The Contributions of Pubertal Maturation to the Neurobiological Mechanisms of Cognitive and Affective Development

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Puberty, the major biological process defining adolescence, is thought to demarcate a unique period of brain maturation associated with significant cognitive and affective development. Notably, pubertal hormones directly affect the brain through interactions with neurotransmitters including gamma-aminobutyric acid (GABA), glutamate, and dopamine, particularly in regions that are also key nodes of the brain's cognitive and affective systems, including the hippocampus, striatum, thalamus, and prefrontal cortex (PFC). These neurotransmitters support critical period plasticity in the brain, which facilitates neurocognitive development from adolescence into adulthood. However, while puberty likely contributes to adolescent brain maturation, little is known about the neurobiological mechanisms underlying puberty's influence on cognitive and affective development. This study used a multimodal longitudinal dataset of adolescents ages 10-18 to examine how pubertal development affects cognitive and emotional development, and whether this influence is exerted through neurotransmitters underlying critical period plasticity (GABA, glutamate, and dopamine). Pubertal development was measured using self-reported pubertal stage, with follow-up analyses incorporating testosterone, dehydroepiandrosterone (DHEA), estradiol, and progesterone as potential hormonal mechanisms. Associations were tested with measures of cognition (antisaccade task), emotion regulation (Behavioral Indicator of Resilience to Distress task), and neurotransmitters across the PFC, striatum, thalamus, and hippocampus (in vivo neuroimaging measures of GABA, glutamate, and dopamine). Pubertal

stage was significantly associated with antisaccade performance and Behavioral Indicator of Resilience to Distress (BIRD) performance, and DHEA was significantly associated with BIRD performance in males only. Principal components analysis identified systematic relationships across neurotransmitters, resulting in three components of combined neurotransmitter function. Pubertal stage was significantly related to the third component, which captured hippocampal GABA levels and anterior cingulate cortex (ACC) GABA/glutamate levels. Follow-up analyses revealed that this component was also associated with progesterone levels in females. However, this component did not mediate relationships between pubertal stage and behavioral performance. These findings suggest a nuanced role of puberty in cognitive and emotional development and provide additional support for puberty's theorized role in demarcating the adolescent critical period of brain development. This study has important implications for future study design, and findings will provide behavioral and neurobiological targets for further examination of pubertal contributions to neurocognitive development.

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Preface

I would like to thank everyone who has helped me along the path to obtaining my Ph.D. My deepest gratitude to: my husband, who has loved and supported me every day of my time in graduate school; my parents, who have supported me in my academic journey since I was just a child; my sister, who always puts a smile on my face, no matter how difficult things were; my friends, who have always provided space to vent and shoulders to cry on; the members of the Laboratory of Neurocognitive Development, who have been the greatest coworkers and have always been willing to spare their time to lend a helping hand; and finally, my advisor, Dr. Beatriz Luna, who has provided me with countless opportunities and without whom I would not be here.

1.0 Introduction

Puberty is a major biological process that defines adolescence, a period of significant cognitive and affective development (Geier et al., 2009; Guyer et al., 2016; Luna, 2009), occurring in parallel with specialization of brain processes reflective of critical period plasticity in executive regions (Larsen & Luna, 2018). This is also a time of heightened vulnerability for psychiatric disorders such as mood and anxiety disorders, which are associated with cognitive and affective dysfunction (Castellanos-Ryan et al., 2014; Paus et al., 2008; Pfeifer et al., 2011; Toren et al., 2000). Previous work has demonstrated that pubertal development, including accompanying hormonal changes, may demarcate a period of unique neurocognitive maturation associated with functional changes across both cognitive and affective systems, including in cortical thickness, fronto-subcortical white matter volume, and cortico-subcortical resting state connectivity (Herting et al., 2015, 2017; van Duijvenvoorde et al., 2019), as well as in facial emotion processing (Ferri et al., 2014; Forbes et al., 2011; Moore et al., 2012), reward processing (Forbes et al., 2010; Urošević et al., 2014), and inhibitory control (Ordaz et al., 2018; Ravindranath et al., 2022). Thus, it is important to consider not only the effects of puberty on cognitive and affective systems individually, but also the influence of puberty on both systems together, particularly since their integration undergoes significant specialization through adolescence (Ladouceur, 2012).

Puberty is characterized by substantial increases in gonadal and adrenal hormones, including estradiol, progesterone, dehydroepiandrosterone (DHEA), and testosterone. These hormones are critical for development of the reproductive system, but also have direct effects on the brain through their interactions with neurotransmitters including gamma-aminobutyric acid (GABA), glutamate, and dopamine (Micevych & Mermelstein, 2008; Murphy et al., 1998; Purves-

Tyson et al., 2014; Sinclair et al., 2014). These interactions, as well as the distribution of hormone-specific receptors, have been shown to be concentrated in the amygdala, hippocampus, striatum, thalamus, and prefrontal cortex (PFC) (Beyenburg et al., 2000; Blurton-Jones & Tuszynski, 2002; González et al., 2007; Perlman et al., 2005), regions that are also key nodes of the brain's cognitive and affective systems. Across adolescence, these neurotransmitters are also known to undergo substantial changes in function (Larsen & Luna, 2018) that suggest the presence of critical period plasticity in association cortex, facilitating improvements in and stabilization of cognitive and affective function into adulthood. Based on these findings, it is likely that pubertal hormones contribute to maturational changes within the brain via their actions at hormone receptors in the brain as well as via interactions with these major neurotransmitter systems. However, little is known about these neurobiological mechanisms that may underlie the influence of puberty on the maturation of cognitive and affective function.

1.1 The Current Study

The current study aimed to fill some of these gaps in the literature by leveraging an existing dataset to understand how puberty affects cognitive and emotional development across adolescence using both self-reported pubertal stage and pubertal hormones as indices of pubertal development. We hypothesized a model in which this influence is exerted through pubertal effects on developmentally-relevant neurotransmitters, including dopamine, GABA, and glutamate. Though evidence supporting some of these associations has been found in prior animal and human research (Forbes et al., 2010, 2011; Piekarski, Boivin, et al., 2017; Purves-Tyson et al., 2012, 2014; Ravindranath et al., 2022; van Duijvenvoorde et al., 2019), this study was uniquely able to assess

multiple mechanisms in order to create a holistic and nuanced understanding of puberty's role in adolescent cognitive and emotional development. Specifically, while much of this research has previously been done in animals, this study examined molecular mechanisms of human brain development in vivo through the use of novel and cutting-edge methodologies, including the estimation of tissue iron using functional magnetic resonance imaging (MRI)-acquired T2*-weighted images as a proxy measurement of subcortical dopamine, the measurement of GABA and glutamate across multiple brain regions with 7T magnetic resonance spectroscopic imaging (MRSI), and the acquisition of pubertal hormone levels from hair samples. Elucidating the relationship between pubertal stage, neurotransmitter function, and behavior through this multimodal approach may be the first step toward uncovering novel markers of risk or intervention targets for neuropsychiatric disorders that emerge during adolescence, many of which are associated with both cognitive and affective dysfunction.

2.0 Background

While critical progress has been made in understanding how pubertal processes support neurocognitive and affective changes across adolescence, the mechanisms that underlie these developmental changes remain obscure. Here, we provide a brief summary of the current literature on adolescence, puberty, cognitive and affective development, and their neurobiological mechanisms.

2.1 Adolescent Brain Development

Adolescence is a developmental period beginning at the onset of puberty and normatively ending around the time when one takes on adult roles and responsibilities into the twenties (Sawyer et al., 2018). This period is characterized by heightened emotional reactivity (Guyer et al., 2016) and availability of prefrontal executive processes that continue to specialize into adulthood (Luna et al., 2015). Studies of these affective and cognitive systems and their integration across adolescence have led to the creation of dual systems models of adolescent development (Luna & Wright, 2016; Shulman et al., 2016; Steinberg, 2008). These models posit that phenotypic adolescent sensation seeking, or the tendency to seek out novel and exciting experiences (Zuckerman, 1971), is driven by overactive affective systems that outweigh and influence executive function abilities until early adulthood when affective system activity attenuates to an optimal balance with prefrontal executive function. While problematic adolescent risk-taking is often attributed to this heightened sensation seeking and lack of reliable executive control

(Chambers et al., 2003; Romer & Hennessy, 2007), which can manifest in detrimental substance use and dangerous behaviors resulting in injury and death (Clark et al., 1999; Kann, 2016; Karch et al., 2011; Sells & Blum, 1996; Substance Abuse and Mental Health Services Administration, 2009), it also plays an adaptive role in brain development. Specifically, this drive for new experiences may provide vital input needed for the specialization of brain networks and their underlying neurobiological mechanisms (Murty et al., 2016; Romer et al., 2017). Relatedly, protracted PFC maturation suggests the presence of critical period plasticity, a highly experience-dependent developmental process that recent work suggests may be occurring in the PFC during adolescence (Larsen & Luna, 2018; Perica et al., 2022). This period of heightened prefrontal plasticity, in combination with increased exploratory behavior and novel experience afforded by greater independence, allows for significant brain maturation and specialization that shapes the brain for optimal function in adulthood.

Supporting this maturation, dynamic changes in neurotransmitter signaling and function in the brain occur across adolescence. This literature largely consists of animal studies but suggests that the adolescent period is characterized by a peak in certain aspects of dopamine function, a neurotransmitter believed to underlie major cognitive and affective functions such as reward processing and working memory (Kelley & Berridge, 2002; Landau et al., 2009; Sawaguchi & Goldman-Rakic, 1991; Wise, 2004). Specifically, this work has found that dopamine receptor density peaks in mid-adolescence, followed by a peak in dopamine innervation in late adolescence and early adulthood (Lidow et al., 1991; Lidow & Rakic, 1992; Rosenberg & Lewis, 1995). In parallel with the development of dopaminergic function, evidence from postmortem human brains and primate models indicates developmental shifts in key aspects of GABA function, the brain's main inhibitory neurotransmitter, and glutamate function, the primary excitatory neurotransmitter,

the balance between which underlies the onset and maintenance of critical period plasticity (Hensch & Fagiolini, 2005; Larsen & Luna, 2018). This body of work implicates dopamine, GABA, and glutamate as key molecular mechanisms driving increased brain plasticity through development. Importantly, not only do these neurotransmitter systems undergo significant maturation during adolescence, but their high concentrations and activity in regions such as the PFC, striatum, thalamus, amygdala, and hippocampus signal their importance in the cognitive and affective circuits formed by these regions.

Interactions across these neurotransmitter systems also play a crucial role in adolescent development. Within the PFC, almost all GABAergic neurons also express dopamine receptors, and many of these neurons are also part of major glutamatergic pathways, such as the hippocampus-PFC brain circuit underlying normative working memory function (Caballero et al., 2016). In addition, the development of frontostriatal dopamine circuitry may play an important role in the initiation of adolescent critical period plasticity, in that increased dopamine release helps to drive the development of specific GABAergic inhibitory neurons in the PFC (Larsen & Luna, 2018). Thus, dopamine facilitates change in the balance of excitation (driven by glutamate) and inhibition (driven by GABA), which may play a role in triggering the opening of the adolescent critical period. The development of these neurotransmitter systems and their interaction is likely a key mechanism in the maturation of essential cognitive and affective processes including inhibitory control, reward processing, emotion regulation, and working memory (Bouarab et al., 2019; Constantinidis & Luna, 2019; Floresco & Magyar, 2006; Gleich, Lorenz, et al., 2015; Glickstein et al., 2005; Goldman-Rakic, 1996; Kilb, 2012; Levar et al., 2017; Mizoguchi et al., 2009; Silveri et al., 2013; Taber et al., 2012; Vlachou & Markou, 2010; Winter et al., 2009). Notably, pubertal processes have also been theorized as a possible trigger opening the adolescent

critical period (Larsen & Luna, 2018; Piekarski, Boivin, et al., 2017; Piekarski, Johnson, et al., 2017). However, while a growing body of research exists on the neurobiological mechanisms of adolescent brain and behavioral development, little is known about how puberty contributes to neurodevelopment during this period.

2.2 Puberty and its Measurement

In humans, the earliest phase of pubertal maturation is a process known as adrenarche, defined by the secretion of adrenal androgens, particularly DHEA, around 6 to 8 years of age (Parker, 1991). This initial pubertal process is unique to humans and higher-order primates, making research challenging since much of the existing research on hormones and the brain originated in rodents and other non-primate mammals. Adrenarche is followed a few years later by the onset of gonadarche (Cutler & Loriaux, 1980; Witchel & Topaloglu, 2019), the reactivation of reproductive glands by increased pituitary hormone production, leading to increased levels of circulating gonadal hormones such as estrogen and testosterone.

The process of puberty is known to involve many other growth processes throughout the body that affect most organs and culminate in the full ability to conceive and successfully raise offspring. The onset of adrenarche leads to the beginning of skeletal maturation and the start of pubic hair growth. Following this, gonadarche initiates reproduction-specific maturation including the growth of gonadal organs (testes and ovaries) and secondary sex organs (breast and penis development), as well as gross physical growth including the growth spurt in height and the significant increase in overall body mass. Other related bodily changes that occur throughout puberty include voice deepening and facial hair growth in males, hip growth in females, and

increases in skin oil and body hair across sexes. Additionally, the onset of menses (menarche) in females occurs later in puberty and is associated with an increase in progesterone, which fluctuates along with estradiol (the most prominent form of estrogen in the human body) to drive the menstrual cycle (Owen, 1975; Sherman & Korenman, 1975). On average, puberty occurs between one and two years earlier in individuals assigned female at birth compared to those assigned male at birth (Styne et al., 2008; Styne & Grumbach, 2002).

Scientists and clinicians generally quantify progression through puberty using the Sexual Maturity Rating system, also known as Tanner stage (Marshall & Tanner, 1969, 1970). This five-stage rating system uses growth of breasts, testes, penis, and pubic hair to estimate how far an individual has progressed through their pubertal development. Tanner stage 1 is considered "prepubertal", meaning no signs of pubertal development are present thus far. Girls enter Tanner stage 2 when the beginning of breast growth is evident while boys enter Tanner stage 2 when the testes begin to increase in volume. Thus, the transition from Tanner stage 1 to Tanner stage 2 is believed to signify the onset of gonadarche. Peak growth in height and body mass occurs between Tanner stages 2 and 3 for girls and across stage 3 for boys. Menarche is not tied to any specific Tanner stage but tends to occur around two years after the beginning of breast development (Wheeler, 1991). Traditionally, Tanner stage is assessed by a clinician who physically inspects the relevant bodily features. However, other methods of quantifying pubertal development have been created for research purposes that rely on self-report. One example is the use of line drawings to depict growth in the features associated with Tanner stages. Participants are provided with these images and then asked to choose which drawing best matches their own stage of breast/testes/penis/pubic hair development. Another self-report measure is the Pubertal Development Scale (PDS), a two-part questionnaire consisting of a six-item multiple-choice

section asking individuals to rate their level of development in various secondary sex characteristics such as facial hair growth, skin changes, growth in height, and more (Petersen et al., 1988). This scale, which results in a four-point measure of pubertal development, can also be converted using evidence-based formulas into a five-point scale that parallels Tanner stage (Shirtcliff et al., 2009).

More recently, researchers have been obtaining measurements of circulating steroid hormones to gain further insight into pubertal processes. These hormones can be measured using samples of saliva, blood, urine, or hair, depending on the type of measurement needed and logistical considerations. Hair samples are a newer method of obtaining hormone measurements which provide an "average" hormonal level across a period of one to five months depending on the length of hair sampled (Short et al., 2016). Blood, saliva, and urine assays of hormones provide a measurement of hormone levels from the moment that the sample is collected and are thus affected by diurnal and monthly fluctuations in these hormones, making it difficult to acquire a comprehensive and reliable measure. In contrast, the average hormonal levels derived from hair samples provide a more stable measure to identify individual differences in hormone levels as they relate to other variables.

A critical and ongoing dilemma in the study of puberty and brain development is the statistical challenge of separating puberty-specific effects from others associated with chronological age, due to their significant collinearity. Conceptually, it is also important to consider which specific processes underlie developmental effects that are associated with chronological age, since the progression of age encompasses many biological processes, one of which is puberty. Other contributing factors to age-related changes in the brain and behavior include genetic and biological growth programming underlying fundamental human maturational

processes, as well as environmental effects and accumulated experience, which is particularly relevant during adolescence, when key experience-dependent maturational mechanisms such as synaptic pruning and myelination occur in the brain (Petanjek et al., 2011, Yakovlev et al., 1967). While some of these processes may interact with or rely on pubertal development, others may be independent. Indeed, one rodent study aiming to disentangle these age- and puberty-related processes found that pruning of dendritic spines in the frontal cortex was not dependent on gonadal hormones (Boivin et al., 2018), while another found that gonadal hormones are essential to the adolescent increase in inhibitory neurotransmission that triggers critical period plasticity (Piekarski, Boivin, et al., 2017). Thus, additional studies are needed to pinpoint which of the many mechanisms driving adolescent neurocognitive development rely on the biological processes of puberty. Recent and ongoing studies of puberty have attempted to address this question using statistical methods such as including age as a covariate or comparing model fit between models of puberty and those of age (Ojha et al., 2022; Ravindranath et al., 2022; van Duijvenvoorde et al., 2019). However, due to the conceptual overlap between age and puberty and their significant collinearity, these approaches, while valuable, are still limited in their ability to directly isolate the effects of pubertal development. Another novel approach that may more directly assess a specific type of pubertal effect is to examine associations between pubertal hormones and neurocognitive measures.

2.3 Puberty and Pubertal Hormones in the Brain

The hormones of interest in this study – estradiol, testosterone, DHEA, and progesterone – are all not only involved in puberty-related processes but are also steroid hormones that are

synthesized in the brain. These hormones, commonly known as "neurosteroids," have a variety of actions in the brain, including through dedicated hormone receptors in the brain that are concentrated in the hypothalamus, amygdala, hippocampus, striatum, thalamus, and PFC (Aldred & Waring, 1999; Bixo et al., 1995; González et al., 2007; Intlekofer & Petersen, 2011; Meffre et al., 2013; Österlund et al., 1998, 1999, 2000; Österlund & Hurd, 2001; Perlman et al., 2005; Shealy, 1995; Sun et al., 2016). However, their primary effect on neuronal processes is through their modulation of GABA and other neurotransmitter receptors.

Most research on hormones and the brain thus far has used rodent models, as this allows for direct manipulation of hormone levels and subsequent observation of changes in neurotransmitter function. Despite DHEA being the most abundant neurosteroid in the human body, the bulk of this research has been on estradiol, due to its known neuroprotective effects and the relative ease of identifying and labeling estrogen receptors in the brain. While estradiol occurs at higher levels in female mammals, it plays critical roles in the brain across sexes. Estradiol has been found to decrease GABA signaling in hippocampus and striatum (Hu et al., 2006; Murphy et al., 1998) and increase GABA receptor expression in the thalamus (Umorin et al., 2016). Further, estrogen receptors appear to extensively colocalize with GABAergic neurons in the cortex, amygdala, and hippocampus (Blurton-Jones & Tuszynski, 2002, 2006). Similar effects have been found across most of these pubertal hormones. DHEA, testosterone, and progesterone all act as $GABA_A$ receptor modulators, particularly in the hippocampus, striatum, and thalamus (Baulieu, 1998; Canonaco et al., 1989; Dubrovsky, 2005), such that DHEA metabolite binding lowers GABA sensitivity of neurons (Birzniece et al., 2006; Spivak, 1994), while progesterone and testosterone metabolite binding increases $GABA_A$ receptor sensitivity and even acts on extrasynaptic GABA receptors to increase tonic inhibition (Birzniece et al., 2006; Farrant &

Nusser, 2005; Majewska et al., 1986; Reddy & Jian, 2010; Shen et al., 2007). Sex differences in hormonal effects on GABA are thus far difficult to identify since many of these studies include only one sex rather than comparing findings across sexes. However, some rodent research has found sex differences in GABA activity and concentration, such that GABA activity may be greater in the striatum for females and in the PFC for males (Flügge et al., 1986; Ovtscharoff et al., 1992; Willing & Juraska, 2015), which may result from differences in hormonal interactions with GABA receptors. This body of work indicates that while these hormones may vary in how they impact GABAergic neurotransmission, their effects are numerous and significant. Thus, when the concentration of these hormones increases throughout the body during puberty, they may have important contributions to the development of GABAergic inhibitory activity in the brain.

Similarly, these hormones have major modulatory roles in glutamate and dopamine function across the brain. Estradiol, progesterone, and DHEA have all been shown to modulate N-methyl-D-aspartate (NMDA), but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), receptor expression and sensitivity, which in turn determines neuronal glutamate sensitivity in the hippocampus, striatum, thalamus, and cortex (Asbury et al., 1998; Cyr et al., 2001; El-Bakri et al., 2004; Gazzaley et al., 1996; Umorin et al., 2014, 2016; Weiland, 1992; Woolley et al., 1997). This hormonal influence is particularly significant since NMDA receptors are the glutamate receptor type believed to be a critical component of cortical circuitry development through their distinct role in experience-dependent plasticity (Feldman & Knudsen, 1998). Furthermore, estradiol and DHEA have been found to increase glutamate release in the hippocampus (Dong et al., 2007; Meyer et al., 2002), decrease glutamate levels in the thalamus (Naderi et al., 2014), and regulate glutamate uptake (Liang et al., 2002). Notably, DHEA modulation of glutamate release is believed to occur through activation of dopamine receptors,

one of many examples of how the actions of steroid hormones and neurotransmitters within the brain are heavily intertwined (Zheng, 2009). Similar to GABA, sex differences in these interactions between glutamate and pubertal hormones have not been adequately studied, but some human research on glutamate alone may indicate higher levels of cortical glutamate in those assigned male at birth and greater glutamate concentrations in subcortical structures of those assigned female at birth (Hädel et al., 2013; O'Gorman et al., 2011; Zahr et al., 2013; Zlotnik et al., 2011). Thus, neurosteroids during puberty may significantly affect glutamatergic signaling in the brain and influence the glutamate-based processes that underlie adolescent cortical development.

Associations with dopamine activity seem to vary dramatically across hormones. While estradiol has been shown to increase dopamine turnover in the striatum, DHEA has been found to decrease striatal dopamine turnover (Di Paolo et al., 1985; Pérez-Neri et al., 2008). Estradiol also shows sexually dimorphic effects on striatal dopamine receptor binding in rats, with decreases in females, but increases in males – while similar amounts of progesterone do not show these effects (Bazzett & Becker, 1994). Similarly, estradiol, but not progesterone, has been found to inhibit dopamine transporter activity (Disshon et al., 1998) and increase thalamic dopamine receptor expression (Apostolakis et al., 1996) in female rats. In addition, both testosterone and DHEA metabolites have been found to increase tyrosine hydroxylase expression, the rate-limiting enzyme in dopamine synthesis (Abreu et al., 1988; Charalampopoulos et al., 2005), and testosterone may actually induce greater dopamine synthesis in the striatum of male rats (Purves-Tyson et al., 2012, 2014). While there is slightly more research on sex difference in hormonal effects on dopamine, this literature is still highly limited. However, studies examining sex differences in dopamine itself generally suggest greater striatal levels of dopamine and dopamine transporter availability in

female rats and participants assigned female at birth (Bhatt & Dluzen, 2005; Hsiao et al., 2013; Lavalaye et al., 2000; Staley et al., 2001; Varrone et al., 2013). These findings, though inconsistent, suggest that there are definitive mechanisms through which neurosteroids influence the dopamine system, although the nature of that influence is still unclear.

While human studies cannot test the effects of hormones on neurotransmitters as directly as animal studies, a body of prior literature does imply that hormones can significantly affect neurotransmitter activity and related brain functions in humans. This research examines these effects by either measuring hormone levels or administering supplemental hormones and correlating these measures with behaviors known to be strongly driven by specific neurotransmitters (i.e., dopamine and working memory) or with neurotransmitter levels as measured by Positron Emission Tomography or magnetic resonance spectroscopy, an MRI method allowing for the quantification of neurotransmitters and their metabolites noninvasively in vivo. A number of human studies have shown significant associations between estradiol levels in participants assigned female at birth and performance in dopamine-dependent cognitive functions such as working memory, spatial memory, and learning, suggesting a strong link between estradiol and dopamine (Bimonte & Denenberg, 1999; Hampson & Morley, 2013; Joseph et al., 2012; Nguyen et al., 2019). Similarly, testosterone levels have been consistently correlated with sensation seeking, another dopamine-driven behavior, in individuals assigned male at birth (Campbell et al., 2010; Gerra et al., 1999; O'Carroll, 1984; Zuckerman et al., 1980). These findings imply that estradiol and testosterone may interact with dopamine in the brain to affect these dopamine-dependent behaviors.

In addition, a variety of emotion and psychopathology literature also supports the notion that pubertal hormones strongly influence neurotransmitter activity. Progesterone, testosterone,

and DHEA have all been associated with anxiety, both through correlations between endogenous hormone levels and symptoms, as well as based on observed anxiolytic effects following hormonal treatment (Brambilla et al., 2005; Hermans et al., 2006, 2007; Jin, 2019; Söderpalm et al., 2004; Söndergaard et al., 2002; Strous et al., 2003). Other correlational studies of testosterone and GABA measurements derived from magnetic resonance spectroscopy have found that greater serum testosterone is associated with greater GABA levels in the posterior cingulate cortex, while exogenous testosterone treatment is associated with reduced GABA levels in the hippocampus (Flores-Ramos et al., 2019; Spurny-Dworak et al., 2022). Moreover, there is a fairly significant body of literature examining the effects of low endogenous estradiol and estradiol supplementation on mood and anxiety, though this has resulted in mixed findings (Baca-Garcia et al., 2010; Bernardi et al., 1989; Cover et al., 2014; Lebron-Milad et al., 2012; Morrison et al., 2004; Rubinow et al., 2015). This research suggests that pubertal hormones are related to the regulation of mood and anxiety, although the extent and exact mechanisms of their effects are still unclear. Additionally, neuroimaging studies have found that levels of estradiol, progesterone, and testosterone are significantly associated with brain activity in regions widely associated with higher-order cognitive and affective functions, including the amygdala, anterior cingulate cortex (ACC), and inferior frontal gyrus (Manuck et al., 2010; Toffoletto et al., 2014; van Wingen et al., 2009), further implicating these hormones in the integration of cognitive and affective brain systems.

These studies examining the behavioral correlates of hormones in humans are becoming more abundant, but it can be difficult to synthesize their findings due to inconsistent results, varying methods, and a dearth of research in certain areas. This may be because, as rodent studies have shown and some of the human studies above have implied, most hormonal action in the brain

occurs through neurotransmitters and their receptors. Thus, individual differences in these neurotransmitters may interact with hormonal effects on the brain, making the nature of these effects difficult to ascertain. For example, some notable human research examining the effects of estradiol on cognition has shown that these effects may be dependent on baseline dopamine availability (Jacobs & D'Esposito, 2011). Given that the relationship between dopamine and cognitive function follows an inverted-U-shaped curve with too little or too much dopamine associated with poorer cognition (Goldman-Rakic, 1998), this evidence suggests that higher levels of estradiol may be associated with improved working memory performance in individuals with low baseline dopamine availability, while higher estradiol levels may impair performance in individuals with optimal or high levels of baseline dopamine availability (Colzato & Hommel, 2014; Hidalgo-Lopez & Pletzer, 2017). It seems likely that similar patterns may be present for other combinations of hormones and neurotransmitters, or even that multiple hormones and neurotransmitters may be interacting to affect a single brain function. Currently, there is functionally no literature on associations between pubertal development and the development of GABA, glutamate, and dopamine brain systems in humans, though some work on related processes, such as the reward literature summarized later, may provide early insight into these effects. Thus, considering the influence of puberty and pubertal hormones on these interrelated neurotransmitter systems and their development may be a critical next step toward understanding how hormones affect the adolescent brain.

2.4 Puberty and Affective Development

It has been established that puberty is associated with an increase in emotional distress (Forbes et al., 2004; Ge et al., 2006; Mendle, 2014; Oldehinkel et al., 2011; Silk et al., 2011), which is likely related to the increased prevalence of mood and anxiety disorders after pubertal onset (Angold et al., 1998; Kessler & Walters, 1998; Lewinsohn et al., 1998; Weissman & Olfson, 1995). There is also a wealth of literature that has associated early and late pubertal onset with elevated depressive symptoms, heightened aggression, disordered eating behaviors, and greater externalizing symptoms (Ge et al., 1996, 2003; Ge & Natsuaki, 2009; Kaltiala-Heino et al., 2001, 2003; Mendle et al., 2010; White et al., 2012). Thus, puberty likely plays a key role in affective development. While we have already discussed some direct effects of hormones on affective dysfunction in adults, there is also a growing body of literature on the effects of pubertal development and hormones during this period on affective development. One study found that adolescents in mid-to-late puberty rated themselves as more emotional than pre-pubertal or early-pubertal adolescents and exhibited greater pupil reactivity, a measure representing cognitive and affective load, in response to emotional words (Silk et al., 2009), suggesting that emotional reactivity increases as a function of pubertal development, possibly prior to the stabilization of pubertal hormones.

In the brain, more advanced pubertal maturation has been associated with lower amygdala reactivity to emotionally neutral faces (Ferri et al., 2014; Forbes et al., 2011) but greater amygdala, hippocampus, and visual cortex activation in response to emotional faces (Moore et al., 2012; Vijayakumar et al., 2019) and greater amygdala and ventral striatum reactivity to opposite-sex emotional faces, compared to same-sex faces (Telzer et al., 2015). These findings may reflect that greater integration of amygdala circuitry occurs during adolescent affective development, which

likely supports improvements in facial emotion recognition that appear in mid-to-late puberty (Lawrence et al., 2015). Additionally, adolescents assigned female at birth demonstrate significantly greater emotion recognition abilities than those assigned male at birth prior to puberty but this gap in ability closes substantially by mid-to-late puberty (Lawrence et al., 2015). These differences may be driven by distinct developmental trajectories of relevant brain regions such as the ACC, ventromedial PFC, striatum, and lateral PFC (Vijayakumar et al., 2019).

While emotion regulation ability is highly relevant to increases in emotional reactivity and related disorders during puberty and adolescence, studies thus far examining the specific relationship between pubertal mechanisms and emotion regulation are minimal. In adults assigned female at birth, both endogenous and exogenous estradiol have been associated with more effective emotion regulation, as well as lower orbitofrontal cortex and hippocampus activation, and greater superior frontal gyrus and dorsomedial PFC activation during regulation (Graham et al., 2017; Rehbein et al., 2021). However, one study also found that higher endogenous estradiol was correlated with increased maladaptive emotion regulation strategies such as rumination (Graham et al., 2018). In addition, progesterone metabolite and DHEA administration have both been associated with lower amygdala activity and greater amygdala connectivity during emotion regulation in participants assigned male at birth (Sripada, Marx, King, Rajaram, et al., 2013; Sripada, Marx, King, Rampton, et al., 2013). In adolescents, higher estradiol and testosterone have both been associated with greater PFC activity during emotion regulation, or a more adult-like pattern of activation suggesting top-down control of emotions (Chung et al., 2019; Tyborowska et al., 2016). Notably, adolescents with lower testosterone levels displayed greater amygdala and striatal activation (Tyborowska et al., 2016), a bottom-up pattern of activation characteristic of children. Additionally, pubertal timing is related to both levels of self-reported rumination and

depressive symptoms (Alloy et al., 2016) and more advanced pubertal maturation has been found to moderate the association between low sleep quality and greater emotion regulation difficulties (Lustig et al., 2021) in adolescents assigned female at birth. Many of these studies only included participants in one sex category, making it difficult to understand how sex differences may affect these associations, but thus far, findings suggest that while there may be differences in emotion processing and its neurobiological correlates, the effects of hormones on emotion processing and regulation may be more consistent across sexes. The research on puberty and affective development, while sparse, suggests that pubertal processes, including pubertal hormones and their effects on the brain, may drive significant aspects of emotion regulation development.

These results suggest that puberty is a unique period where affective circuitry undergoes significant maturation underlying increased sensitivity to affective events and stimuli in adolescence, which may define the developmental trajectory of emotion regulation. Furthermore, this role of puberty in the development of emotion regulation suggests that pubertal hormones and related biological mechanisms may be critical for the maturation of top-down cognitive regulation of affective processes and thus, the integration of cognitive and affective systems across the transition from adolescence to adulthood.

2.5 Puberty and Cognitive Development

The research examining behavioral associations between puberty and cognitive development is far less substantial. Only a handful of studies exist, largely focused on inhibitory control development. One study of antisaccade task performance found an association between decreasing response latency and pubertal maturation in participants assigned female at birth but

no association with antisaccade correct response rate (Ordaz et al., 2018). This study also found a significant association between estradiol levels and response latency, which may underlie the association with pubertal stage. Another study replicated this association between pubertal stage and response latency in the antisaccade task across sexes, and found related pubertal associations with ventrolateral PFC activation and task-related connectivity (Ravindranath et al., 2022). Another study also using the antisaccade task found that above and beyond age effects, pubertal stage was associated with developmental change in frontostriatal resting state functional connectivity, correct responses, and latency (Ojha et al., 2022). In addition, a study of inhibitory control using the Stroop task found that more advanced pubertal maturation was related to both greater cortical activation during high cognitive load and lower activation during low cognitive load across sexes (Schulte et al., 2020), while another study using drift-diffusion modeling showed that the interaction between puberty and sex assigned at birth predicts the amount of information considered for a decision during an inhibitory control task (Castagna & Crowley, 2021). Furthermore, a study of puberty and executive function found that earlier pubertal maturation may relate to greater improvements in attentional skills across sexes, but worse self-control in participants assigned female at birth only (Chaku & Hoyt, 2019). Together, these results suggest that while cognitive abilities such as inhibitory control mature and stabilize across the adolescent transition to adulthood, puberty may play a specific role in the maturation of processes underlying fast and flexible engagement of systems needed to generate an executive response independently of the relevant cognitive ability itself. Importantly, this shows that puberty has distinct associations with affective processes and cognitive abilities.

3.0 Study Aims

This project aimed to longitudinally characterize the role of puberty in cognitive and affective development, and to explore the differential contribution of pubertal processes across these systems. While some past studies have investigated contributions of puberty to cognitive and affective function, we began to extend the literature by examining the mechanisms underlying these relationships, including hormones and relevant neurotransmitters, as well as testing comprehensive models of associations between puberty, neurotransmitters, and both cognitive and emotional function (Figure 1). We hypothesized a model in which puberty plays distinct roles in the development of cognitive and emotional control systems (Aim 1) and key neurotransmitter systems (Aim 2). Furthermore, we posited that puberty exerts its influence on the development of cognitive and emotional control through its effects on neurotransmitter function (Aim 3). In this study, we focused on neurotransmitters in the PFC, hippocampus, thalamus, and striatum because these brain regions are major nodes of the brain's cognitive and affective systems and, along with the hypothalamus and amygdala, are believed to contain the greatest concentrations of steroid hormone receptors. Thus, these regions are most likely to undergo direct changes as a result of the hormone surges that occur during puberty. Furthermore, the existing literature thus far, as summarized above, has provided substantial evidence of puberty- and hormone-related changes across these brain regions.

We leveraged an innovative accelerated longitudinal dataset using task-based measures to assess cognitive and emotional development as well as high-field-strength neuroimaging to precisely characterize prefrontal and subcortical GABA and glutamate levels obtained using 7T MRSI, in addition to dopamine availability in the dorsal striatum and thalamus obtained indirectly

using MRI measures of tissue iron (Larsen et al., 2020). We also employed mul-

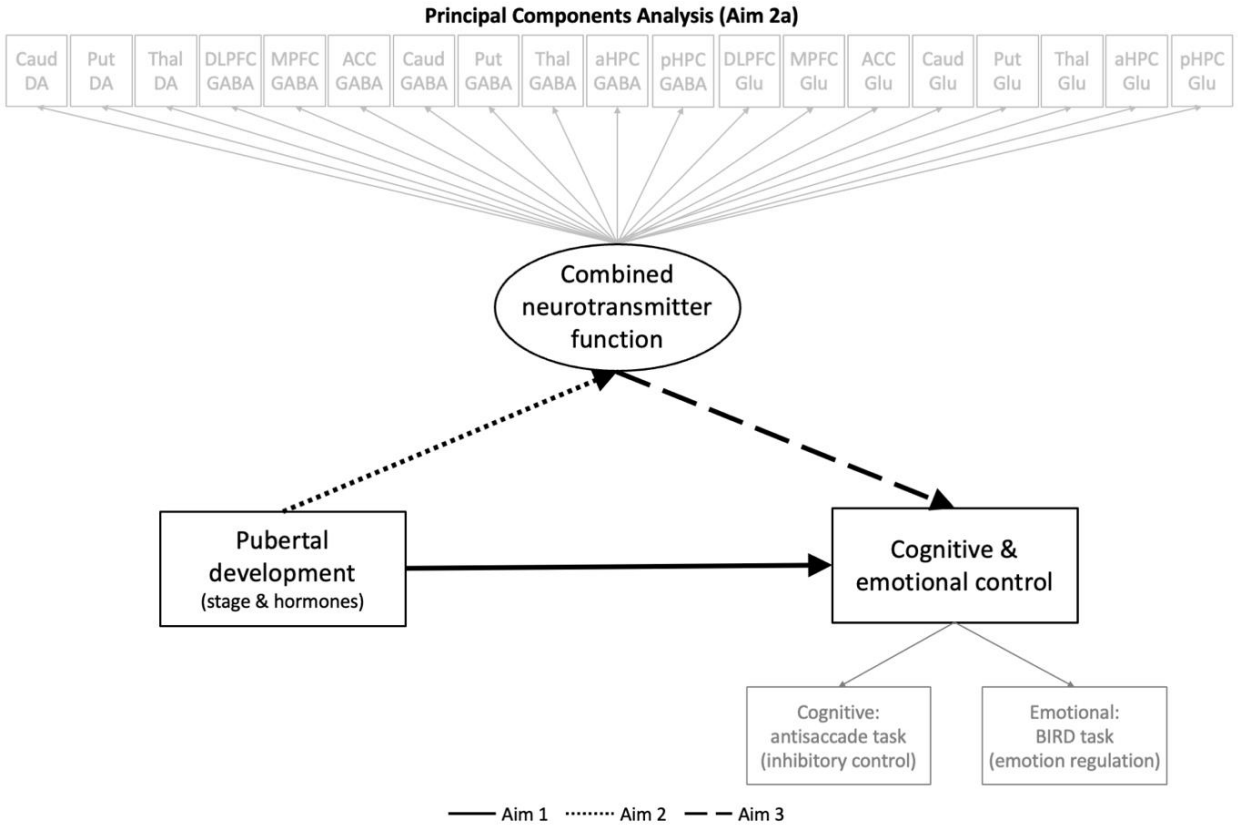

Figure 1: Model and paths that were tested across the three study aims.

(GABA: gamma-aminobutyric acid, Glu: glutamate, DA: dopamine, Caud: caudate, Thal: thalamus, Put: putamen, DLPFC: dorsolateral prefrontal cortex, MPFC: medial prefrontal cortex, aHPC: anterior hippocampus, pHPC: posterior hippocampus, BIRD: Behavioral Indicator of Resilience to Distress)

tiple measures of pubertal development to comprehensively examine associations between puberty and neurocognitive development. Critically, self-report measures of pubertal stage are best used with multiple individual timepoints, allowing pubertal progression to be assessed relative to individual developmental trajectories. Indeed, when the PDS was initially validated, the authors recommended that use of the measure be limited to longitudinal studies or cross-sectional studies in which a rough measure (early or late) is sufficient (Petersen et al., 1988). Thus, longitudinal assessment of self-reported pubertal stage is better suited to statistical methods of disentangling

effects of chronological age from pubertal effects, such as including age as a covariate. Because longitudinal data points in this study were limited, we took an alternative approach to isolating pubertal effects from other age-related developmental influences by incorporating measures of pubertal hormone levels using hair samples (Wang et al., 2019, 2020). By directly quantifying hormones as specific mechanisms of pubertal development, these hormones can be examined in relation to cognitive, emotional, and neurotransmitter development in order to determine whether associations with pubertal stage might be specific to puberty. Importantly, as noted throughout the reviewed literature above, most existing research on hormones and the brain has restricted samples to a single sex category, limiting the ability to consider sex differences in these effects. Thus, these hormone analyses are conducted in participants assigned both male and female at birth individually wherever possible to allow for comparison of these associations.

3.1 Aim 1: To characterize the influence of puberty on the development of cognitive and emotional control.

We examined associations between pubertal measures (pubertal stage and pubertal hormones) and cognitive and emotional control using two representative behavioral tasks. For cognitive control, the antisaccade task was used as a measure of inhibitory control, while emotional control was characterized using the Behavioral Indicator of Resilience to Distress (BIRD) task, which requires negative emotion regulation to maintain optimal task performance. Post hoc analyses were conducted examining the relationship between puberty and self-report measures of emotion regulation to clarify whether significant associations between puberty and the BIRD task were specific to emotion regulation ability. Based on prior literature that has examined associations

between puberty and inhibitory control (Ordaz et al., 2018; Ravindranath et al., 2022), we hypothesized that pubertal measures would be negatively associated with antisaccade response latency, such that increasing pubertal stage (and pubertal hormones) would be associated with faster response latency; however, pubertal measures would not be significantly associated with correct antisaccade response rate. We also hypothesized that based on the extant literature showing increased emotion reactivity and immature emotional control in adolescence (Ahmed et al., 2015; Crone & Dahl, 2012; Guyer et al., 2016; Pfeifer & Blakemore, 2012; Pitskel et al., 2011), pubertal measures would also be associated with BIRD task performance such that increasing pubertal stage and pubertal hormones would be associated with improvements in BIRD task performance (better performance and faster responses) and decreasing change in self-reported negative affect across the task.

3.2 Aim 2: To investigate associations between puberty and adolescent neurotransmitter development.

3.2.1 Aim 2a: To identify shared components of GABA, glutamate, and dopamine function across cognitive and affective brain regions with high hormone receptor concentrations.

Next, we characterized the molecular mechanisms that might underlie cognitive and emotional control. Based on findings that pubertal hormones primarily affect the brain through the modulation of GABA, glutamate, and dopamine receptors and that these neurotransmitters underlie adolescent critical period plasticity, we performed a principal components analysis (PCA)

to test for shared variance between GABA, glutamate, and dopamine in regions with high concentrations of both pubertal hormones and these neurotransmitter receptors, including the PFC (GABA and glutamate), dorsal striatum (GABA, glutamate, and dopamine), thalamus (GABA, glutamate, and dopamine), and the hippocampus (GABA and glutamate). This will indicate components of shared variance among these neurotransmitter measures, suggesting patterns of combined neurotransmitter function in the brain. Based on substantial evidence of prefrontal glutamate's essential role in regulating striatal dopamine function (Adrover et al., 2020; Ferenczi et al., 2016; Gleich, Deserno, et al., 2015), we hypothesized that a component would be retained including striatal dopamine and frontal glutamate. Additionally, due to research suggesting that prefrontal excitation-inhibition balance may underlie plasticity and optimal cognitive function (Jocham et al., 2012; Lam et al., 2022; Sprekeler, 2017), while sustained imbalance may confer vulnerability to psychiatric illness (Howes & Shatalina, 2022; Sohal & Rubenstein, 2019), we hypothesized that another component would be retained capturing GABA and glutamate across the PFC.

3.2.2 Aim 2b: To examine associations between puberty and combined neurotransmitter function.

We then examined associations between pubertal measures and combined neurotransmitter function, as represented by the components derived from the PCA in Aim 2a. While there is no prior literature to indicate how pubertal development might affect these neurotransmitters, there is evidence suggesting that pubertal hormones affect these neurotransmitters directly within the brain. Thus, based on the significant developmental change that occurs in dopamine across the

striatum and glutamate in the PFC during adolescence (Larsen et al., 2020; Parr et al., 2021; Perica et al., 2022), we hypothesized that puberty would be related to glutamate-dopamine combined function across the striatum and PFC. Drawing on findings that have shown changes in the balance of excitation and inhibition in association cortex during adolescence (Larsen et al., 2021; Perica et al., 2022), we also hypothesized that puberty would be related to GABA-glutamate combined function in the PFC. These hypothesized findings would suggest that pubertal mechanisms, including direct effects of pubertal hormones in the brain, may underlie key neurotransmitter development in adolescence.

3.3 Aim 3: To characterize how neurotransmitter development contributes to the relationship between puberty and the development of cognitive and emotional control.

Finally, we applied mediation models, with combined neurotransmitter function (as measured by neurotransmitter principal components derived in Aim 2a) mediating the relationship between pubertal development and cognitive and emotional control. Throughout all analyses, we also tested models with age as a covariate as one tool to understand if puberty-related effects are substantial and unique enough to be statistically separated from other developmental processes that might be captured by age. Combined neurotransmitter function mediating the influence of puberty on cognitive and/or emotional control would suggest that one way that puberty exerts its effects on adolescent behavioral development is through its effects on the development of neurotransmitter systems, likely because of its role as a trigger for adolescent critical period plasticity. These findings will provide mechanistic evidence of the role of puberty in developmental changes across these critical domains in adolescence.

4.0 Methods

4.1 Study Design & Participants

This project utilized a developmental neuroimaging dataset from an ongoing accelerated longitudinal study. The initial sample was recruited based on a uniform age distribution, spanning early adolescence to adulthood (10-30 years old), with equal representation of sex assigned at birth within each age bin. Participants were recruited from the community using flyers, mass emails, and the University of Pittsburgh's research participant database. Following the completion of an online screening questionnaire, potential participants were excluded if they reported that they or a first-degree relative had been diagnosed with a psychiatric or neurological disorder, or if they reported MRI contraindications such as metal in the body. Following the first behavioral study visit, participants were additionally excluded if they scored above clinical cutoffs for any symptom scales on the Child Behavioral Checklist (CBCL; subjects < 11 years old) (Achenbach, 2001), Youth Self-Report (YSR; subjects 11-18 years old) (Achenbach, 1991) or Adult Self-Report (ASR; subjects > 18 years old) (Achenbach & Rescorla, 2003) assessments, or if their estimated IQ was below 80 based on the Reynolds Intellectual Screening Test (Reynolds & Kamphaus, 2005). Two participants were dropped from the study after completing one or more parts of the initial baseline visit due to a psychiatric diagnosis discovered later and an ASR score above clinical cutoffs, so their data was excluded from all analyses. After the initial baseline visit, participants completed up to two 18-month follow-up visits. Participants were excluded from follow-up visits if they had been diagnosed with a psychiatric or neurological disorder since their previous study visit or if they scored above clinical cutoffs for any of the symptom scales on the CBCL, ASR, or YSR.

The final adolescent sample included 101 participants (48 assigned female at birth) at baseline with 1-3 visits each for a total of 154 study visits (mean visits=1.42, 42 participants with 2 visits, 11 participants with 3 visits, Figure 2, Table 1), although sample sizes and distributions varied across measures as a function of data quality exclusions (sample sizes for each analysis are included in statistical tables). No significant differences were found in age or pubertal stage by self-reported race (Figure 3A and B) or income group across the full sample (Figure 4A and B). There was an expected significant difference in pubertal stage by sex assigned at birth, such that those assigned female at birth were generally more pubertally advanced than those assigned male at birth (Figure 5A). However, since this sample was recruited with the goal of equally distributed sex assigned at birth across age, there was no significant difference in age by sex assigned at birth (Figure 5B). Please note that in all sections that follow, "male" refers to assigned male at birth and "female" refers to assigned female at birth, unless otherwise specified.

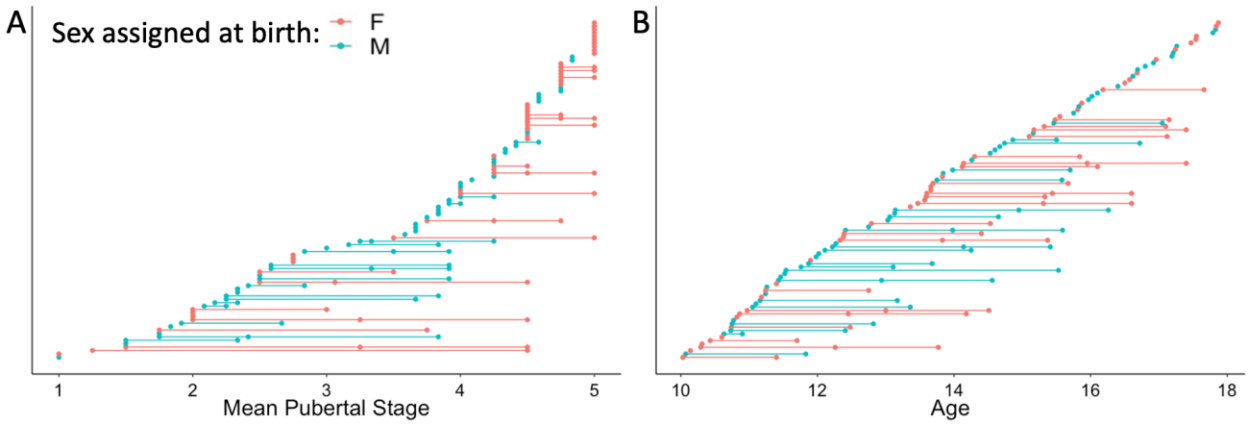

Figure 2: Waterfall plots of individual participants (y-axis) & study visit (x-axis) distributions by mean pubertal stage (A) and age (B).

The University of Pittsburgh's Institutional Review Board approved this study. Adult participants provided informed consent. For minors, parents provided informed consent and youth (10 to 17-years-old) provided assent. All participants were compensated for completing research assessments.

Table 1: Demographics table showing percentage of study visits by pubertal stage, sex assigned at birth, race, and income level ($N_{participants}$=101, N_{visits}=154)

Variable	N (visits)	Percent
Mean Pubertal Stage		
1	11	7.14
2	28	18.18
3	34	22.08
4	58	37.66
5	20	12.99
Sex Assigned at Birth		
Male	77	50.00
Female	77	50.00
Race		
Asian	2	1.30
Black	33	21.43
Multi	39	25.32
White	77	50.00
Unspecified	3	1.95
Income Level		
<$100,000	27	17.53
$100,000-$200,000	42	27.27
$200,000-$300,000	26	16.88
<$300,000	24	15.58
Unspecified	35	22.73

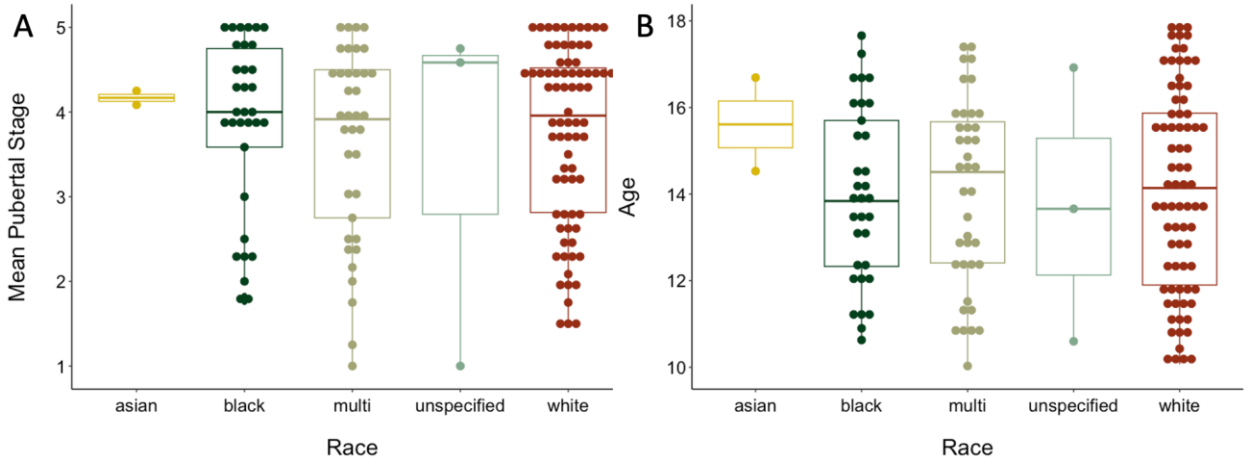

Figure 3: Sample distributions within each racial group by A) mean pubertal stage and B) age.

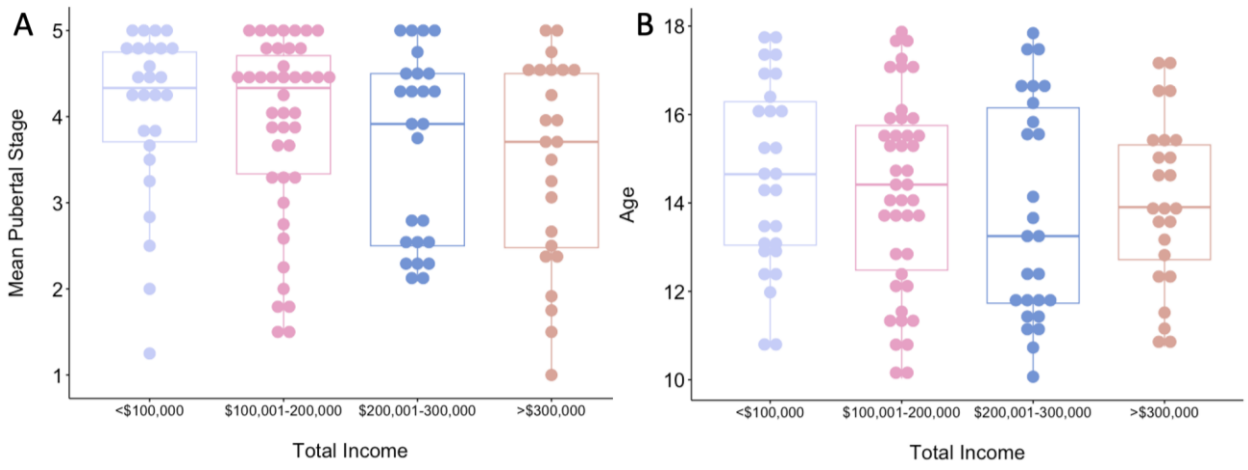

Figure 4: Sample distributions within each household income group by A) mean pubertal stage and B) age.

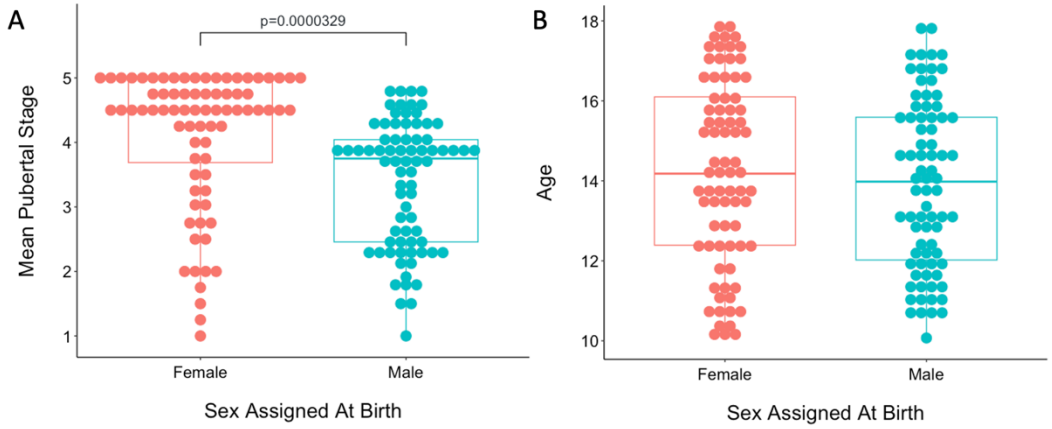

Figure 5: Sample distributions across sex assigned at birth by A) mean pubertal stage, and B) age.

4.2 Measures

4.2.1 Pubertal Development

Pubertal stage was assessed based on two self-report questionnaires, which were administered to all participants under the age of 18 at the time of their study visit. The first questionnaire is a pictorial Tanner staging questionnaire (Morris & Udry, 1980), in which line

drawings of breast development, pubic hair growth, testes/scrotum/penis development, and testicular size are provided for the five Tanner stages. Participants are asked to select the drawing that best corresponds with their own current level of development, which generates an overall Tanner score for the individual. The second questionnaire is the PDS (Petersen et al., 1988), in which participants are asked questions about the development of various primary and secondary sexual characteristics (i.e., body hair growth, skin changes, height growth) and choose from several options along the lines of "has not yet started growing", "has barely started growing", "is definitely underway", and "seems completed". The scoring of this questionnaire provides a pubertal stage measurement on a four-point scale, which was converted to a five-point scale analogous to Tanner Stage using a previously-created evidence-based coding mechanism (Shirtcliff et al., 2009). For this study, the five-point PDS score and the Tanner score were averaged to create a Mean Pubertal Stage measure that was used to represent pubertal status based on physical development in all analyses (Ravindranath et al., 2022). We chose to use mean pubertal stage due to the high correlation between these measures (r=0.867) and wide use of both measures across the literature, indicating no data- or hypothesis-driven reason to choose one over the other. Furthermore, these measures have been combined in previous work (Barendse et al., 2022; Ellis et al., 2011; Ladouceur et al., 2019; Ravindranath et al., 2022) and a prior study showed strong agreement between these measures within each stage (Bond et al., 2006). Further, since pubertal stage is a subjective measure that is difficult to quantify, utilizing all available information is likely to produce the best possible estimate of true pubertal stage.

4.2.2 Inhibitory Control

Performance from an antisaccade task was included as a measurement of inhibitory control (Figure 6A). Outside of the scanner, participants completed one 48-trial run of an antisaccade task to assess inhibitory control (Hwang et al., 2010; Ordaz et al., 2013; Velanova et al., 2008, 2009). Intertrial intervals (ITI, 0.5-6 seconds) in this task are pseudo-randomly distributed to permit estimation of trial-related activation (Dale, 1999). Each trial begins as participants fixate on a red crosshair for the length of the ITI. The crosshair then disappears for 200 milliseconds followed by the appearance of the target stimulus, a yellow circle, which appears at one of six horizontal eccentricities (±3°, 6°, or 9°) for one second. Participants are instructed to inhibit the reflexive saccade toward the target and to look instead to its horizontal mirror location, after which a blank screen appears for 20 milliseconds before the fixation crosshair returns.

Eye movement measurements were obtained during the performance of this task using a desk-mounted eye-tracking system (EYE-TRAC®6 Series, Applied Science Laboratories) with a sampling rate of 60 Hz. At the beginning of the session, a nine-point calibration was performed to ensure stable and accurate eye tracking across the task run. Scoring algorithm thresholds for correct responses were set to best align with manual scoring, such that trials in which the first eye movement after target stimulus appearance with velocity greater than or equal to 30°/second was toward the mirror location of the target stimulus were considered correct. Trials in which no saccade was recorded, a blink occurred before the first saccade or within 60 milliseconds of target stimulus appearance, or eye tracking quality was too poor were dropped from analyses. Subject visits were only included in analyses if they retained at least 25% of antisaccade trials. Correct response rate was calculated as the ratio of correct response trials to the total number of usable trials, and response latency was calculated as the mean response latency across all correct trials. It

should be noted that the number of dropped trials per visit was significantly associated with pubertal stage (β=-0.191, $p<0.05$) but all models examining antisaccade performance metrics were rerun with number of dropped trials as a covariate, and significant findings did not change.

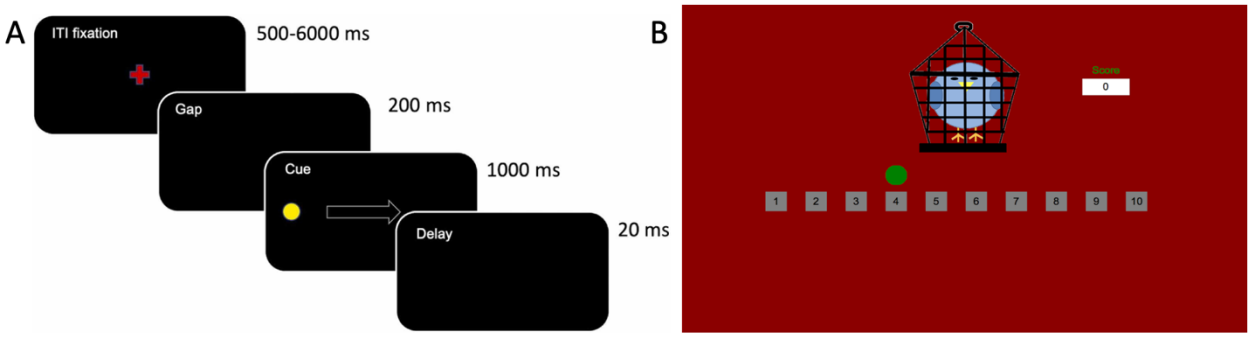

Figure 6: A) Visual depication of antisaccade trial design and B) main screen for the Behavioral Indicator of Resilience to Distress task.

4.2.3 Emotion Regulation

Performance metrics from the Behavioral Indicator of Resilience to Distress (BIRD) task were used as a measure of emotion regulation ability (Figure 6B). A screen with ten boxes is shown and a dot appears in random boxes one at a time. Participants must click the box before the dot disappears in order to earn points. The duration that the dot remains in each box changes based on the participant's performance and increases in difficulty throughout three levels in order to induce frustration in the participant. During the third level, participants have the option to quit the task but are warned that quitting will result in lower compensation. Preliminary analyses in our data as well as previous studies have shown that this task reliably increases negative affect in both adolescents and adults (Amstadter et al., 2012; Ravindranath, 2019). In addition, affective state was assessed using the Positive and Negative Affective Schedule (PANAS) (Watson et al., 1988)

before the task and between the second and third levels, providing a measure of negative affective reactivity. Difference scores derived from the PANAS were also analyzed as a measure of the ability to regulate changes in affect during a distressing task.

Scores from two questionnaires were additionally included as post hoc measures of self-reported emotion regulation ability. The Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004) asks participants to rate the applicability of 36 statements about how they relate to their feelings on a five-point Likert scale. This questionnaire yields a total score, with higher scores indicating more emotion regulation issues, and six subscale scores, including lack of emotional awareness, lack of emotional clarity, limited access to emotion regulation strategies, and others. The second questionnaire is the Distress Tolerance Scale (DTS) (Simons & Gaher, 2005), in which participants rate how strongly they agree with 16 statements about how they react to distress on a five-point Likert scale. This yields one total score, with higher scores indicating greater distress tolerance, and four subscale scores, including the ability to tolerate distress, subjective appraisal of one's distress, absorption of attention by negative emotion, and effort dedicated toward alleviating distress.

The measures of BIRD task performance used in this study, total score and average latency on correct trials, have not been used in previous literature, but earlier work from our lab found that total score was significantly associated with both DERS and DTS score in our full sample (J. Pan, 2019), suggesting that this score may capture the ability to regulate emotions in order to perform optimally in a distressing situation. Further, the BIRD latency measure was derived specifically from correct trials in the second half of the second level and the entire third level, the period of the task that actively induces distress. Thus, this latency measure also reflects performance optimization during a time of high distress. Importantly, because general reaction time also

improves significantly across childhood and adolescence, each participant's base reaction time was calculated based on their performance in the first level of the task, prior to the onset of the difficult, more distressing trials, and this base reaction time was used as a covariate in all analyses of BIRD latency. This allowed us to separate developmental effects on general processing speed from possible developmental effects on reaction time specific to emotion regulation within the context of the BIRD task.

4.2.4 MR Data: Acquisition and Preprocessing

Data was acquired on a 7T Siemens Magnetom MRI scanner. Structural images were acquired using an MP2RAGE T1-weighted acquisition (1.0mm isotropic resolution, TR = 6000 ms; TE = 2.87 ms; flip angle 1 = 4°, flip angle 2 = 5°). Functional images were acquired using a 3D blood oxygenation level dependent (BOLD) echo-planar imaging sequence (TR = 2180 ms; TE = 23 ms; flip angle = 7°; voxel size = 2.0×2.0×2.0 mm). The resting state acquisition included 220 volumes, for a total duration of eight minutes (eyes open, blank screen). Structural MRI data preprocessing included skull stripping and warping to the MNI standard brain using both linear (FLIRT) and non-linear (FNIRT) transformations (Jenkinson et al., 2012). Functional images were processed using a pipeline previously developed by our group to reduce the effects of head motion (Hallquist et al., 2013), including 4D slice-timing and head motion correction (Gorgolewski et al., 2011), wavelet despiking (Patel et al., 2014), co-registration to the structural image and non-linear warping to MNI space (Avants et al., 2011; Jenkinson et al., 2012), local spatial smoothing with a 4mm Gaussian kernel, intensity normalization, and nuisance regression based on head motion (based on six degrees of freedom motion estimates and their derivatives) and non-gray matter signal (white matter, cerebrospinal fluid, and their derivatives). Framewise motion estimates were

computed and volumes containing framewise displacement > 0.3mm were censored from computations.

4.2.4.1 Generating Tissue Iron Data and Defining Tissue Iron ROIs

The time-invariant aspects of the T2*-weighted signal derived from functional MRI (fMRI) BOLD measurements (Larsen & Luna, 2015) have been shown to reflect tissue-iron properties, which have been associated with dopamine availability in the striatum and thalamus (Larsen et al., 2020; Péran et al., 2009). Details of the preprocessing procedures that were used for the T2*-weighted images have been published elsewhere (Larsen & Luna, 2015; Peterson et al., 2019; Price et al., 2021; Vo et al., 2011). Briefly, normalized T2*-weighted signal were aggregated voxel-wise across all available fMRI volumes of resting state fMRI scans, using the median, resulting in one normalized T2*-weighted image for each participant (nT2*w). High motion time points were defined as volumes containing framewise displacement > 0.3mm, and were excluded from analyses (Siegel et al., 2014). nT2*w values were extracted separately across caudate, putamen, and thalamus ROIs using the Brainnetome atlas (Fan et al., 2016).

4.2.4.2 Magnetic Resonance Spectroscopic Imaging (MRSI)

MRSI is a method for quantifying metabolite levels in the brain in vivo across a full slice of the brain, rather than a single voxel as is traditionally the case in magnetic resonance spectroscopy. Details of MRSI data acquisition, processing, ROI definition, and data quality control procedures that were used are described in Perica et al., 2022. Briefly, a J-refocused spectroscopic imaging sequence was used along with radiofrequency-based outer volume suppression (Hetherington et al., 2010; J. W. Pan et al., 2010). Two oblique axial slices were acquired, one intersecting with the PFC, and the other intersecting with the hippocampus and

positioned using an in-house program – Quantitative Partial Acquisition Slice-Alignment – to ensure consistent slice placement across participants. ROIs for this data are defined in MNI space using a custom ROI atlas, including regions in the PFC (dorsolateral PFC, medial PFC, and ACC), hippocampus (anterior and posterior), thalamus, and striatum (caudate and putamen), selected based on their high concentrations of hormone-related receptors and their critical roles in cognitive and emotional processing. For each participant, one voxel was manually selected per ROI in each slice based on gray matter ratio in the voxel and manual inspection of spectrum quality. Quantification of neurotransmitters was then achieved by fitting MRSI data derived from each selected voxel using LCModel (Provencher, 2001). Brain neurotransmitter levels are derived as ratios of the neurotransmitter to creatine in order to control for inter-subject variability in overall neurotransmitter levels. LCModel fits were visually inspected and data containing obvious artifacts or other observable data quality issues were excluded. Data were also excluded based on several quantitative measures of MRSI data quality that are standard in the field, including the Cramer-Rao Lower Bounds (CRLB). It should be noted that associations between pubertal stage and CRLB were tested for GABA and glutamate measures in all included regions, and pubertal stage was significantly associated with the CRLB for medial PFC (mPFC) GABA (β=0.224, p_{unc}<0.05) and right caudate GABA (β=0.234, p_{unc}<0.05). However, neither of these measures were major contributors to the puberty-associated principal component of neurotransmitter function described later. Thus, the identified MRSI data quality associations with pubertal stage are unlikely to be driving this component's significant association with puberty. To control for the effects of white matter and other non-gray-matter present within the voxels from which values were derived, residuals were computed to partial out the effect of gray matter percentage on all

GABA and glutamate measures and these GABA and glutamate residuals were included in the PCA.

4.2.5 Hormonal Measures

Hormone levels in this study were derived from hair samples, collected at each visit year from all participants who consented to participate in hair sampling and who had hair at a minimum length of 2.5 inches to ensure an adequate amount of hair to assay all hormones of interest. These hair hormone levels represent a three-month average and have been shown to correlate strongly with circulating hormone levels measured via more standard sources such as saliva and urine samples (Short et al., 2016; Wang et al., 2019). Hair samples were obtained by parting hair at the back of the head horizontally in line with approximately the middle of the ears, and then cutting approximately 40-100 strands as close to the scalp as possible. These strands were then fastened together with a rubber band, wrapped in a piece of foil without bending, sealed, and stored in a cool environment until being shipped for assay. These samples were assayed in collaboration with Dr. Elizabeth Shirtcliff at the University of Oregon for testosterone, DHEA, and cortisol levels in all participants, and additionally for estradiol and progesterone in female participants only (for full details on assay procedure, see Wang et al., 2019). In this study, we included all assayed hormones except cortisol. For logistical purposes, hormones were assayed in three batches, so data was tested for potential batch effects. A significant effect of batch was found for estradiol only, so batch number was included as a covariate in all analyses using estradiol levels.

Following standard procedures in the field, values greater than three standard deviations away from the mean within each hormone were winsorized to three standard deviations from the mean. Additionally, data for each hormone was log-transformed to approximate normal

distributions. Because the use of hormonal medications such as contraceptives can affect these measurements, all hormone analyses were repeated excluding participants who reported using hormone medications, and results were broadly consistent. While menstrual cycle is often another consideration in studies including sex steroid hormones, menstrual cycle phase was not incorporated into these analyses since the method of obtaining hormone measurements from this segment of hair produces an average spanning a three-month period, and thus, multiple menstrual cycles.

4.3 Statistical Analysis

Analyses for all aims were conducted in R (R Core Team, 2020). Across all aims where relevant, false discovery rate (FDR) correction for multiple comparisons was applied to significance values. To address Aim 1, generalized additive mixed models (GAMMs) were used to examine associations of pubertal stage with performance metrics from the antisaccade and BIRD tasks (solid black arrow in Fig. 1). Using GAMMs provides a data-driven way to investigate these associations while accounting for possible nonlinearities in the developmental trajectories of cognitive and emotional control. Participant ID was included as a random effect to account for longitudinal data points and analyses included sex assigned at birth as a covariate. Follow-up analyses also included age as a covariate to provide insight into whether associations with puberty were substantial enough to be statistically separated from age. The resulting p-values were corrected for multiple comparisons using FDR correction across the five cognitive and emotional measures being tested. In addition, follow-up analyses were conducted examining associations between pubertal stage and self-reported emotion regulation ability (using total DERS score and

total DTS score) to understand whether associations with BIRD task performance were specific to emotion regulation. For task performance measures that were significantly associated with pubertal stage controlling for sex assigned at birth, post hoc analyses were conducted separately in males and females to examine associations between each pubertal hormone and the task metric. P-values from these analyses were corrected for multiple comparisons using FDR correction across the two hormones being tested in males and the four hormones being tested in females.

Aim 2 took an exploratory approach to examine three developmentally-relevant neurotransmitters – GABA, glutamate, and dopamine – as another potential mechanism by which puberty affects brain development. To address Aim 2a, we performed a PCA incorporating subcortical tissue iron data as an indirect measure of dopamine from the caudate, putamen, and thalamus, and MRSI data (GABA, glutamate) from the following prefrontal and subcortical regions: dorsolateral PFC (DLPFC), mPFC, ACC, caudate, putamen, thalamus, anterior hippocampus, and posterior hippocampus (gray boxes and arrows in Fig. 1). The PCA was performed using the MacroPCA method with the 'cellwise' package in R (Hubert et al., 2019). This PCA method is highly robust to missing values, within-subject outliers, and between-subject outliers, which is critical in this dataset for several reasons. First, due to the nature of longitudinal studies and the occurrence of the COVID-19 pandemic during data collection, as well as the inconsistency of usable data acquisition with MRSI, there were more missing values in this data compared to other datasets. Furthermore, the biological variability of neurotransmitter data means that outliers may either exist because of measurement error or because of real, important variance in individual neurotransmitter levels, but it is nearly impossible to determine which is the cause. Thus, this method allows for the inclusion of outliers while remaining robust to those outliers driving the overall output.

Since we are assessing development as a deviation from maturity, the PCA was first conducted in an adult-only sample derived from the same study, and then this PCA was used to predict principal component scores for the adolescent sample. Based on visual inspection of the scree plot, three principal components were retained. The loadings of individual measures on each of these components were examined in order to understand which aspects of combined neurotransmitter function were represented by each component. In Aim 2b, we used GAMMs to examine how pubertal stage is associated with these indices of combined neurotransmitter function (dotted black arrow in Fig. 1). Like Aim 1, all analyses included participant ID as a random effect and sex assigned at birth as a covariate, while follow-up analyses also added age as a covariate. The resulting p-values were corrected for multiple comparisons using FDR correction across the three retained principal components being tested. Further, the puberty-associated components of neurotransmitter function were then examined in relation to pubertal hormones separately in males and females, correcting p-values for multiple comparisons using FDR correction across the four hormones being tested.

Then, to address Aim 3, we planned to apply a mediation model using the 'mediation' package in R to test whether combined neurotransmitter function (as measured by neurotransmitter principal components derived in Aim 2a) mediates the relationship between pubertal stage and cognitive and emotional control (dashed black arrow in Fig. 1). Post hoc analyses were intended to apply this mediation model to pubertal hormones that were significantly associated with cognitive and/or emotional control within males and/or females separately, correcting p-values for multiple comparisons using FDR correction across the four hormones being tested in females and two hormones being tested in males. However, these analyses could not be completed due to a lack

of significant associations between the puberty-associated neurotransmitter component and the three puberty-associated behavioral measures.

5.0 Results

5.1 Aim 1

Descriptive statistics at baseline and across the full sample can be found in Tables 2 and 3. GAMMs were used to examine the main effect of pubertal stage on antisaccade correct response rate and response latency, controlling for the effect of sex assigned at birth (Table 4). Follow-up analyses added age as a covariate to these models (Table 5).

Table 2: Descriptive statistics in baseline sample for pubertal stage, age, and all outcome measures.

Variable	N	Mean	SD	Median	Min	Max
Pubertal stage at first timepoint	101	3.62	1.17	4.00	1.00	5.00
Age (years)	101	13.75	2.37	13.66	10.03	17.87
Antisaccade correct response rate (correct/total trials)	85	0.48	0.24	0.46	0.02	0.90
Antisaccade response latency (milliseconds)	85	328.81	65.06	327.19	174.00	502.80
BIRD total score (number of correct trials)	93	404.54	59.52	408.00	267.00	568.00
BIRD challenge latency (milliseconds)	93	362.39	101.95	377.75	53.62	598.63
BIRD baseline latency (milliseconds)	93	975.02	142.99	958.13	586.89	1442.31
PANAS difference scores (negative affect after - negative affect before)	93	1.34	3.27	1.00	-10.00	14.00
DERS Total Score	86	3.77	0.82	3.90	1.54	5.00
DTS Total Score	86	70.39	19.06	64.50	36.00	131.00
Principal Component #1 Score	83	-0.5	2.08	-0.61	-5.62	4.69
Principal Component #2 Score	83	0.66	2.22	0.39	-4.78	6.45
Principal Component #3 Score	83	-0.66	1.46	-0.71	-4.44	2.59

Table 3: Descriptive statistics across full longitudinal sample for pubertal stage, age, and all outcome measures.

Variable	n (visits)	n (participants)	Mean	SD	Median	Min	Max
Pubertal stage	154	101	3.75	1.08	4.00	1.00	5.00
Age (years)	154	101	14.07	2.21	14.13	10.03	17.87
Antisaccade correct response rate (correct/total trials)	127	85	0.50	0.24	0.46	0.02	0.96
Antisaccade response latency (milliseconds)	127	85	319.72	61.69	315.04	174.00	502.80
BIRD total score (number of correct trials)	137	93	410.97	59.65	417.00	241.00	568.00
BIRD challenge latency (milliseconds)	137	93	360.38	92.33	369.62	53.62	598.63
BIRD baseline latency (milliseconds)	137	93	951.22	136.81	944.21	586.89	1442.31
PANAS difference scores (negative affect after - negative affect before)	137	93	1.17	3.11	1.00	-10.00	14.00
DERS Total Score	126	86	69.77	18.16	67	36	131
DTS Total Score	125	86	3.81	0.76	3.92	1.54	5
Principal Component #1 Score	118	83	-0.38	2.05	-0.49	-5.62	4.69
Principal Component #2 Score	118	83	0.73	2.15	0.65	-4.78	6.45
Principal Component #3 Score	118	83	-0.61	1.49	-0.72	-4.44	2.69

We found a significant effect of pubertal stage ($F=7.407$, $p_{FDR}<0.005$) on antisaccade correct response rate, with significant change occurring across pubertal stages 3 and 4 (Figure 7). When examining the follow-up model including age as a covariate, we found a significant uncorrected effect of age that did not survive FDR correction ($F=3.492$, $p_{unc}<0.05$), while the effect of pubertal stage was no longer significant. Similarly, we found a significant effect of pubertal stage ($F=10.940$, $p_{FDR}<0.001$) on antisaccade response latency, with significant change occurring inconsistently between stages 2 and 4 (Figure 8). When examining the follow-up model including

age as a covariate, neither age nor pubertal stage were significantly associated with antisaccade response latency. Across all models, there were no significant effects of sex assigned at birth.

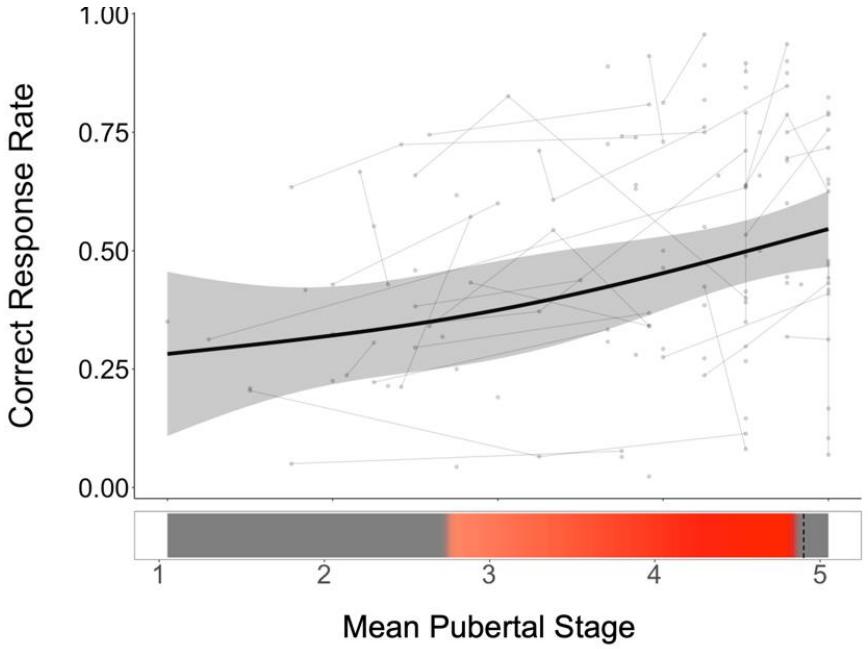

Figure 7: GAMM plot of positive association between mean pubertal stage and antisaccade correct response rate.

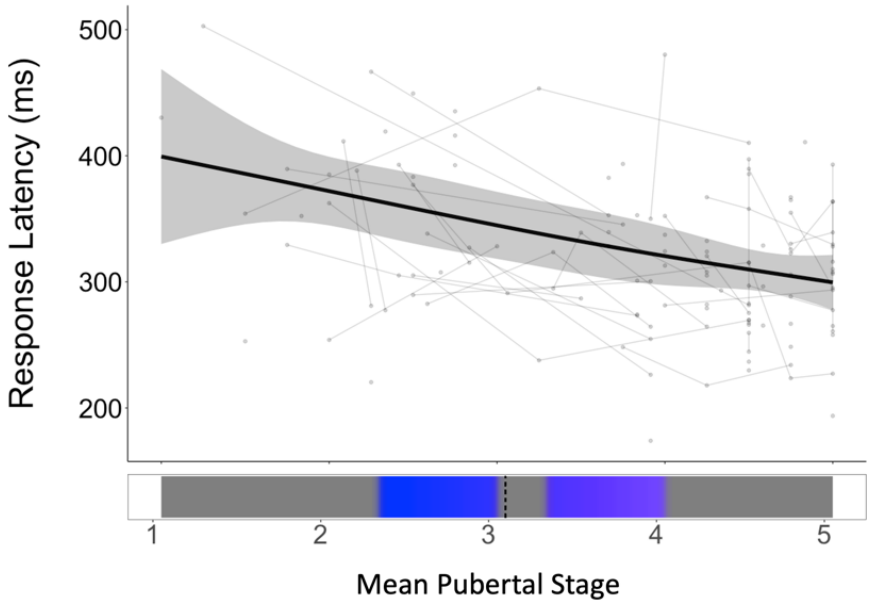

Figure 8: GAMM plot of negative association between mean pubertal stage and antisaccade response latency.

Table 4: Statistical models examining the effects of pubertal stage (with sex assigned at birth as a covariate) on antisaccade and BIRD performance measures.

Measure	Variable	β	F-Statistic	n (visits)	n (participants)	Uncorrected p	FDR q
Antisaccade correct response rate	Pubertal stage		7.407	127	85	9.18×10^{-4}	0.00230
	Sex	0.365				NS	NS
Antisaccade latency	Pubertal stage		10.940	127	85	4.23×10^{-5}	2.12×10^{-4}
	Sex	-0.220				NS	NS
BIRD total score	Pubertal stage		24.830	137	93	2.20×10^{-16}	1.10×10^{-15}
	Sex	0.581				0.00208	0.0104
BIRD challenge latency	Pubertal stage		0.269	137	93	NS	NS
	Sex	0.234				NS	NS
	Base Latency	0.618				5.87×10^{-10}	2.94×10^{-9}
PANAS difference scores	Pubertal stage		0.124	137	93	NS	NS
	Sex	0.430				NS	NS

Table 5: Follow-up statistical models examining the effects of pubertal stage (with age and sex assigned at birth as covariates) on antisaccade and BIRD performance measures.

Measure	Variable	β	F-Statistic	n (visits)	n (participants)	Uncorrected p	FDR q
Antisaccade correct response rate	Pubertal stage		0.011	127	85	NS	NS
	Age		3.492			0.034	NS
	Sex	0.132				NS	NS
Antisaccade latency	Pubertal stage		0.773	127	85	NS	NS
	Age		2.736			NS	NS
	Sex	0.007				NS	NS
BIRD total score	Pubertal stage		3.441	137	93	0.035	NS
	Age		16.927			4.62×10^{-7}	1.45×10^{-6}
	Sex	0.130				NS	NS
BIRD challenge latency	Pubertal stage		0.261	137	93	NS	NS
	Age		1.012			NS	NS
	Sex	0.297				NS	NS
	Base Latency	0.375				7.58×10^{-8}	3.79×10^{-7}
PANAS difference scores	Pubertal stage		0.522	137	93	NS	NS
	Age		0.656			NS	NS
	Sex	0.510				0.021	NS

Because both antisaccade correct response rate and response latency were associated with pubertal stage in the main model tested, we conducted post hoc analyses examining associations between pubertal hormones and these antisaccade performance measures, in order to assess whether hormonal changes might be a mechanism underlying these relationships (descriptive statistics for hormone data are given in Tables 6 and 7). Notably, none of the four hormones measured in this study were associated with age or pubertal stage within this sample (Table 8). We used linear mixed models to test these associations separately in males and females within a subset

of participants who had both antisaccade and hormone data. Across all four hormones tested (DHEA and testosterone in males and females, estradiol and progesterone in females), there were no significant associations with antisaccade correct response rate or response latency, with or without the inclusion of pubertal stage as a covariate (Tables 9 and 10).

Table 6: Descriptive statistics across full sample for pubertal stage, age, and all hormone measures for males.

Variable	n (visits)	n (participants)	Mean	SD	Median	Min	Max
Pubertal stage	40	31	3.50	1.02	3.71	1.00	4.84
Age (years)	40	31	14.6	2.15	14.90	10.80	17.90
DHEA (pg/mg, log transformed)	40	31	1.45	0.27	1.48	0.75	2.06
Testosterone (pg/mg, log transformed)	40	31	0.56	0.30	0.48	0.13	1.20

Table 7: Descriptive statistics across full sample for pubertal stage, age, and all hormone measures for females.

Variable	n (visits)	n (participants)	Mean	SD	Median	Min	Max
Pubertal stage	58	37	3.97	1.14	4.50	1.00	5.00
Age (years)	58	37	14.09	2.32	14.10	10.20	17.70
DHEA (pg/mg, log transformed)	58	37	1.25	0.34	1.17	0.68	2.06
Testosterone (pg/mg, log transformed)	58	37	0.27	0.22	0.32	-0.10	0.78
Estradiol (pg/g, log transformed)	58	37	1.52	0.30	1.46	1.01	2.04
Progesterone (pg/mg, log transformed)	58	37	0.46	0.38	0.39	-0.50	1.15

Table 8: Statistical models examining associations between age/pubertal stage and all hormones in males and females separately.

Measure	Sex	Variable	β	n (visits)	n (participants)	Uncorrected p
Pubertal stage	Male	Testosterone	0.273	39	30	NS
		DHEA	-0.058	39	30	NS
	Female	Testosterone	-0.018	39	32	NS
		DHEA	0.091	39	32	NS
		Estradiol	0.177	45	30	NS
		Progesterone	0.036	49	33	NS
Age	Male	Testosterone	0.280	39	30	NS
		DHEA	-0.092	39	30	NS
	Female	Testosterone	-0.060	39	32	NS
		DHEA	0.084	39	32	NS
		Estradiol	0.152	45	30	NS
		Progesterone	0.101	49	33	NS

Table 9: Post hoc statistical models examining the effects of hormones on puberty-associated antisaccade measures in males and females separately.

Measure	Sex Assigned at Birth	Variable	β	n (visits)	n (participants)	Uncorrected p
Antisaccade correct response rate	Male	Testosterone	0.143	34	28	NS
		DHEA	-0.112	34	28	NS
	Female	Testosterone	-0.217	34	28	NS
		DHEA	-0.106	34	28	NS
		Estradiol	-0.174	41	27	NS
		Progesterone	-0.032	44	29	NS
Antisaccade latency	Male	Testosterone	-0.233	34	28	NS
		DHEA	0.071	34	28	NS
	Female	Testosterone	0.236	34	28	NS
		DHEA	0.225	34	28	NS
		Estradiol	0.242	41	27	NS
		Progesterone	-0.165	44	29	NS

Table 10: Post hoc statistical models examining the effects of hormones on puberty-associated antisaccade measures (with pubertal stage as a covariate) in males and females separately.

Measure	Sex Assigned at Birth	Variable	β	n (visits)	n (participants)	Uncorrected p	FDR q
Antisaccade correct response rate	Male	Testosterone	-0.025	33	27	NS	NS
		Pubertal Stage	0.388			0.029	NS
		DHEA	-0.083	33	27	NS	NS
		Pubertal Stage	0.376			0.025	0.049
	Female	Testosterone	-0.227	34	28	NS	NS
		Pubertal Stage	0.277			NS	NS
		DHEA	-0.137	34	28	NS	NS
		Pubertal Stage	0.282			NS	NS
		Estradiol	-0.246	41	27	NS	NS
		Pubertal Stage	0.215			NS	NS
		Progesterone	-0.064	44	29	NS	NS
		Pubertal Stage	0.267			NS	NS
Antisaccade latency	Male	Testosterone	-0.070	33	27	NS	NS
		Pubertal Stage	-0.360			NS	NS
		DHEA	-0.012	33	27	NS	NS
		Pubertal Stage	-0.374			0.045	NS
	Female	Testosterone	0.239	34	28	NS	NS
		Pubertal Stage	-0.591			0.001	0.003
		DHEA	0.282	34	28	NS	NS
		Pubertal Stage	-0.613			2.88×10^{4}	0.001
		Estradiol	0.317	41	27	NS	NS
		Pubertal Stage	-0.358			0.038	NS
		Progesterone	-0.167	44	29	NS	NS
		Pubertal Stage	-0.338			0.039	NS

We also used GAMMs to examine the effect of pubertal stage on BIRD score, BIRD latency, and difference in negative affect across the BIRD task based on the PANAS, with sex assigned at birth as a covariate in all models (Table 4). Follow-up analyses added age as a covariate to these models (Table 5). A significant main effect of pubertal stage on BIRD score was observed ($F=24.830$, $p_{FDR}<0.001$), with greatest change occurring in pubertal stages 1-3 (Figure 9). In addition, a significant main effect of sex assigned at birth was observed ($\beta=0.581$, $p_{FDR}<0.05$), such that males generally scored higher than females. In the follow-up model including age as a covariate, the effect of age was significant ($F=16.927$, $p_{FDR}<0.001$) while the effect of pubertal stage was significant but did not survive correction ($F=3.441$, $p_{unc}<0.05$). To determine whether these effects were specifically tied to emotion regulation, we tested associations between BIRD score, DERS total score, and DTS total score in this sample. Neither BIRD and DTS score, nor BIRD and DERS score were significantly associated (Table 11). However, it should be noted that exploratory analyses in our full sample including adults did show significant associations between BIRD score and both the DERS and DTS scores ($p<0.05$), indicating that the lack of effects may be due to insufficient power in the younger cohort.

Table 11: Post hoc statistical models examining associations between BIRD score and self-report measures of emotion regulation.

Measure	Variable	β	n (visits)	n (participants)	Uncorrected p
BIRD total score	DERS	-0.097	126	86	NS
	DERS	-0.101	126	86	NS
	Sex	0.382			NS
	DTS	0.147	125	86	NS
	DTS	0.135	125	86	NS
	Sex	0.352			NS

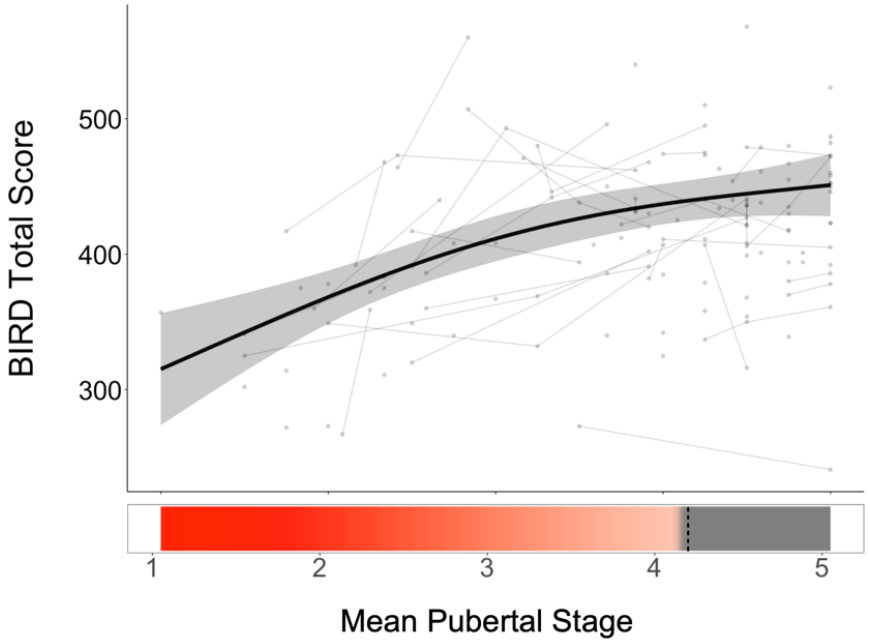

Figure 9: GAMM plot of positive association between mena pubertal stage and BIRD total score.

When examining BIRD latency, we added an additional covariate for baseline reaction time as previously mentioned, in order to separate known development change in processing time generally from reaction time changes specific to emotion regulation within the context of this task. These models revealed that pubertal stage was not associated with BIRD challenge latency in the main model with sex assigned at birth as a covariate (Table 4), and neither pubertal stage nor age were associated with BIRD challenge latency in the follow-up model with age as a covariate (Table 5). When examining differences in negative affect from before to near the end of the BIRD task based on PANAS score, a paired sample t-test demonstrated that on average, the BIRD task increased negative affect in this sample as expected ($t=4.646$, $p=7.822 \times 10^{-6}$, $d=0.394$, Figure 10). However, these differences in negative affect were not associated with pubertal stage when covarying for sex assigned at birth (Table 4), or with pubertal stage nor age in the follow-up model including age as a covariate (Table 5).

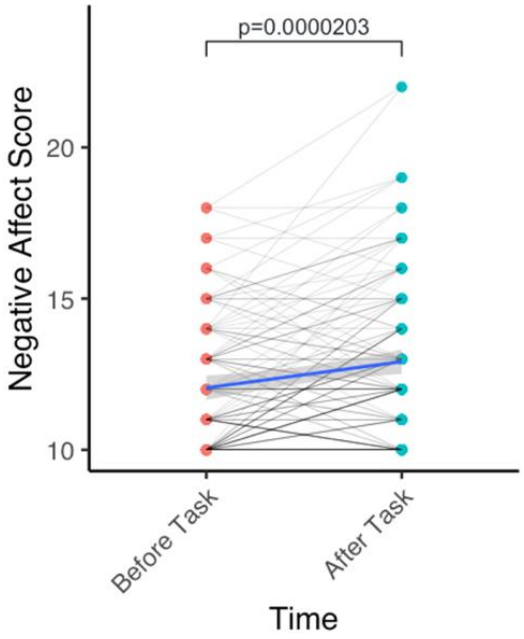

Figure 10: Line plot of significant increase in self-reported negative affect scores (PANAS) from before to the end of the BIRD task.

Since only BIRD score was associated with pubertal stage, we conducted post hoc analyses examining the association between pubertal hormones and BIRD score, in order to assess whether hormonal changes might be a mechanism underlying this relationship. We used linear mixed models to test these associations separately in males and females within subsets of participants who had both BIRD data and data available for each hormone. Across all four hormones tested (DHEA and testosterone in males and females, estradiol and progesterone in females), there were no significant associations with BIRD score without the inclusion of pubertal stage as a covariate (Tables 12 and 13). However, when controlling for pubertal stage, DHEA was significantly associated with BIRD score in males, such that increasing DHEA levels were associated with decreased BIRD scores (β= -0.364, p_{FDR}<0.05, Figure 11). This association was not present in females when controlling for pubertal stage, and no other significant associations were present between hormones and BIRD score when including pubertal stage as a covariate.

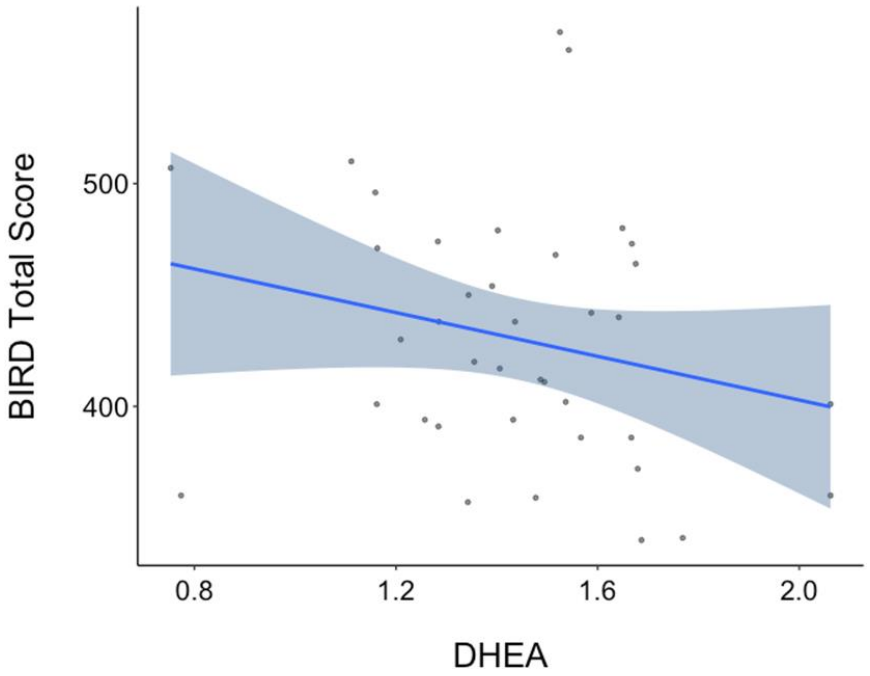

Figure 11: Linear regression plot of negative association between DHEA level and BIRD score in males.

Table 12: Post hoc statistical models examining the effects of hormones on puberty-associated BIRD measures in males and females separately.

Measure	Sex Assigned at Birth	Variable	β	n (visits)	n (participants)	Uncorrected p
BIRD total score	Male	Testosterone	0.138	38	30	NS
		DHEA	-0.326	38	30	NS
	Female	Testosterone	-0.085	32	26	NS
		DHEA	-0.030	32	26	NS
		Estradiol	-0.117	37	26	NS
		Progesterone	-0.034	41	29	NS

Table 13: Post hoc statistical models examining the effects of hormones on puberty-associated BIRD measures (with pubertal stage as a covariate) in males and females separately.

Measure	Sex Assigned at Birth	Variable	β	n (visits)	n (participants)	Uncorrected p	FDR q
BIRD total score	Male	Testosterone	0.011	38	30	NS	NS
		Pubertal Stage	0.400			0.022	0.043
		DHEA	-0.364	38	30	0.018	0.036
		Pubertal Stage	0.432			0.007	0.013
	Female	Testosterone	-0.105	32	26	NS	NS
		Pubertal Stage	0.433			0.006	0.024
		DHEA	-0.060	32	26	NS	NS
		Pubertal Stage	0.433			0.006	0.026
		Estradiol	-0.250	37	26	NS	NS
		Pubertal Stage	0.462			0.011	0.043
		Progesterone	-0.037	41	29	NS	NS
		Pubertal Stage	0.345			0.037	NS

5.2 Aim 2

As described in the Methods section, a PCA was conducted within a sample of adults derived from the same study but excluded from the rest of this project due to a lack of pubertal measures and assumed completion of puberty (adult sample visualized in Figure 12). Due to high levels of missingness, the right posterior hippocampal GABA and glutamate measures were dropped from the PCA and are not included in the resulting principal components. Based on visual inspection of a scree plot (Figure 13), three principal components were retained in the adult PCA across neurotransmitter measures, which together accounted for 40% of the variability in these

measures (individual measure loadings for each retained component are visually represented in Figure 14). The first principal component appeared to largely capture subcortical dopamine (as represented by tissue iron), and to some extent, prefrontal glutamate levels. The loadings of the second principal component suggested that it was driven by GABA and glutamate levels in the dorsal striatum and DLPFC. Finally, the third principal component captured relative levels of posterior hippocampal GABA compared to ACC GABA and glutamate, although the influence of posterior hippocampal GABA is much stronger.

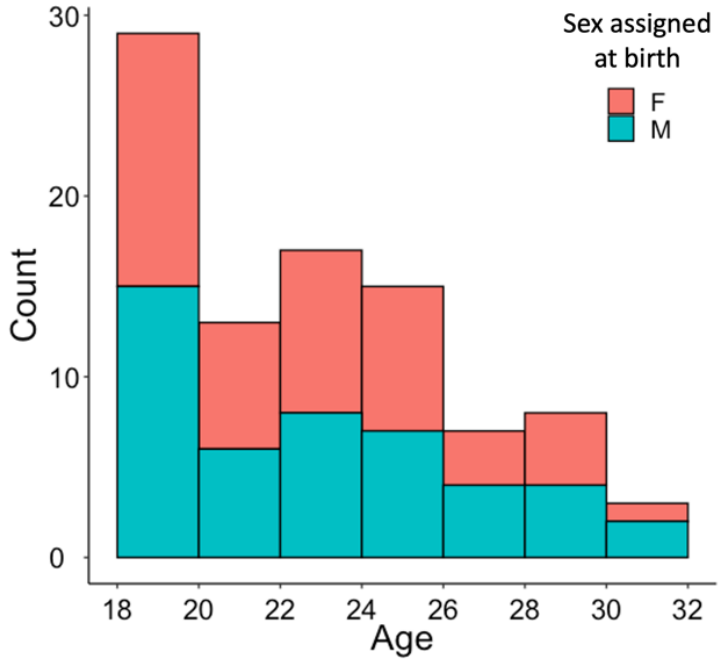

Figure 12: Histogram of adult baseline visits used in neurotransmitter PCA (N=92).

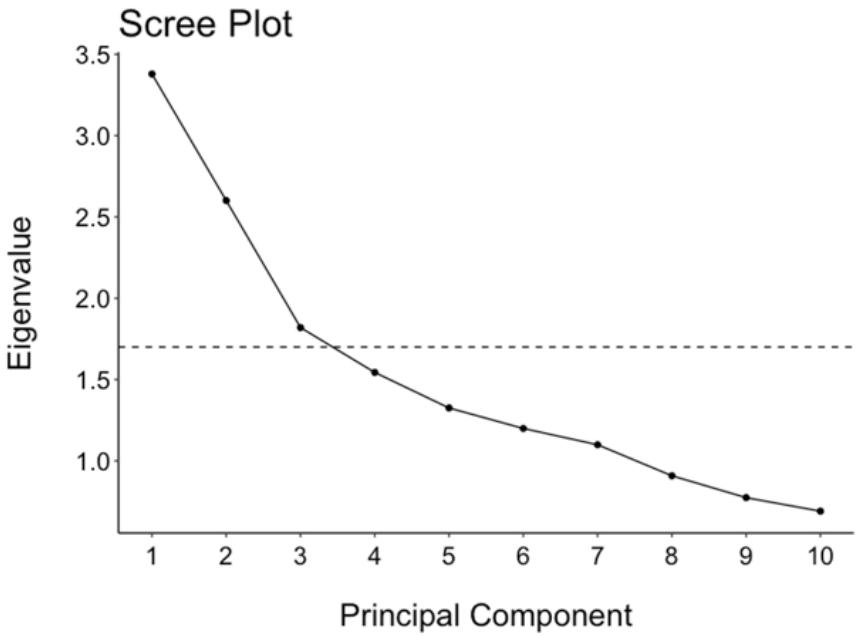

Figure 13: Screen plot of principal component eigenvalues from adult neurotransmitter PCA.

After obtaining these principal components in the adult sample, we used this PCA to predict principal component scores for these three components within the adolescent sample used throughout this project. We then used these predicted scores to test whether any of these three components of neurotransmitter levels were associated with pubertal stage. There were no significant effects of pubertal stage on the first or second principal components when controlling for sex assigned at birth (Table 14) nor when adding age as a covariate (Table 15). However, the third principal component was significantly associated with increasing pubertal stage ($F=4.476$, $p_{FDR}<0.05$) when controlling for sex assigned at birth, with the significant period of change occurring through the second half of pubertal stage 2 and the first half of pubertal stage 3 (Figure 15). When age was added as a covariate to this model, neither age nor pubertal stage was significantly associated with the third principal component. However, it should be noted that in a model of age alone controlling for sex assigned at birth, age was not significantly associated with

this hippocampus-ACC principal component, thus pubertal stage may be a more reliable predictor of this component.

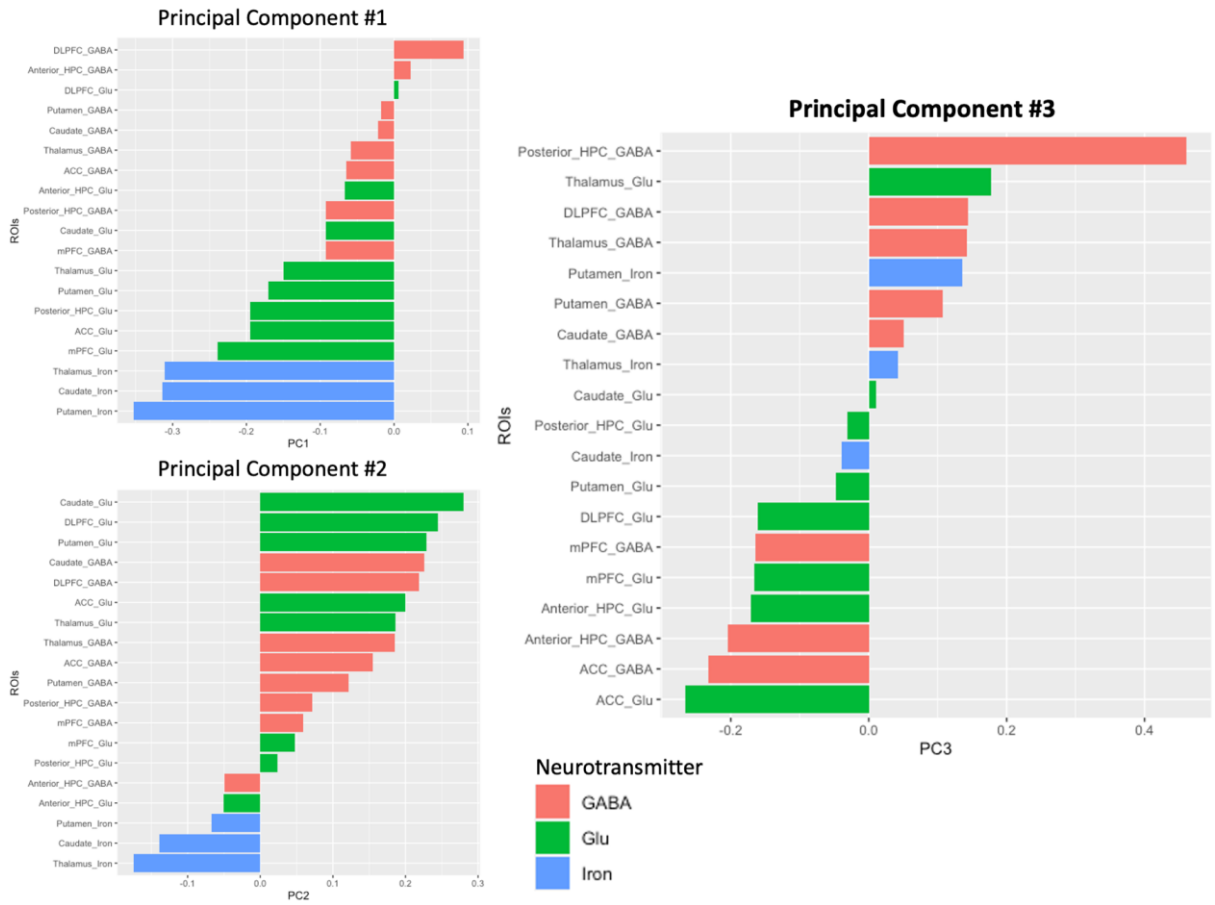

Figure 14: Bar graphs of individual measure loadings on each retained component.

(HPC=hippocampus, DLPFC=dorsolateral PFC, mPFC=medial PFC, ACC=anterior cingulate cortex)

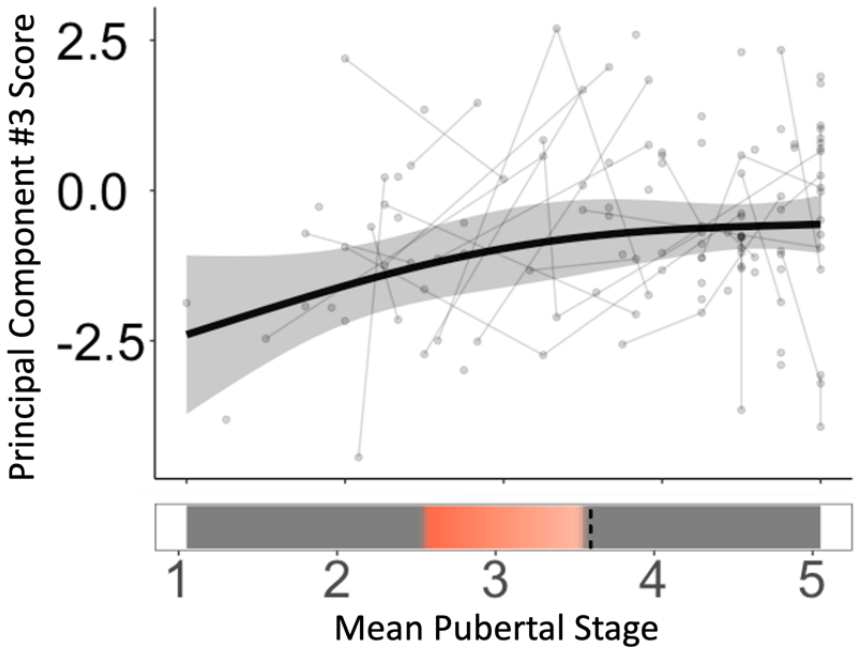

Figure 15: GAMM plot of positive association between mean pubertal stage and the third principal component of neurotransmitter function.

Table 14: Statistical models examining the effects of puberty (with sex assigned at birth as a covariate) on principal components of combined neurotransmitter function.

Measure	Variable	β	F-Statistic	n (visits)	n (participants)	Uncorrected p	FDR q
Principal Component #1	Pubertal stage		2.293	118	83	NS	NS
	Sex	-0.316				NS	NS
Principal Component #2	Pubertal stage		0.182	118	83	NS	NS
	Sex	-0.103				NS	NS
Principal Component #3	Pubertal stage		4.476	118	83	0.0134	0.0402
	Sex	0.348				NS	NS

Table 15: Statistical models examining the effects of puberty (with age and sex assigned at birth as covariates) on principal components of combined neurotransmitter function.

Measure	Variable	β	F-Statistic	n (visits)	n (participants)	Uncorrected p
Principal Component #1	Pubertal stage		0.966	118	83	NS
	Age		0.090			NS
	Sex	-0.295				NS
Principal Component #2	Pubertal stage		0.184	118	83	NS
	Age		0.0160			NS
	Sex	-0.123				NS
Principal Component #3	Pubertal stage		2.372	118	83	NS
	Age		0.255			NS
	Sex	0.382				NS

Because the third hippocampus-ACC principal component was associated with pubertal stage, we completed post hoc analyses examining associations between the hippocampus-ACC principal component of neurotransmitter function and pubertal hormones in males and females separately to explore potential mechanisms underlying this association. Across three of the four hormones tested (DHEA and testosterone in both males and females, estradiol in females only), this principal component was not significantly associated with hormone levels (Table 16). Progesterone levels, assessed only in female participants, were significantly associated with the hippocampus-ACC neurotransmitter principal component but this effect did not survive correction across the four hormones tested (β=0.433, p_{unc}<0.05, Figure 15). It should be noted that post hoc power analyses using the 'SIMR' package (Green & MacLeod, 2016) found that these hormone analyses were underpowered to detect significant small (power = 38.50% [35.47,41.60]) or medium (power = 34.00% [31.06, 37.03]) effects after correction for four multiple comparisons. Importantly, when pubertal stage was added to this model, the association between the

neurotransmitter principal component and pubertal stage became nonsignificant (Table 17), suggesting that progesterone may account for a large proportion of the puberty-related change in hippocampal-ACC neurotransmitter function.

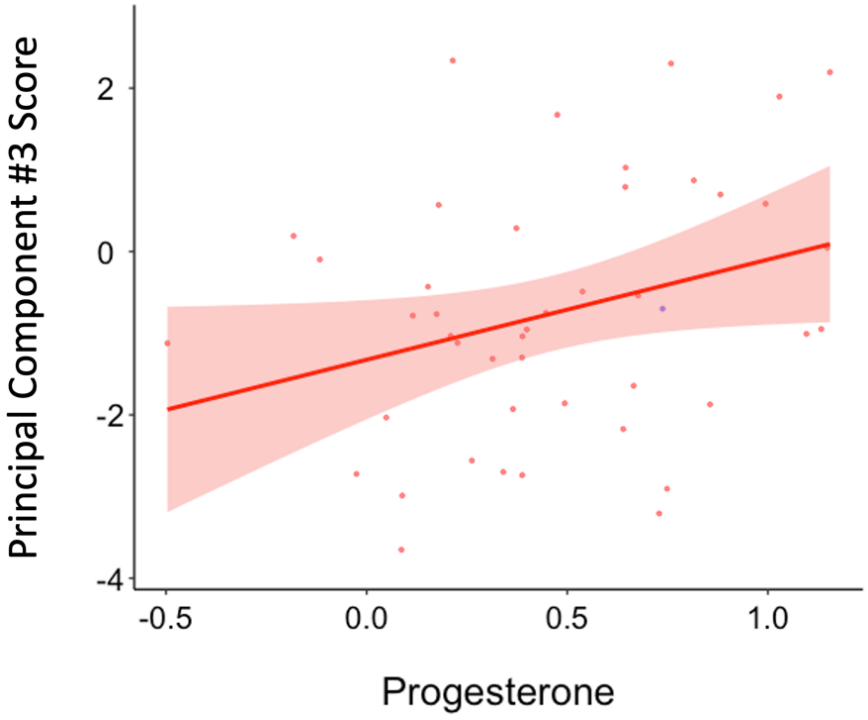

Figure 16: Linear regression plot of positive association between progesterone levels and the third principal component of neurotransmitter function in females.

Table 16: Post hoc statistical models examining the effects of hormones on puberty-associated third principal component of combined neurotransmitter function in males and females separately.

Measure	Sex Assigned at Birth	Variable	β	n (visits)	n (participants)	Uncorrected p	FDR q
Principal Component #3	Male	Testosterone	-0.243	36	27	NS	NS
		DHEA	-0.145	36	27	NS	NS
	Female	Testosterone	0.260	35	31	NS	NS
		DHEA	0.090	35	31	NS	NS
		Estradiol	0.513	39	29	NS	NS
		Progesterone	0.433	44	33	0.015	NS

Table 17: Post hoc statistical models examining the effects of hormones on puberty-associated third principal component of combined neurotransmitter function (with pubertal stage as a covariate) in males and females separately.

Measure	Sex Assigned at Birth	Variable	β	n (visits)	n (participants)	Uncorrected p	FDR q
Principal Component #3	Male	Testosterone	-0.325	36	27	NS	NS
		Pubertal Stage	0.298			NS	NS
		DHEA	-0.093	36	27	NS	NS
		Pubertal Stage	0.203			NS	NS
	Female	Testosterone	0.253	35	31	NS	NS
		Pubertal Stage	0.537			0.004	0.017
		DHEA	0.053	35	31	NS	NS
		Pubertal Stage	0.536			0.006	0.023
		Estradiol	0.394	39	29	NS	NS
		Pubertal Stage	0.201			NS	NS
		Progesterone	0.041	44	33	0.0214	NS
		Pubertal Stage	0.200			NS	NS

5.3 Aim 3

To integrate these findings, our final aim consisted of testing mediation models to examine whether this hippocampus-ACC principal component of neurotransmitter function mediated associations that were identified between pubertal stage and antisaccade correct response rate, antisaccade response latency, and BIRD score. However, statistical analyses revealed that this hippocampus-ACC neurotransmitter component was not significantly associated with any of these

puberty-associated behavioral measures, with or without pubertal stage as a covariate (Table 18). Thus, full mediation analyses were not appropriate.

Table 18: Statistical models examining the effect of the puberty-associated third principal component on puberty-associated antisaccade and BIRD measures (with sex as a covariate, and with sex and puberty stage as covariates).

Measure	Variable	β	n (visits)	n (participants)	Uncorrected p
Antisaccade correct response rate	Principal Component #3	0.045	106	76	NS
	Sex	0.118			NS
	Principal Component #3	-0.044	106	76	NS
	Pubertal stage	0.398			1.07×10^{-4}
	Sex	0.387			NS
Antisaccade latency	Principal Component #3	-0.111	106	76	NS
	Sex	0.057			NS
	Principal Component #3	-0.025	106	76	NS
	Pubertal stage	-0.389			3.85×10^{-4}
	Sex	-0.216			NS
BIRD total score	Principal Component #3	0.122	106	75	NS
	Sex	0.345			NS
	Principal Component #3	0.018	106	75	NS
	Pubertal stage	0.426			2.02×10^{-5}
	Sex	0.648			0.003

6.0 Discussion

In this study, we find that self-reported pubertal stage is associated with measures of inhibitory control and some, but not all, measures of emotional control, with most significant change occurring largely in early and mid-puberty. While none of these inhibitory control measures were associated with pubertal hormone levels, a broad measure of emotional control was associated with DHEA levels in male participants when controlling for pubertal stage. We also found that dopamine, glutamate, and GABA levels cluster together into three main components, encompassing 1) subcortical dopamine and prefrontal glutamate levels, 2) GABA and glutamate levels across the dorsal striatum and DLPFC, and 3) opposing variation in GABA and glutamate within the hippocampus and ACC. Of these three components of combined neurotransmitter function, increases in the hippocampal and ACC GABA/glutamate component were associated with increasing pubertal stage, and this component may also be associated with progesterone levels in females. Finally, the hippocampal-ACC GABA/glutamate component was not associated with antisaccade response rate, antisaccade latency, or BIRD total score and thus, could not be tested as a mediator of the association between puberty and these measures.

Based on our findings, it is likely that the major influences of puberty on cognitive and emotional development occur in the early and middle stages of puberty, rather than in late puberty or across the transition from puberty to adulthood. If these effects arise from hormonal interactions with the brain, this is consistent with the significant surge of estradiol and testosterone that occurs near the onset of puberty and the progesterone rise occurring in mid-puberty. Although analyses including age as a covariate are difficult to interpret due to the challenges of separating age and pubertal stage, the fact that age remains significant in this model for antisaccade correct response

rate and BIRD score suggests that pubertal development may explain a smaller portion of the development-related variance in these measures. Developmental trajectories of these measures may instead be more influenced by other processes associated with chronological age such as the accumulation of experience. However, BIRD score was associated with DHEA levels in males when controlling for pubertal stage, providing some evidence for a biological mechanism of emotional development. This association may have been specific to the inclusion of pubertal stage as a covariate because this controls for other large-scale puberty-related changes, revealing an effect of DHEA which may represent a direct hormonal effect in the brain rather than a potential mechanism of pubertal influence. In contrast, neither age nor pubertal stage remained significant in the combined model for antisaccade response latency, suggesting that puberty may account for more of the development-related variance in this measure. Further, these findings support prior work from our lab showing that pubertal development may be more implicated in optimization of inhibitory control performance, represented by improvements in response latency, than in the overall development of inhibitory control ability (Ojha et al., 2022; Ordaz et al., 2018; Ravindranath et al., 2022), potentially reflecting greater influence of puberty-related biological processes such as prior hormone surges or changing distributions of hormone receptors in the brain. Critically, while these findings cannot confirm that pubertal effects on cognitive and emotional control are independent of other age-related processes, they do suggest that pubertal development and associated hormonal changes may contribute to both cognitive and emotional development, but possibly in subtle ways that are difficult to disentangle using currently available methods.

It is important to consider that pubertal hormone levels in this sample were not associated with pubertal stage or age. Thus, it is difficult to know if associations with these hormone levels

are in fact related to pubertal development. However, it should be noted that the sample sizes for hormone levels were unexpectedly small due to unforeseen methodological constraints and thus, statistical power may not have been sufficient to detect small developmental effects. In addition, this sample does not comprehensively capture the transition into puberty, when surges in hormones are believed to be greatest, so it is possible that while hypothesized increases with age and pubertal stage may still be occurring, they are too subtle to reach statistical significance in this age range. When looking at a larger sample encompassing all participants through the age of 30, testosterone and progesterone were both associated with age, supporting the idea that statistical power may be a major reason for the lack of developmental effects. Further, hormone levels vary widely between individuals, and we did not have a way to normalize these levels to account for individual differences in baseline levels. Using data with several longitudinal timepoints for each participant would help to counteract this issue and may better lend itself to detecting associations with age or pubertal stage. Additionally, some recent work attempting to create a latent factor of puberty using self-report measures, salivary hormone levels, and hair hormone levels, showed that self-reported pubertal development and salivary hormone levels loaded onto a single latent factor while hair hormones did not fit well into this model (Byrne et al., 2023). This finding demonstrates that hormone levels derived from hair may not match well with pubertal development as indexed by self-report measures. One reason for this may be that diurnal variation in these hormones is significant, with hormone levels peaking in the morning and decreasing to low levels by evening, and this variation is even more pronounced and erratic during puberty. Thus, capturing hormone levels at a particular moment, possibly early in the morning when these levels are highest, may correspond better with how those hormones are affecting overall pubertal development, rather than the average hormone level derived from hair, which may obscure important variability.

The post hoc analyses examining associations between hormone levels and BIRD score found that DHEA levels in males were significantly associated with BIRD score, such that higher DHEA related to worse BIRD performance. Notably, the effect was only significant when pubertal stage was included as a covariate in the model, indicating that this association is independent of other puberty-driven changes in DHEA. This may also suggest that this association is specific to adrenally-produced DHEA, as opposed to gonadally-produced DHEA which might be more strongly linked to pubertal stage. The prior, albeit limited, literature examining the relationship between DHEA and emotion regulation has produced conflicting results. Some studies have suggested that higher DHEA is associated with better emotion regulation (Sripada, Marx, King, Rajaram, et al., 2013; Strous et al., 2003) and lower DHEA with greater negative affect (Susman et al., 1991) as well as risk for psychiatric disorders involving mood dysregulation such as Major Depressive Disorder (Berr et al., 1996; Goodyer et al., 1996). However, others have found associations between greater DHEA and higher suicide risk (Butterfield et al., 2005; Chatzittofis et al., 2013) as well as higher anxiety in males (Barendse et al., 2020). One possible reason for this inconsistency may be that the effects of DHEA follow an inverted-U pattern, such that too much or too little DHEA might be detrimental, but a medium level might be optimal for emotion regulation and mental health. Another explanation might be that these measured DHEA levels may not accurately reflect DHEA levels in the brain or do not accurately represent how DHEA is influencing the brain. DHEA is part of the synthesis pathway for both testosterone and estradiol, and is believed to be frequently used by neurons to synthesize these neurosteroids due to the abundance of DHEA throughout the body (Soma et al., 2015). Thus, measured DHEA levels may reflect levels of synthesized testosterone or estradiol or may in fact reflect brain DHEA levels, depending on the person and the method of hormone measurement. This may also relate the

specificity of this association to males, who have higher levels of DHEA than females (Arlt, 2004; Rehman & Carr, 2004), because higher DHEA levels may increase its likelihood of conversion to other neurosteroids required by the brain. Based on this, the relationship between DHEA level and brain or behavioral measures might be better elucidated in relation to other hormones, i.e., high/low DHEA in combination with high/low testosterone may indicate something about how much DHEA is synthesized into testosterone, how poorly DHEA is metabolized, or other related processes that could affect brain function. Analogously, DHEA might influence brain through interactions with neurotransmitters, like the notable variation in estradiol's effects on cognition dependent on individual differences in baseline dopamine availability. Finally, it is possible that studies have used inconsistent measures of emotion regulation that differentially relate to DHEA depending on the aspect of emotion regulation being captured. Future studies should incorporate larger sample sizes, combined measures of multiple hormones or hormones with neurotransmitters, and additional measures of emotion regulation in order to further explore this association.

When interpreting the puberty-related change in BIRD performance and association with DHEA levels found in this study, it is necessary to also consider the aspects of emotion processing and regulation that are captured by this task. This task induces distress or negative affect, specifically frustration in most cases, and requires participants to sustain optimal performance on a basic motor task while this negative emotion occurs and/or increases. Because the activity that participants are engaging in while in the negative affective state is not cognitively demanding, it is unlikely that this task captures anything related to emotion-cognition interactions. Rather, this task may emulate a realistic situation in which people must continue engaging in an activity regardless of their emotional state, which likely requires some level of emotion regulation in order to successfully continue the activity. However, maintaining optimal performance could be a result

of multiple different combinations of emotion processing and regulation characteristics, i.e. participants who perform better could just experience less negative affect or frustration related to this task, or be better at regulating increases in negative emotion, or might just be skilled enough at this simple motor task that their performance is unaffected by changes in their emotional state. In this sample, BIRD score was unrelated to scores on the DERS, DTS, or PANAS, making it difficult to evaluate which of these processes might be more implicated in the developmental changes. However, it should be noted that in the larger sample encompassing participants up to 30 years old, BIRD score was significantly related to both DERS and DTS total scores, suggesting that the lack of association is related to low power, and that the developmental change in BIRD score may in fact be related to improvements in emotion regulation and distress tolerance across pubertal development.

The puberty-associated third component of neurotransmitter function largely captured hippocampal GABA levels and to a lesser extent, GABA and glutamate levels in the ACC. Individually, these are both regions that undergo dramatic development during adolescence underlying major behavioral maturation such as the development of error monitoring, emotion regulation, working memory, and future planning (Ahmed et al., 2015; Calabro et al., 2020; Geier et al., 2009; Isbell et al., 2015; Luna et al., 2015; Murty et al., 2016; Ordaz et al., 2013; Pfeifer et al., 2011). However, when we tested these highly-loading measures individually (posterior hippocampal GABA, ACC glutamate, ACC GABA) for associations with pubertal stage, all were nonsignificant, suggesting that the developmental effect here is related to this specific combination of brain regions and neurotransmitters, rather than being driven by one specific measure or region. Notably, loadings of hippocampal GABA and ACC GABA/glutamate were in opposing directions, which may also suggest that the association with puberty is specific to the *relative* change between

hippocampal GABA and GABA/glutamate in the ACC. This is particularly relevant because changes in the balance between glutamate-driven excitation and GABA-driven inhibition within the PFC are believed to underlie adolescent critical period plasticity (Larsen et al., 2021; Larsen & Luna, 2018). Thus, combined measures of GABA and glutamate capturing this relative change (i.e., ratio, correlation, or residuals) may provide unique insights into developmental change in these neurotransmitters and their contributions to critical period plasticity (Perica et al., 2022; Steel et al., 2020). While we did not incorporate these combined measures in this study, the hippocampal-ACC GABA/glutamate component may identify another relative change in GABA and glutamate underlying brain maturation and plasticity during this period.

One of the few existing studies examining puberty-specific effects on resting state connectivity development identified the hippocampus and ACC as one of several specific connectivity pairs that were more associated with pubertal stage than age among a variety of cortical-cortical, subcortical-subcortical, and cortical-subcortical connectivity pairs (van Duijvenvoorde et al., 2019). Thus, these regions and neuronal signals between them may be more affected by puberty-related changes in the body than other brain regions. Functionally, disruptions in hippocampus-ACC connectivity have been identified in post-traumatic stress disorder (Fani et al., 2016), major depressive disorder (Krug et al., 2022), schizophrenia (Kraguljac et al., 2016), and physical disorders encompassing emotion dysregulation such as hyperthyroidism (Zhang et al., 2014) and chronic pain (Yu et al., 2021), suggesting a role for this connectivity pair in emotion processing and regulation. While this component was not found to mediate the effect of pubertal stage on BIRD score, our primary measure of emotion regulation, our mediation subsamples were small and thus these mediation analyses were likely underpowered (see Limitations section). Further, the BIRD task only encompasses one specific type of emotion regulation—distress

tolerance during a goal-directed task. Thus, it is possible that this hippocampal-ACC component may be more specifically related to other facets of emotion regulation that were not measured in this study.

The association between progesterone and this hippocampal-ACC GABA/glutamate principal component is noteworthy because of progesterone's known effects on the brain. First, animal studies have identified an important role for progesterone and its metabolites in the modulation of hippocampal GABA levels. Specifically, progesterone metabolites have been shown to act as allosteric modulators of both synaptic and extrasynaptic $GABA_A$ receptors, increasing GABA receptor sensitivity and tonic inhibition (Birzniece et al., 2006; Farrant & Nusser, 2005; Majewska et al., 1986; Pletzer et al., 2023; Shen et al., 2007). It is particularly intriguing that this effect may be reversed during puberty, such that progesterone may actually decrease GABA binding and tonic inhibition in the hippocampus during this period (Shen et al., 2007). Additionally, progesterone is a modulator of NMDA (but not AMPA) receptor expression and sensitivity in the hippocampus, striatum, and cortex, driving changes in neuronal sensitivity to glutamate (Cyr et al., 2001; El-Bakri et al., 2004). Major shifts in the balance of inhibition and excitation are believed to drive the opening and closing of critical periods in the brain (Dorrn et al., 2010; Hensch & Fagiolini, 2005; Long et al., 2005). Thus, it is possible that progesterone's actions in other areas of the brain that have not yet been studied, or through the hippocampus's interactions with the PFC, may play a role in demarcating PFC critical period plasticity during adolescence. This is further supported by research that has shown progesterone to increase myelination, another mechanism believed to drive the closing of critical periods, by inducing synthesis of myelin protein in oligodendrocytes through binding at $GABA_A$ receptors (Schumacher et al., 2012, 2014). Importantly, white matter that may connect the hippocampus and ACC, such

as the cingulum bundle and superior medullary lamina, undergoes maturation and myelination across the adolescent period (Benes, 1989; Benes et al., 1994; Lebel et al., 2008; Simmonds et al., 2014). While progesterone's role in myelination has not yet been studied in adolescence, those studies that have been done have focused on fetal and postnatal development (Ghoumari et al., 2020), another period of increased progesterone synthesis and action during which progesterone is also believed to play a fundamental role in neurogenesis and neural circuit formation (González-Orozco & Camacho-Arroyo, 2019). This finding and the supporting literature provide novel evidence for progesterone as a potential mechanism by which puberty triggers the beginning and ending of adolescent critical period plasticity.

This association may also speak to a potential role for progesterone in the known development of neural synchrony across adolescence. Theta band activity, defined as neural oscillations occurring in the 5-10Hz range, plays a critical role in the organization of higher frequency activity and interactions between the hippocampus and PFC (Benchenane et al., 2011). Past work from our group has shown protracted development through adolescence of theta band activity within the ACC and anterior insula, which may underlie important behavioral maturation across adolescence such as improvements in cognitive control (Marek et al., 2018). Relatedly, a recent study found that progesterone concentrations in humans across sexes were associated with greater amplitude of frontal midline theta oscillations, which likely correspond to an area of the brain including the ACC (Riddle et al., 2020). While the current study cannot directly speak to the role of theta, these prior findings suggest theta band oscillations as another mechanism through with progesterone may influence hippocampal-ACC GABA/glutamate function. Importantly, while some of these roles that progesterone plays in the brain have been identified across sexes, substantially more research has been done in females. Further, the association between

progesterone and the hippocampal-ACC GABA/glutamate component in this study was also specific to females due to lack of data in males. Thus, it will be critical for future studies to examine whether progesterone reliably fills these roles across individuals, regardless of sex characteristics.

The other principal components of combined neurotransmitter function identified here were not related to development, but their loadings may still indicate important relationships between these neurotransmitter systems. In particular, the first principal component, capturing subcortical tissue iron and prefrontal glutamate, is somewhat consistent with one of our hypotheses predicting a component that included striatal dopamine and prefrontal glutamate, due to crucial interactions between these two systems that support executive function (Tseng & O'Donnell, 2004). While we do not have direct measures of dopamine in this sample, such as PET imaging, tissue iron has been associated with presynaptic striatal dopamine availability (Larsen et al., 2020; Péran et al., 2009). Importantly, previous work has shown that subcortical tissue iron, particularly in the striatum, increases across development (Larsen & Luna, 2015; Parr et al., 2021), while prefrontal glutamate decreases across development (Perica et al., 2022). Since the loadings of these measures are all in the same direction for this component, it is likely that these developmental effects cancel each other out, which may explain the lack of association between this component and age or pubertal stage.

The second principal component was not one we hypothesized and seems to largely capture GABA and glutamate in the dorsal striatum and DLPFC. Connectivity between the dorsal striatum and DLPFC has been associated with executive control functions such as delay discounting and impulse control (Bos et al., 2014; Kim & Im, 2019; van den Bos et al., 2015). Notably, glutamatergic projections have been identified from the DLPFC which synapse on GABAergic neurons in the caudate (Khundakar et al., 2011), providing a potential mechanism for interactions

across these regions. Though this component was not associated with pubertal development, frontostriatal connectivity and related functions are known to change with development. Because of these known developmental changes, and the dearth of available information on GABA and glutamate across these regions, it is difficult to understand the lack of significant age- or puberty-related change in this component. However, one explanation may be that these principal components were defined in adults, and it is possible that the identified components do not all reflect the relationships between neurotransmitters and brain regions that exist in adolescence. Thus, the structure of these relationships may itself be changing from adolescence to adulthood, making it impossible to observe those developmental changes using the current method. Further, many participants in this sample had not completed puberty by age 18, and many of these brain maturational processes are known to continue past this age, so the restricted age range of this sample may have limited our ability to observe some significant developmental changes.

6.1 Limitations and Future Directions

Several limitations of this study should be noted. First, our total sample size, as well as the number of participants with longitudinal timepoints, was smaller than anticipated due to unexpectedly high attrition during and following the COVID-19 pandemic. In addition, due to methodological constraints, sample sizes in the hormone data were significantly smaller than anticipated relative to the study's total sample. Relatedly, across all analyses, differing subsamples of participants were available depending on which participants had complete and usable data for each measure, which was highly variable and led to smaller sample sizes for certain analyses. These unexpected limitations resulted in many analyses that were likely underpowered, including

post hoc hormonal analyses and the mediation analyses in Aim 3. They also prevented us from effectively examining interactions between the effects of sex assigned at birth and pubertal development, and effects of hormonal medications, such as birth control, on the hormone measurements. Though this study is largely exploratory due to the limited statistical power resulting from low sample size, these findings will provide important insights that can inform the design and hypotheses of future, large-scale studies examining puberty and brain development.

Based on the demographic makeup of this sample, the generalizability of these findings may be limited. Specifically, while this sample has plenty of variability in household income, and the racial makeup is similar to that of the city of Pittsburgh, about half of the sample is white, and most are upper middle class or above. This is particularly important in puberty research, since pubertal onset timing and tempo have been found to vary as a function of race, household income, and other demographic factors (Bleil et al., 2017; Deardorff et al., 2011; Kelly et al., 2017). While we confirmed that age, pubertal stage, and hormone levels were not associated with race or household income group in our sample, it is likely that these variables might have a larger influence in a sample that more comprehensively captures the onset of puberty. Thus, future studies should emphasize the construction of diverse samples in order to promote greater generalizability to the broader population. Further, the collection of detailed information regarding these variables is critical in order to extend our current understanding of how these individual differences affect the progression of puberty and its influence on the brain.

Across this study, sex assigned at birth was included as a covariate and main effects were noted, but sufficient power was not available to examine puberty-by-sex interactions. However, it is important to consider that sex is more complex than the binary variables commonly used in psychological research. The fields of biology and to some extent, psychology, have recognized for

some time that biological sex characteristics and gender identity are too complex to be well-captured by just two categories (Ainsworth, 2015; Hyde et al., 2019). Even with this knowledge, much of psychological science has still not changed to reflect this fact. Thus, representing sex using only the binary variable derived from sex assigned at birth is likely to obscure meaningful differences in neurocognitive development that vary as a function of the sex and gender spectra. This is particularly important when studying the nuanced effects of puberty, a process that is intrinsically tied to sex characteristics and reproductive differences. Developing new strategies for measuring and conceptualizing sex as a nonbinary and/or continuous variable (Reilly, 2019; Vosberg et al., 2020) and applying those strategies to understanding the effects of pubertal development will be crucial to improving our understanding of puberty's influence on brain development.

While the BIRD task provides a somewhat realistic measure of the ability to maintain performance while regulating changes in emotion, it is difficult to pinpoint the aspect of emotion regulation being captured by this task or for some participants, whether emotion regulation is even involved, as mentioned above. In addition, the examination of developmental change in BIRD score and the BIRD challenge latency is confounded by continued improvement in response latency through this age range, a limitation which is difficult to control for due to the nature of this task. Thus, the interpretation of findings from this task as they relate to overall emotional development is ambiguous due to the nature of this task. Because this study identified some significant puberty-related associations with this task, it may be important for future studies to incorporate more targeted measures of emotion processing and regulation, as well as a wider variety of these measures, in order to better contextualize these findings. Laboratory tasks of interest might include a combination of explicit emotion regulation tasks, which attempt to induce

various emotions in participants and then ask them to actively modulate those emotions, and implicit emotion regulation tasks (like the BIRD task) which induce emotion and then elicit automatic, unconscious regulation of the emotion. However, it might be even more beneficial to incorporate ecological momentary assessment methods, such as a daily task asking participants at a random time to rate their current mood/affective state, complete a short task, and then answer some questions about any conscious emotion regulation that occurred during the task. These measures might allow researchers to examine how mood states induced by real-life activities and events, and the ability to regulate these states, affects task performance and relates to self-reported regulation, and how these processes change across adolescence.

This study utilizes a novel method of studying neurotransmitters across the brain by conducting a PCA to understand how their combined function is influenced by puberty as well as how it affects behavioral development. However, interpreting the resulting component loadings posed a challenge due to the large number of heterogeneous measures, with three different neurotransmitters and eight different brain regions. Thus, while this study used the MacroPCA method due to the high volume of missing and outlying data in this sample, it may be helpful to consider developing or using a sparse PCA method that is similarly robust to missing and outlying data so that fewer neurotransmitters are included within each component to aid in interpretability. Importantly, PCA also assumes statistical independence of the components that are identified, which may be inconsistent with the known interrelatedness of these neurotransmitter systems across regions. Future studies might consider instead using another form of dimensionality reduction that does not assume orthogonality of the resulting components or factors, such as non-negative matrix factorization (Khambhati et al., 2018). In addition, future studies of puberty's impact on neurotransmitter development should consider incorporating measures of

GABA/glutamate balance, such as correlations or residuals (Perica et al., 2022; Rideaux, 2021; Steel et al., 2020). Studying associations between pubertal development and these relative measures, particularly within the PFC, may provide a more direct way to examine puberty's role in the onset of critical period plasticity during adolescence. Additionally, because changes in dopamine function have also been implicated in the opening of this critical period (Benoit-Marand & O'Donnell, 2008; Larsen & Luna, 2018; O'Donnell, 2010; Porter et al., 1999; Tseng & O'Donnell, 2004), a similar PCA incorporating tissue iron measures with these GABA/glutamate balance measures may result in combined neurotransmitter components that more directly relate to plasticity processes. Furthermore, the resulting reduction in the number of input measures would also improve the interpretability of identified components.

Relatedly, because the use of PCA is a data-driven approach to understanding which combinations of neurotransmitters to examine, it may be useful in future studies to derive these principal components of combined neurotransmitter function *prior to* choosing behavioral measures of interest. Many aspects of emotional and cognitive function develop significantly across adolescence and, as discussed in the Introduction, few have been studied with puberty specifically, so identifying behavioral measures on which to focus can be challenging. Further, because this PCA method is novel and these neurotransmitters have been minimally studied in combination with pubertal development in humans, it is difficult to hypothesize about the number of principal components that will be retained and how they will be structured. Thus, first deriving the relevant principal components, but refraining from conducting developmental analyses or behavioral associations, may allow researchers to select behavioral measures that are mechanistically relevant to the neurotransmitters and brain regions loading highly onto the derived components, while still preserving the scientific integrity of the study.

As discussed in the Introduction, the measurement of pubertal development itself is challenging since the most widely accepted measures of pubertal stage, Tanner staging and the PDS, are both subjective measures. This study took an additional step by incorporating pubertal hormone levels as a quantitative measure of pubertal development. However, other quantitative measures of puberty-related processes are becoming more common, such as bone age/growth plate fusion (Emons et al., 2011; Flor-Cisneros et al., 2006; Shim, 2015) and testicular/ovarian volume (Kabay et al., 2009; Reding et al., 2021), all of which can be obtained noninvasively via imaging technologies. Refining the study of pubertal development as it relates to brain maturation will require that future studies begin to incorporate several of these subjective and objective measures within the same studies. This will allow for several different approaches to examining puberty – 1) each metric of pubertal development can be considered to represent a different aspect of pubertal processes and compared to brain metrics accordingly, 2) reliability of these measures and effect sizes of associations between these measures and brain or behavioral metrics can be compared to understand which pubertal measure(s) might be best suited for neurocognitive research, and 3) several pubertal measures can be combined via a factor analysis or another dimensionality reduction method to derive a latent factor of pubertal development that may better represent where an individual is in their pubertal development than any individual measure alone.

The insights gained from this project emphasize the importance of recruiting a sample that is specifically tailored toward asking questions about pubertal development. Because this participant sample was recruited with the primary goal of examining age-related change, rather than pubertal development, study recruitment was designed to generate a final sample with even numbers of participants at each age, and even distributions of sex assigned at birth within each age. However, this did not produce a sample that was evenly distributed across pubertal stages or

with sex assigned at birth distributed evenly across these stages. This issue was exacerbated by the fact that this sample's age range begins at 10 years old, which led to relatively few participants in Tanner Stage 1. This limited our ability to understand how the transition into puberty, a highly influential period and the time particularly implicated in triggering critical period plasticity, affects cognitive and emotional development. Thus, future puberty-focused studies should consider assessing pubertal stage as part of the screening process in order to recruit participants evenly across all pubertal stages, including prepubertal (Tanner Stage 1) children.

Additionally, when examining some of our outcome measures of interest, including the self-report emotion regulation questionnaires and the neurotransmitter principal components, it was apparent that developmental change continued past the age of 18 in some measures (based on age associations with these measures in our full adolescent and adult sample). Notably, many participants in our sample, particularly males, had not reached Tanner Stage 5 by the age of 17-18, suggesting that the collection of pubertal stage data past 18 years old would have allowed for more complete pubertal trajectories to be studied. This additional data may have helped to clarify whether some of these later-maturing characteristics are in fact associated with pubertal development. It may have also helped to confirm whether analyses showing that greatest puberty-related change occurred in early-to-mid puberty were accurate or were influenced by the lack of data at later stages in males. Therefore, it would be beneficial for future studies of puberty and brain development to collect pubertal stage data through the early-to-mid 20s in order to fully represent pubertal trajectories, including the transition out of puberty into adulthood.

7.0 Conclusions and Implications

This innovative, multimodal study provides a novel, integrative perspective on the neural mechanisms underlying pubertal development and their role in driving developmental changes in cognitive and emotional function supporting the transition from adolescence to adulthood. The behavioral and neurobiological findings presented here will provide important new targets for future studies of puberty and brain development, a critical and thus far under-researched topic considering the substantial biological changes occurring during puberty and their associations with psychiatric illness. Through this study and those that follow, characterizing the relationship between puberty and the development of cognitive and emotional control will shed light on a key biological mechanism of brain development, particularly as it relates to risk for psychiatric disorders and the known increase in psychopathology risk that occurs during puberty. These findings highlight the importance of targeting pubertal mechanisms to leverage heightened neuroplasticity during adolescence for the prevention and treatment of psychiatric disorders. Furthermore, they provide a first step toward identifying much-needed neurobiological intervention targets for psychopathology arising from individual differences in pubertal development and their underlying molecular mechanisms.

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