene protocols were followed. Breaks were also offered during testing to minimize fatigue. Participants were also advised that they could discontinue participation or take a break at any point. To ensure confidentiality, each participant was assigned a unique ID number to protect their identity, and only this coded ID number was associated with the subject’s data. Raw data from psychiatric interviews, demographics, and other identifying information were stored in locked rooms and filing cabinets inside the UCLA clinic office and/or in encrypted, password-protected data files and only accessible to direct members of the research team. All data used for analyses related to the present proposal are de-identified and currently stored in a UCLA-approved, encrypted, and password-protected data file storage system.

APPENDIX: UCF IRB LETTER

UNIVERSITY OF CENTRAL FLORIDA

Institutional Review Board
FWA00000351
IRB00001138, IRB00012110
Office of Research
12201 Research Parkway
Orlando, FL 32826-3246

NOT HUMAN RESEARCH DETERMINATION

August 9, 2023

Dear Giulia Salgari:

On 8/9/2023, the IRB reviewed the following protocol:

Type of Review:	Initial Study
Title of Study:	Feedback-Related Negativity, Reward-Based Learning, and ADHD Symptoms: Preliminarily Findings in a Pediatric Sample with Prominent Mood Symptoms
Investigator:	Giulia Salgari
IRB ID:	STUDY00005812
Funding:	None
Documents Reviewed:	• HRP-251 - FORM - Faculty Advisor Scientific-Scholarly Review.pdf, Category: Faculty Research Approval; • Data Points & Variables.docx, Category: Other; • HRP-250 - FORM - Request for NHSR .docx, Category: IRB Protocol;

The IRB determined that the proposed activity is not research involving human subjects as defined by DHHS and FDA regulations.

IRB review and approval by this organization is not required. This determination applies only to the activities described in the IRB submission and does not apply should changes outside of administrative ones (study personnel, timelines, etc.) be made. If non-administrative changes are made (design, information collected, instrumentation, funding, etc.) and there are questions about whether these activities are research involving human in which the organization is engaged, please submit a new request to the IRB for a determination by **clicking Create Modification / CR** within the study.

If you have any questions, please contact the UCF IRB at 407-823-2901 or irb@ucf.edu. Please include your project title and IRB number in all correspondence with this office.

Sincerely,

Kamille C. Birkbeck

Kamille Birkbeck

UNIVERSITY OF CENTRAL FLORIDA

UCF IRB

Institutional Review Board
FWA00000351
IRB00001138, IRB00012110
Office of Research
12201 Research Parkway
Orlando, FL 32826-3246

LIST OF REFERENCES

Admon, R., & Pizzagalli, D.A. (2015). Dysfunctional reward processing in depression. *Current Opinion in Psychology*, *4*, 114–118. https://doi.org/10.1016/j.copsyc.2014.12.011

Alexander, L., Jelen, L.A., Mehta, M.A., & Young, A.H. (2021). The anterior cingulate cortex as a key locus of ketamine's antidepressant action. *Neuroscience & Biobehavioral Reviews*, *127*, 531–554. https://doi.org/10.1016/j.neubiorev.2021.05.003

Ambrosini, P.J. (2000). Historical development and present status of the schedule for affective disorders and schizophrenia for school-age children (K-SADS). *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(1), 49–58. https://doi.org/10.1097/00004583-200001000-00016

Aster, H.C., Waltmann, M., Busch, A., Romanos, M., Gamer, M., Maria van Noort, B., Beck, A., Kappel, V., & Deserno, L. (2024). Impaired flexible reward learning in ADHD patients is associated with blunted reinforcement sensitivity and neural signals in ventral striatum and parietal cortex. *NeuroImage: Clinical*, *42*:103588. https://doi.org/10.1016/j.nicl.2024.103588

Axelson, D., Birmaher, B.J., Brent, D., Wassick, S., Hoover, C., Bridge, J., & Ryan, N. (2003). A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *Journal of Child and Adolescent Psychopharmacol*ogy, *13*(4):463-70. https://doi.org/10.1089/104454603322724850

Barkley, R.A. (2020). The high economic costs associated with ADHD. *The ADHD Report*, *28*(3), 10–12. https://doi.org/10.1521/adhd.2020.28.3.10

Bech, P., Crochet, S., Dard, R., Ghaderi, P., Liu, Y., Malekzadeh, M., Petersen, C.C.H., Pulin, M., Renard, A., Sourmpis, C. (2023) Striatal Dopamine Signals and Reward Learning. *Function*, *4*(6):zqad056. https://doi.org/10.1093/function/zqad056

Bellebaum, C., Polezzi, D., & Daum, I. (2010). It is less than you expected: The feedback-related negativity reflects violations of reward magnitude expectations. *Neuropsychologia*, *48*(11), 3343–3350. https://doi.org/10.1016/j.neuropsychologia.2010.07.023

Birmaher, B., Ehmann, M., Axelson, D.A., Goldstein, B. I., Monk, K., Kalas, C., Kupfer, D., Gill, M.K., Leibenluft, E., Bridge, J., Guyer, A., Egger, H.L., & Brent, D.A. (2009). Schedule for affective disorders and schizophrenia for school-age children (K-SADS-PL) for the assessment of Preschool Children – a preliminary psychometric study. *Journal of Psychiatric Research*, *43*(7), 680–686. https://doi.org/10.1016/j.jpsychires.2008.10.003

Bitsko, R.H., Claussen, A.H., Lichstein, J., Black, L.I., Jones, S.E., Danielson, M.L., Hoenig, J.M., Davis Jack, S.P., Brody, D.J., Gyawali, S., Maenner, M.J., Warner, M., Holland,

K.M., Perou, R., Crosby, A.E., Blumberg, S.J., Avenevoli, S., Kaminski, J.W., & Ghandour R.M. (2022). Contributor. Mental Health Surveillance Among Children - United States, 2013-2019. *MMWR Supplement, 71*(2):1-42. https://doi.org.10.15585/mmwr.su7102a1

Bogdan, R. & Pizzagalli, D.A. (2006). Acute stress reduces reward responsiveness: implications for depression. *Biological Psychiatry*, *60*(10):1147-54. https://doi.org/10.1016/j.biopsych.2006.03.037

Bromberg-Martin, E.S, Matsumoto, M., & Hikosaka, O. (2010a). Distinct tonic and phasic anticipatory activity in lateral habenula and dopamine neurons. *Neuron*, *67*(1):144-55. https://doi.org/10.1016/j.neuron.2010.06.016

Bromberg-Martin, E.S., Matsumoto, M., & Hikosaka, O. (2010b). Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron*, *68*(5):815-34. https://doi.org/10.1016/j.neuron.2010.11.022

Bussing, R., Fernandez, M., Harwood, M., Wei Hou, Garvan, C.W., Eyberg, S.M., & Swanson, J.M. (2008). Parent and teacher SNAP-IV ratings of attention deficit hyperactivity disorder symptoms: psychometric properties and normative ratings from a school district sample. *Assessment*, *15*(3):317-28. https://doi.org/10.1177/1073191107313888

Button K.S., Ioannidis J.P.A., Mokrysz C., Nosek B.A., Flint J., Robinson E.S.J., & Munafò M.R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5):365–376. https:// doi.org/10.1038/nrn3475

Choy, T., Baker, E., & Stavropoulos, K. (2021). Systemic racism in EEG research: Considerations and Potential Solutions. *Affective Science*, *3*(1), 14–20. https://doi.org/10.1007/s42761-021-00050-0

Chudasama, Y., Daniels, T. E., Gorrin, D. P., Rhodes, S. E. V., Rudebeck, P. H., & Murray, E. A. (2013). The role of the anterior cingulate cortex in choices based on reward value and reward contingency. *Cerebral Cortex*, *23*(12), 2884–2898. https://doi.org/10.1093/cercor/bhs266

Cohen J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates, Publishers.

Crowley, M. J., Wu, J., Hommer, R. E., South, M., Molfese, P. J., Fearon, R. M., & Mayes, L. C. (2013). A developmental study of the feedback-related negativity from 10–17 years: Age and sex effects for reward versus non-reward. *Developmental Neuropsychology*, *38*(8), 595–612. https://doi.org/10.1080/87565641.2012.694512

Cubillo, A., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit

hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex*, *48*(2), 194–215. https://doi.org/10.1016/j.cortex.2011.04.007

Daviss, W.B. (2008). A review of co-morbid depression in pediatric ADHD: Etiologies, phenomenology, and treatment. *Journal of Child and Adolescent Psychopharmacology*, *18*(6), 565–571. https://doi.org/10.1089/cap.2008.032

Del Campo, N., Chamberlain, S. R., Sahakian, B. J., & Robbins, T. W. (2011). The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *69*(12). https://doi.org/10.1016/j.biopsych.2011.02.036

Delorme, A., & Makeig, S. (2004). EEGLAB: An open-source toolbox for analysis of single-trial EEG Dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Eckstrand, K.L., Forbes, E.E., Bertocci, M.A., Chase, H.W., Greenberg, T., Lockovich, J., Stiffler, R., Aslam, H.A., Graur, S., Bebko, G., & Phillips, M.L. (2019). Anhedonia reduction and the association between left ventral striatal reward response and 6-month improvement in life satisfaction among young adults. *JAMA Psychiatry*, *76*(9):958-965. https://doi.org/10.1001/jamapsychiatry.2019.0864.

Erskine, H.E., Norman, R.E., Ferrari, A.J., Chan, G.C.K., Copeland, W.E., Whiteford, H.A., & Scott, J.G. (2016). Long-term outcomes of attention-deficit/hyperactivity disorder and conduct disorder: A systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(10), 841–850. https://doi.org/10.1016/j.jaac.2016.06.016

Faraone, S.V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J.K., Ramos-Quiroga, J.A., Rohde, L.A., Sonuga-Barke, E.J., Tannock, R., & Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, *1*(1). https://doi.org/10.1038/nrdp.2015.20

Faul, F., Erdfelder, E., Lang, A.G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175-191. https://doi.org/10.3758/bf03193146

Ferdinand, N.K., Mecklinger, A., Kray, J., & Gehring, W.J. (2012). The processing of unexpected positive response outcomes in the mediofrontal cortex. *Journal of Neuroscience*, *32*(35), 12087–12092. https://doi.org/10.1523/jneurosci.1410-12.2012

Forbes, E.E., & Dahl, R.E. (2012). Research review: Altered reward function in adolescent depression: What, when and how? *Journal of Child Psychology and Psychiatry*, *53*(1), 3–15. https://doi.org/10.1111/j.1469-7610.2011.02477.x

Frank, D.W., Stevens, E.M., Versace, F. (2019). A neurophysiological measure of reward sensitivity and its association with anhedonia in psychiatrically healthy adolescents and young adults. I*nternational Journal of Psychophysiology, 141*, 56-64. https://doi.org/10.1016/j.ijpsycho.2019.05.002

Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., & Balottin, U. (2012). Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. *American Journal of Psychiatry, 169*(3), 264-72. doi: https://doi.org/10.1176/appi.ajp.2011.11060940

Gehring, W.J., & Willoughby, A.R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science, 295*, 2279–2282. https://doi.org/10.1126/science.1066893

Geller, B., Williams, M., Zimerman, B., & Frazier, J. Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS), Washington University, St Louis (1996)

Geller, B., Zimerman, B., Williams, M., Bolhofner, K., Craney, J.L., DelBello, M.P., & Soutullo, C. (2001). Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(4):450-5. https://doi:10.1097/00004583-200104000-00014

Glimcher, P.W. (2011). Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis. *Proceedings of the National Academy of Sciences*, *108*(supplement_3), 15647–15654. https://doi.org/10.1073/pnas.1014269108. Erratum in: Proc Natl Acad Sci U S A. *108*(42):17568-9

Goyer, J.P., Woldorff, M.G., & Huettel, S.A. (2008). Rapid electrophysiological brain responses are influenced by both valence and magnitude of monetary rewards. Journal of *Cognitive Neuroscience*, *20*, 2058–2069. https://doi.org/10.1162/jocn.2008.20134

Grace, A.A. (2016). Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nature Reviews Neuroscience*, *17*(8), 524–532. https://doi.org/10.1038/nrn.2016.57

Greimel, E., Bakos, S., Landes, I., Töllner, T., Bartling, J., Kohls, G., & Schulte-Körne, G. (2018). Sex differences in the neural underpinnings of social and monetary incentive processing during adolescence. *Cognitive, Affective, & Behavioral Neuroscience*, *18*(2), 296–312. https://doi.org/10.3758/s13415-018-0570-z

Haber, S.N., & Behrens, T.E.J. (2014). The neural network underlying incentive-based learning: Implications for interpreting circuit disruptions in psychiatric disorders. *Neuron, 83*(5), 1019–1039. https://doi.org/10.1016/j.neuron.2014.08.031

Hajcak, G, Holroyd, C.B., Moser, J.S., & Simons, R.F. (2005). Brain potentials associated with expected and unexpected good and bad outcomes. *Psychophysiology*, *42*(2):161-70. https://doi.org/10.1111/j.1469-8986.2005.00278.x

Hajcak, G., Moser, J.S., Holroyd, C.B., & Simons, R.F. (2007). It's worse than you thought: The feedback negativity and violations of reward prediction in gambling tasks. *Psychophysiology*, *44*(6), 905–912. https://doi.org/10.1111/j.1469-8986.2007.00567.x

Hajcak, G., Moser, J.S., Holroyd, C.B., & Simons, R.F. (2006). The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. *Biological Psychology*, *71*(2):148-54. https://doi.org/10.1016/j.biopsycho.2005.04.001

Hämmerer, D., Li, S.C., Müller, V., & Lindenberger.U. (2011). Life span differences in electrophysiological correlates of monitoring gains and losses during probabilistic reinforcement learning. *Journal of Cognitive Neuroscience*, *23*(3):579-92. https://doi.org/10.1162/jocn.2010.21475

Hauser, T. U., Iannaccone, R., Stämpfli, P., Drechsler, R., Brandeis, D., Walitza, S., & Brem, S. (2014a). The feedback-related negativity (FRN) revisited: New insights into the localization, meaning and network organization. *NeuroImage*, *84*, 159–168. https://doi.org/10.1016/j.neuroimage.2013.08.028

Hauser, T.U., Iannaccone, R., Ball, J., Mathys, C., Brandeis, D., Walitza, S. & Brem, S. (2014b). Role of the medial prefrontal cortex in impaired decision making in juvenile attention-deficit/hyperactivity disorder. *JAMA Psychiatry*, *71*(10):1165-73. https://doi.org/10.1001/jamapsychiatry.2014.1093

Hautus, M.J. (1995). Corrections for extreme proportions and their biasing effects on estimated values OFD′. *Behavior Research Methods, Instruments, & Computers*, *27*(1), 46–51. https://doi.org/10.3758/bf03203619

Holroyd, C.B., & Coles, M.G. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*(4), 679–709. https://doi.org/10.1037/0033-295x.109.4.679

Holroyd, C.B., & Coles, M.G. (2008). Dorsal anterior cingulate cortex integrates reinforcement history to guide voluntary behavior. *Cortex*, *44*(5):548–59. http://doi.org/10.1016/j.cortex.2007.08.013

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (rdoc): Toward a new classification framework for research on Mental Disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Jucaite, A., Fernell, E., Halldin, C., Forssberg, H., & Farde, L. (2005). Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(3):229-23815691523. https://doi.org/10.1016/j.biopsych.2004.11.009

Kaufman, J., & Schweder, A.E. (2004). The Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime version (K-SADS-PL). In M. J. Hilsenroth & D. L. Segal (Eds.), *Comprehensive handbook of psychological assessment, Vol. 2. Personality assessment* (pp. 247–255). John Wiley & Sons, Inc.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and Lifetime version (K-SADS-PL): Initial reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kennerley, S.W., Walton, M.E., Behrens, T.E., Buckley, M.J., & Rushworth, M.F. (2006). Optimal decision making and the anterior cingulate cortex. *Nature Neuroscience*, *9*(7), 940–947. https://doi.org/10.1038/nn1724

Keller, A.S., Leikauf, J.E., Holt-Gosselin, B., Staveland, B.R., & Williams, L.M. (2019). Paying attention to attention in depression. *Translational Psychiatry, 9*, 279. https://doi.org/10.1038/s41398-019-0616-1

Klein, M.O., Battagello, D.S., Cardoso, A.R., Hauser, D.N., Bittencourt, J.C., & Correa, R.G. (2019). Dopamine: Functions, signaling, and association with neurological diseases. *Cellular and Molecular Neurobiology*, *39*(1), 31–59. https://doi.org/10.1007/s10571-018-0632-3

Larson, K., Russ, S.A., Kahn, R.S., & Halfon, N. (2011). Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. *Pediatrics*, *127*(3), 462–470. https://doi.org/10.1542/peds.2010-0165

Lenartowicz, A., Delorme, A., Walshaw, P.D., Cho, A.L., Bilder, R.M., McGough, J.J., McCracken, J.T., Makeig, S., Loo, S.K. (2014). Electroencephalography correlates of spatial working memory deficits in attention-deficit/hyperactivity disorder: vigilance, encoding, and maintenance. *Journal of Neuroscience, 34*(4):1171-82. https://doi.org/10.1523/JNEUROSCI.1765-13.2014

Luking, K.R., Neiman, J.S., Luby, J.L., & Barch, D.M. (2017). Reduced hedonic capacity/approach motivation relates to blunted responsivity to gain and loss feedback in children. *Journal of Clinical Child & Adolescent Psychology*, *46*(3), 450–462. https://doi.org/10.1080/15374416.2015.1012721

Luman, M., Van Meel, C.S., Oosterlaan, J., Sergeant, J.A., & Geurts, H.M. (2009). Does reward frequency or magnitude drive reinforcement-learning in attention-deficit/hyperactivity

disorder? *Psychiatry Research*, *168*(3), 222–229. https://doi.org/10.1016/j.psychres.2008.08.012

Maia, T.V., & Frank, M.J. (2011). From reinforcement learning models to psychiatric and neurological disorders. *Nature Neuroscience*, *14*(2), 154–162. https://doi.org/10.1038/nn.2723

Makeig, S., Jung, T.P., Ghahremani, D., & Sejnowski, T.J. (1996). Independent component analysis of simulated ERP data. Institute for Neural Computation, University of California: technical report INC-9606

Martin, L.E., Potts, G.F., Burton, P.C., & Montague, P.R. (2009). Electrophysiological and hemodynamic responses to reward prediction violation. *Neuroreport*, *20*(13):1140–3. https://doi.org/10.1097/WNR.0b013e32832f0dca

Marx, I., Höpcke, C., Berger, C., Wandschneider, R., & Herpertz, S.C. (2013). The impact of financial reward contingencies on cognitive function profiles in adult ADHD. *PLoS ONE*, *8*(6):e67002. https://doi.org/10.1371/journal.pone.0067002

Morris, B.H., Bylsma, L.M., Yaroslavsky, I., Kovacs, M., & Rottenberg, J. (2015). Reward learning in pediatric depression and anxiety: Preliminary findings in a high-risk sample. *Depression and Anxiety*, *32*(5), 373–381. https://doi.org/10.1002/da.22358

Mueller, E.M., Pechtel, P., Cohen, A.L., Douglas, S.R., & Pizzagalli, D. A. (2015). Potentiated processing of negative feedback in depression is attenuated by anhedonia. *Depression and Anxiety*, *32*(4), 296–305. https://doi.org/10.1002/da.22338

Müller, S.V., Möller, J., Rodriguez-Fornells, A., & Münte, T.F. (2005). Brain potentials related to self-generated and external information used for performance monitoring. *Clinical Neurophysiology*, *116*(1), 63–74. https://doi.org/10.1016/j.clinph.2004.07.009

Oliveira, F.T., McDonald, J.J., & Goodman, D. (2007). Performance monitoring in the anterior cingulate is not all error related: expectancy deviation and the representation of action-outcome associations. *Journal of Cognitive Neuroscience*, *19*(12):1994-2004. https://doi.org/10.1162/jocn.2007.19.12.1994

Pechtel, P., Dutra, S.J., Goetz, E.L., & Pizzagalli, D.A. (2013). Blunted reward responsiveness in remitted depression. *Journal of Psychiatric Research*, *47*(12):1864-9. https://doi.org/10.1016/j.jpsychires.2013.08.011

Pine, A., Sadeh, N., Ben-Yakov, A., Dudai, Y., Mendelsohn, A. (2018). Knowledge acquisition is governed by striatal prediction errors. *Nature Communications*, *9*(1):1673. https://doi.org/10.1038/s41467-018-03992-5

Pizzagalli, D.A. (2014). Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*(1), 393–423. https://doi.org/10.1146/annurev-clinpsy-050212-185606

Pizzagalli, D.A., Iosifescu, D., Hallett, L.A., Ratner, K.G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of Psychiatric Research*, *43*(1):76-87. https://doi.org/10.1016/j.jpsychires.2008.03.001

Pizzagalli, D.A., Jahn, A.L., & O'Shea, J.P. (2005). Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry*, *57*(4), 319–327. https://doi.org/10.1016/j.biopsych.2004.11.026

Portengen, C.M., Sprooten, E., Zwiers, M.P., Hoekstra, P.J., Dietrich, A., Holz, N.E., Aggensteiner, P.M., Banaschewski, T., Schulze, U.M.E., Saam, M.C., Craig, M.C., Sethi, A., Santosh, P., Ouriaghli, I.S., Castro-Fornieles J, Rosa M, Arango C, Penzol MJ, Werhahn JE, Brandeis D, Walitza, S., Oldehinkel, M., Franke, B., Buitelaar, J.K., & Naaijen, J. (2021). Reward and Punishment Sensitivity are Associated with Cross-disorder Traits. *Psychiatry Research*, 298:113795. https://doi.org/10.1016/j.psychres.2021.113795

Proudfit, G.H. (2015). The reward positivity: from basic research on reward to a biomarker for depression. P*sychophysiology*, *52*(4):449–59. https://doi.org/10.1111/psyp.12370

Reilly, E.E., Whitton, A.E., Pizzagalli, D.A., Rutherford, A.V., Stein, M.B., Paulus, M.P., & Taylor, C.T. (2020). Diagnostic and dimensional evaluation of implicit reward learning in social anxiety disorder and major depression. *Depression and Anxiety*, *37*(12), 1221–1230. https://doi.org/10.1002/da.23081

Rogers, R.D., Ramnani, N., Mackay, C., Wilson, J.L., Jezzard, P., Carter, C.S., & Smith, S.M. (2004). Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biological Psychiatry*, *55*(6), 594–602. https://doi.org/10.1016/j.biopsych.2003.11.012

Rosch, K.S., & Hawk, L.W. (2013). The effects of performance-based rewards on neurophysiological correlates of stimulus, error, and feedback processing in children with ADHD. *Psychophysiology*, *50*(11), 1157–1173. https://doi.org/10.1111/psyp.12127

Rushworth, M.F., Walton, M.E., Kennerley, S.W., & Bannerman, D.M. (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Science*, *8*(9):410-7. https://doi.org/10.1016/j.tics.2004.07.009

Santesso, D.L., Dillon, D.G., Birk, J.L., Holmes, A.J., Goetz, E., Bogdan, R., & Pizzagalli, D.A. (2008a). Individual differences in reinforcement learning: Behavioral, electrophysiological, and neuroimaging correlates. *NeuroImage*, *42*(2), 807–816. https://doi.org/10.1016/j.neuroimage.2008.05.032

Santesso, D.L., Dzyundzyak, A., & Segalowitz, S.J. (2011). Age, sex and individual differences in punishment sensitivity: Factors influencing the feedback-related negativity. *Psychophysiology*, *48*(11), 1481–1489. https://doi.org/10.1111/j.1469-8986.2011.01229.x

Santesso, D.L., Evins, A.E., Frank, M.J., Schetter, E.C., Bogdan, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: Evidence from event-related potentials and computational modeling of striatal-cortical function. *Human Brain Mapping*, *30*(7), 1963–1976. https://doi.org/10.1002/hbm.20642

Santesso, D.L., Steele, K.T., Bogdan, R., Holmes, A.J., Deveney, C.M., Meites, T.M., & Pizzagalli, D.A. (2008b). Enhanced negative feedback responses in remitted depression. *NeuroReport*, *19*(10), 1045–1048. https://doi.org/10.1097/wnr.0b013e3283036e73

Schultz, W. (2009). Midbrain dopamine neurons: A retina of the reward system? In Glimcher, P.W., Camerer, C.F., Fehr, E., & Poldrack, R.A. (Eds.), *Neuroeconomics: Decision making and the brain* (pp. 321-329). Academic Press, New York, NY. https://doi.org/10.1016/B978-0-12-374176-9.00021-X

Sun, S., Kuja-Halkola, R., Faraone, S.V., D'Onofrio, B.M., Dalsgaard, S., Chang, Z., & Larsson, H. (2019). Association of psychiatric comorbidity with the risk of premature death among children and adults with attention-deficit/hyperactivity disorder. *JAMA Psychiatry*, *76*(11), 1141. https://doi.org/10.1001/jamapsychiatry.2019.1944

Swanson, J.M., Kraemer, H.C., Hinshaw, S.P., Arnold, L.E., Conners, C.K., Abikoff, H.B., Clevenger, W., Davies, M., Elliott, G.R., Greenhill, L.L., Hechtman, L., Hoza, B., Jensen, P.S., March, J.S., Newcorn, J.H., Owens, E.B., Pelham, W.E., Schiller, E., Severe, J.B., Simpson, S., Vitiello, B., Wells, K., Wigal, T., & Wu, M. (2001). Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and odd symptoms at the end of treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(2), 168–179. https://doi.org/10.1097/00004583-200102000-00011

Telzer, E.H. (2016). Dopaminergic reward sensitivity can promote adolescent health: A new perspective on the mechanism of ventral striatum activation. *Developmental Cognitive Neuroscience*, *17*, 57-67. https://doi.org/10.1016/j.dcn.2015.10.010.

Thoma, P., Edel, M.A., Suchan, B., & Bellebaum, C. (2015). Probabilistic reward learning in adults with attention deficit hyperactivity disorder—an electrophysiological study. *Psychiatry Research*, *225*(1-2), 133–144. https://doi.org/10.1016/j.psychres.2014.11.006

Tripp, G., & Alsop, B. (1999). Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder. *Journal of Clinical Child Psychology*, *28*(3), 366–375. https://doi.org/10.1207/s15374424jccp280309

van Meel, C.S., Heslenfeld, D.J., Oosterlaan, J., Luman, M., & Sergeant, J.A. (2011). ERPs associated with monitoring and evaluation of monetary reward and punishment in children with ADHD. *Journal of Child Psychology and Psychiatry*, *52*(9), 942–953. https://doi.org/10.1111/j.1469-7610.2010.02352.x

van Meel, C.S., Oosterlaan, J., Heslenfeld, D.J., & Sergeant, J.A. (2005). Telling good from bad news: ADHD differentially affects processing of positive and negative feedback during guessing. *Neuropsychologia*, *43*(13), 1946–1954. https://doi.org/10.1016/j.neuropsychologia.2005.03.018

Vartak, D., Jeurissen, D., Self, M.W., & Roelfsema, P.R. (2017). The influence of attention and reward on the learning of stimulus-response associations. *Scientific Reports*, *7*(1):9036. https://doi.org/10.1038/s41598-017-08200-w

Véronneau-Veilleux, F., Robaey, P., Ursino, M., & Nekka, F. (2022). A mechanistic model of ADHD as resulting from dopamine phasic/tonic imbalance during reinforcement learning. *Frontiers in Computatiional Neuroscience*, 16:849323. https://doi.org/10.3389/fncom.2022.849323

Vogt, B.A. (2019). Cingulate impairments in ADHD: Comorbidities, connections, and treatment. *Cingulate Cortex, 166*, 297-314. https://doi.org/10.1016/B978-0-444-64196-0.00016-9

Vrieze, E., Pizzagalli, D.A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., Schmidt, M., & Claes, S. (2013). Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry*, *73*(7), 639–645. https://doi.org/10.1016/j.biopsych.2012.10.014

Wagenmakers, E.J., Love, J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Selker, R., Gronau, Q. F., Dropmann, D., Boutin, B., Meerhoff, F., Knight, P., Raj, A., van Kesteren, E.J., van Doorn, J., Šmíra, M., Epskamp, S., Etz, A., Matzke, D., … Morey, R.D. (2018). Bayesian inference for psychology. part II: Example applications with JASP. *Psychonomic Bulletin & Review*, *25*(1), 58–76. https://doi.org/10.3758/s13423-017-1323-7

Walentowska, W., Severo, M.C., Moors, A., & Pourtois, G. (2019). When the outcome is different than expected: Subjective expectancy shapes reward prediction error at the FRN level. *Psychophysiology*, *56*(12):e13456. https://doi.org/10.1111/psyp.13456

Whitton, A.E., Kakani, P., Foti, D., Van't Veer, A., Haile, A., Crowley, D.J., & Pizzagalli, D.A. (2016). Blunted neural responses to reward in remitted major depression: A high-density

event-related potential study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1*(1):87-95. https://doi.org/10.1016/j.bpsc.2015.09.007

Whitton, A.E., Kumar, P., Treadway, M.T., Rutherford, A.V., Ironside, M.L., Foti, D., Fitzmaurice, G., Du, F., & Pizzagalli, D.A. (2023). Distinct profiles of anhedonia and reward processing and their prospective associations with quality of life among individuals with mood disorders. *Molecular Psychiatry*, *28*(12):5272-5281. https://doi.org/10.1038/s41380-023-02165-1

Wise, R.A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, *5*(6), 483–494. https://doi.org/10.1038/nrn1406

Yeung, N., & Sanfey, A.G. (2004). Independent coding of reward magnitude and valence in the human brain. *Journal of Neuroscience, 24*(28), 6258-64. https://doi.org/10.1523/JNEUROSCI.4537-03.2004

Yi, F., Chen, H., Wang, X., Shi, H., Yi, J., Zhu, X., & Yao, S. (2012). Amplitude and latency of feedback-related negativity. *NeuroReport*, *23*(16), 963–969. https://doi.org/10.1097/wnr.0b013e328359d1c4

Yucel, K., McKinnon, M.C., Chahal, R., Taylor, V.H., Macdonald, K., Joffe, R., & MacQueen, G.M. (2008). Anterior cingulate volumes in never-treated patients with major depressive disorder. *Neuropsychopharmacology*, *33*(13), 3157–3163. https://doi.org/10.1038/npp.2008.40

Zottoli, T.M. & Grose-Fifer, J. (2012). The feedback-related negativity (FRN) in adolescents. *Psychophysiology*, *49*(3), 413-20. https://doi.org/10.1111/j.1469-8986.2011.01312.x