SENSITIVE PERIODS FOR SOCIAL DEVELOPMENT IN ADOLESCENCE: EXPLORING MECHANISMS RELATING EXPERIENCE AND TIMING TO NEURAL CHANGE

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ABSTRACT

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TITLE: Sensitive Periods for Social Development in Adolescence: Exploring Mechanisms Relating Experience and Timing to Neural Change

Social relationships during adolescence have outsized effects on long-term physical and mental health. The theory that adolescence is a sensitive period suggests that adolescent experiences might profoundly shape development. Part of this dissertation reviewed empirical evidence in consideration of the theory that adolescence is a sensitive period for sociocultural development. Despite clearer knowledge about neurodevelopmental and social changes occurring during adolescence, we identified major remaining gaps in our understanding of how adolescent experiences may become neurally embedded in the long-term.

The current investigation used pediatric neuroimaging to evaluate evidence for such neural embedding within a frontostriatal circuit thought to undergo protracted development in adolescence (specifically, nucleus accumbens and ventromedial prefrontal cortex). We tested a long-term phasic modeling hypothesis that phasic, task-evoked brain connectivity sculpts or influences more "intrinsic" or baseline measures of connectivity over long developmental times-scales. Adolescent self-disclosure was examined as a candidate process for long-term phasic modeling due to its ubiquity,

frequency, and significance in deepening peer relationships, as well as its ability to elicit neural signal within the target circuit. Analyses of data from a longitudinal community sample that recruited adolescent girls (initial N=174; initial ages 10.0-13.0 years, 18 mos. between waves) examined (1) developmental trajectories, (2) developmental mechanisms, and (3) behavioral outcomes associated with frontostriatal connectivity across states of task and rest.

Results identified nonlinear puberty-related changes to functional connectivity during self-disclosure and found that this connectivity may be related to friendship quality. However, results did not identify developmental patterns consistent with long-term phasic modeling hypothesis, an alternative (reverse) hypothesis, or with sensitive periods in frontostriatal connectivity. Instead, a developmental pattern consistent with the long-term phasic modeling hypothesis described connectivity between one of the nodes (the nucleus accumbens) and a control region within the primary visual cortex and further suggested that connectivity between these regions may be related to real world friendship behaviors. More work is needed to understand the robustness, specificity, and translational relevance of this effect. This research highlights a viable analysis strategy for examining developmental and sensitive period mechanisms with multiple waves of longitudinal data.

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CHAPTER I

REVISITING ADOLESCENCE AS A SENSITIVE PERIOD FOR SOCIOCULTURAL PROCESSING

Preamble

Social relationships during adolescence leave a profound mark on development, but from a mechanistic perspective, we do not know why. Sensitive period theories of adolescence provide a unifying and interdisciplinary framework across animal species and human cultures that may explain how social experiences become neurally embedded across development. The overarching aims of this dissertation were (a) to assess the state of the field of developmental cognitive neuroscience in understanding adolescence as a sensitive period for sociocultural development and (b) to interrogate neurodevelopmental patterns and mechanisms that might relate close adolescent friendships to outcomes including relationship quality and mental health.

Chapter 1 of this thesis is a theoretical review intended to update and expand our understanding of adolescence as a sensitive period for sociocultural learning, and to further identify progress and gaps in this field of research. Following this review is a set of three interrelated and novel empirical analyses focused on frontostriatal connectivity during the transition into adolescence. This empirical work is integrated with Chapter 1 because analyses are informed by and interpreted in light of developmental mechanisms of change, and included exploring sensitive period effects. This work aimed to characterize developmental trajectories of frontostriatal connectivity across states of task and rest (Chapter 2), to evaluate neurodevelopmental mechanisms of change within this

circuit, including an exploration of sensitive period mechanisms (Chapter 3), and to estimate effect sizes between functional connectivity and behavioral variables (Chapter 4). Together, the theoretical and empirical work presented here (as discussed in Chapter 5) speaks to the importance of understanding neurodevelopmental trajectories and explicitly testing mechanisms that may relate experience to developmental change.

Introduction to the Review Paper

In developmental cognitive neuroscience, many studies of adolescence are at least partly motivated by the notion that adolescence is a period of developmental opportunity. In an influential and expansive review, Blakemore and Mills (2014) specifically consider whether adolescence is a sensitive period for sociocultural processing. They integrate findings from psychology and neuroscience to suggest that adolescents are especially sensitive to social information in their environments, and yet conclude that evidence is still needed to establish this sensitive period, particularly in humans (Blakemore & Mills, 2014, p. 191; reiterated in Fuhrmann et al., 2015). The present chapter updates and expands this prior review to identify both progress and gaps in the growing field of developmental cognitive neuroscience as it pertains to whether adolescence is a sensitive period for sociocultural processing.

Defining Sensitive Periods

A *sensitive period* is a limited window of time during development when the effect of experience on brain function is particularly strong and lasting (Hensch et al., 2005). The mechanisms that facilitate sensitive periods are posited to support efficient learning of environmental information that is shared across members of a species

(Greenough et al., 1987). Sensitive periods do not preclude the possibility of further learning after this window of time closes. The related term "critical period" typically implies that learning is not possible afterward, and as this is not established for most social processes in adolescence, we use the term "sensitive periods" throughout.

Sensitive period timing is flexible rather than fixed (Bavelier et al., 2010), leading some to argue that sensitive periods ought to be defined by unique learning mechanisms (or "experience-expectant" mechanisms) rather than specific developmental windows or ages (Gabard-Durnam & McLaughlin, 2020). However, there are at least two challenges to this view. First, unique and time-limited neurobiological mechanisms may not be needed to achieve sensitive period effects. This is because cumulative effects of the same general or basic learning mechanisms over time may result in early periods during which information from the environment has a disproportionately large impact (Arcaro et al., 2019; Achille et al., preprint). Second, the distinction between experience-expectant mechanisms and ongoing learning mechanisms across the lifespan is not clear cut, especially across species (Frankenhuis, 2020). In some cases this distinction and its associated vocabulary may be a barrier to clarity and collaboration with researchers in related disciplines (Frankenhuis, 2020). For our purposes, I adopt a functional and pragmatic (rather than mechanism-based) definition of sensitive periods; under this view, establishing adolescence as a sensitive period for sociocultural learning requires evidence for impacts of adolescent experience on sociocultural development that are unique in their quality and extent.

In considering evidence for adolescence as a sensitive period, I suggest a need to distinguish between *sensitive periods* and *periods of heightened sensitivity*. Social

reorientation theory suggests that adolescence is a period in which the focus of social engagement shifts away from caregivers and toward peers and prospective romantic partners (Nelson et al., 2005; Nelson et al., 2016). Adolescents exhibit heightened sensitivity to peer rejection (Sebastian et al., 2010) and peer influence (e.g., O'Brien & Bierman, 1988; Gardner & Steinberg, 2005). Whereas studies of sensitive periods in sensory and language domains typically rely on concrete learning benchmarks to characterize learning, these benchmarks may sometimes be less sharply operationalized in the socioaffective domain. In some subdomains, this may have resulted in a somewhat greater focus in the literature on heightened sensitivity to the socioaffective stimuli themselves, particularly peer faces, behaviors, attitudes, etc., rather than what is learned from them, learned in order to decipher them, and/or generally how they are embedded in development over time. These and other developmental trends may provide evidence of a *period of heightened sensitivity* whereby certain stimuli demand attention and evoke affective reactivity/salience to a greater degree within a certain developmental period.

Sensitive periods and heightened sensitivity conceptualizations of adolescence may be at times conflated because they are indeed highly complementary rather than orthogonal or antagonistic. Substantial literature suggests that salience enhances learning (Makintosh, 1975), for example, by guiding the manner in which children navigate the environment in order to support learning. In adolescence, heightened sensitivities to the social environment are thought to promote motivation, learning, and adaptation to social contexts (Forbes & Dahl 2010; Crone & Dahl, 2012). However, heightened sensitivities are not logically required to establish sensitive periods, as it is possible that information from the environment impacts development implicitly, and/or in the absence of overtly

heightened responses. For example, while the heightened relevance (bordering on obsession) of music preferences is a common trope of adolescence, one study found that music experienced during childhood (rather than preschool or adolescence) was preferred by adults during an acute stress manipulation and uniquely supported emotion regulation; this suggests a sensitive period for the role of auditory cues in safety learning about environments that occurs *prior* to adolescence (Gabard-Durnam et al., preprint). Additionally, some efforts to understand how heightened sensitivities promote learning using computational learning models have produced mixed results. For example, peaks in adolescent reward sensitivity do not tend to be associated with advantages in a variety of learning tasks, which instead tend to consistently identify better performance with age (Flournoy, 2018).

Scope of the Present Review

In this updated and expanded review, we examine and review literature on typically developing adolescents from the more recent part of the last decade. We cover domains discussed in the original review by Blakemore and Mills (2014), including trends in structural and functional neural development as they pertain to social cognition, as well as the impact of social experiences on adolescent development more broadly. Finding evidence for sensitive period theories of adolescence requires the identification of effects that are developmentally and socially-specific. To address developmental specificity, we prioritize studies that use large age ranges and/or longitudinal follow-up (Fuhrmann et al., 2015; Woodard & Pollak, 2020). Tying developmental changes to puberty suggests adolescent-specificity, and we expand upon the prior review by emphasizing potential roles of puberty in influencing adolescent social development. To

address *social* specificity, we consider that social development is not a single entity, but emerges from multiple and co-occurring processes with unique trajectories (like systems for emotional processing; Woodard & Pollack, 2020). While evidence of change in various non-social processes does not necessarily pose a direct challenge to sensitive period conceptualizations of adolescence, we note when studies make explicit comparisons to non-social conditions or control variables, as well as the degree to which studies rule out other confounds when making claims about uniquely social effects. Additionally, there is a need to clearly distinguish between heightened sensitivity and sensitive periods theories in the literature, both to better understand these phenomena separately and to understand how they might complement one another. Overall, we aim to identify progress and gaps in our understanding of adolescence as a sensitive period for sociocultural processing with an eye toward translational opportunities for supporting healthy adolescent development.

Review of the Literature

Structural Brain Development

The brain undergoes significant structural remodeling during adolescence. While studies examining developmental trajectories of structural development do not directly test sensitive period theories, our understanding of how and when large scale neural changes occur contributes to our ability to consider whether sensitive periods are neurobiologically plausible, and by what mechanisms they might operate. In considering the precision with which we are able to understand developmental change, it is important to note that longitudinal and cross-sectional studies can reveal different patterns

(Pfefferbaum & Sullivan, 2015). While longitudinal studies can model inter- and intra-individual variability, cross-sectional studies lack measures of within-person change and may need to exercise care to avoid such interpretations (Kraemer et al., 2000).

Trends in Global and "Social Brain" Cortical Development

Recent examinations of structural brain development have used team and open science approaches to replicate and challenge key findings demonstrating that the brain undergoes significant structural remodeling during adolescence. One team effort involving replication across four longitudinal samples identified the following major trends in average structural brain development: (1) whole-brain volume increases until ages 10-15 and then decreases into the early 20s, (2) cortical gray matter volume tends to be highest in childhood and decreases across adolescence, and (3) cortical white matter volume increases until mid-to-late adolescence (Mills et al., 2016; see also Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Wierenga et al. 2014). Among these, the decrease in cortical gray matter volume notably contrasts with earlier studies positing early adolescent peaks (Lenroot et al., 2007; Giedd et al., 1999) and is consistent with a large number of more recent longitudinal studies (reviewed in Ducharme et al., 2016).

While these global trajectories suggest that adolescence is a period of significant ongoing neurodevelopment, it is relevant to this review to identify whether regions of the brain implicated in sociocultural processing undergo pronounced changes during adolescence. Social processes are very diverse and recruit an extensive set of regions sometimes referred to as the "social brain" (Alcalá-López, 2018). Using longitudinal data, Mills and colleagues (2014) identified changing trajectories of gray matter volume, cortical thickness, and surface area within a set of regions strongly implicated in

mentalizing and social cognition, including medial prefrontal cortex (mPFC; defined as medial Brodmann Area 10), temporoparietal junction (TPJ), posterior superior temporal sulcus, and the anterior temporal cortex. Gray matter volume and cortical thickness decreases in three of the four regions were replicated (anterior temporal cortex exhibited a distinct pattern and was not examined in replication analyses; Becht et al., 2020), providing confirmatory evidence of adolescence-specific neurodevelopmental changes within the social brain.

Relating Structural Trajectories to Developmental Mechanisms of Plasticity

Although structural trajectories of brain development are increasingly well-characterized, metrics from current non-invasive human neuroimaging methods often cannot be attributed to a specific cellular process and may not capture critical cellular-level changes during adolescence, such as synaptic plasticity (Paus et al., 2008; Mills & Tamnes, 2014). Methodological advancements have not fully resolved this difficulty, but diffusion tensor imaging and magnetization-transfer imaging provide additional clues about the brain's white matter microstructure and degree of myelination, respectively. Two of the most common indices reported from diffusion tensor imaging studies are fractional anisotropy and mean diffusivity. Higher levels of fractional anisotropy may reflect increases in myelination but also capture changes in axonal size and/or packing, while higher mean diffusivity is thought to reflect lower axonal integrity (Beaulieu, 2002; Paus, 2010). Research using diffusion MRI has identified non-linear increases in fractional anisotropy and decreases in mean diffusivity across childhood and into adolescence, with tracts associated with fronto-temporal regions exhibiting the most protracted trajectories (Lebel et al., 2019). Finally, findings from magnetization-transfer

imaging suggest that reductions in cortical thickness across adolescence are driven by increases in intracortical myelination (Whitaker et al., 2016), a mechanism known for relating experience and phasic activity to cellular remodeling (Chang et al., 2016; Fields, 2015).

Puberty involves dramatic increases in hormone levels across the adrenal, gonadal, and growth axes, and pubertal hormones may be a significant driver of neurodevelopmental change. Like age, pubertal stage and testosterone levels tend to be associated with reduced gray matter volume in diverse regions across the cortex, and particularly across frontal and temporal lobes (although this may partly be because the prefrontal cortex is commonly the focus of studies; see Vijayakumar et al., 2018 for a systematic review). Beyond the cortex, gray matter volumes for some subcortical structures are accelerated in early or mid-puberty (Goddings et al., 2014) and are better explained by pubertal status as compared to age (Wierenga et al., 2018). In particular, converging evidence suggests that puberty is associated with sexually dimorphic changes in the amygdala (Goddings et al., 2014; Herting et al., 2014; Vijayakumar et al., 2018). While puberty has sometimes been more directly tied to heightened socio-affective sensitivities, its hormonal processes have been proposed to directly regulate both the opening and closing of sensitive periods during the transition to adolescence (Piekarski et al., 2017). With respect to understanding the influence of puberty on structural brain development, there remain a number of major challenges (notably, inconsistencies in pubertal modeling, particularly in models considering both age and puberty), as well as a limited number of longitudinal studies; these likely both contribute to inconsistencies in this literature (Herting & Sowell, 2017; Vijayakumar et al., 2018).

Summary

Structural neuroimaging studies have identified changes in whole-brain volume, cortical gray/white matter volume, subcortical gray matter volume, white matter microstructure, and indirect measures of myelination during adolescence. Changes occur in regions and tracts supporting higher-level social cognitive and socio-affective processes, and an emerging area considers how some changes are related to pubertal development. Overall, studies of brain structure suggest that adolescence is a period of significant neural remodeling. While studies of this type typically cannot identify the specific cellular mechanisms driving these changes, they implicate mechanisms that may be sensitive to experience. Taken together, this contributes evidence toward the plausibility of developmentally specific neural changes occurring during adolescence.

Animal Models of Social Isolation

Animal research, largely carried out in social species of rodents, has identified potent and causal effects of social isolation occurring during animals' juvenile and peri-pubertal periods (Burke et al., 2017). A series of classic experiments by Einon and Morgan (1977) found that rats isolated during a period of peak social play (postnatal days 25-45; a period that is analogous to early adolescence) exhibited greater anxiety-like behaviors. A subset of these effects were both irreversible by resocialization in adulthood and distinct from the effects of isolation during adulthood. Resocialization typically refers to returning isolated animals to group housing and experimentally identifies whether further experience at a later point in time can recover behavioral and neural changes due to social isolation (ascertaining the developmental specificity of isolation effects). Recent studies have found that isolating rodents during a post-weaning, pre-

adulthood period increases aggression (Toth et al., 2011), anxiety-like (Lukkes et al., 2009a) behaviors, and preferences for drug and reward-related stimuli (Whitaker et al., 2013; Walker et al., 2020) in a manner that is not fully ameliorated by resocialization during adulthood.

Several studies have identified high quality, species-typical social experiences as "active ingredients" in ameliorating the effects of social isolation. A subset of behavioral changes resulting from social isolation did not develop if rodents who were otherwise housed in isolation received an hour of daily contact with a peer that engaged in social play during their "adolescence" (again from postnatal days 25-45; Einon et al., 1978). More recent work suggests that the quality of social experiences during resocialization influences the degree of rehabilitation following social isolation. Rodents that were socially isolated as juveniles and resocialized with other isolates saw fewer gains to myelin and mPFC activity than those resocialized with rodents that had been socially-housed throughout development (Makinodian et al., 2017).

Social isolation is thought to impact behavior via multiple mechanisms, including by altering dopaminergic (e.g., Fabricius et al., 2010; Yorgason et al., 2016) and serotonergic (e.g., Lukkes et al., 2009b) functioning within mesolimbic regions fundamentally impacting processing reward and value (the ventral tegmental area and nucleus accumbens), as well as decreased inhibitory activity within aspects of the amygdala, a key region in emotional and fear processing (Lukkes et al., 2012; for reviews, see Burke et al., 2017; Novick et al., 2018; Orben et al., 2020). Research has additionally identified altered prefrontal myelination, dendritic pruning, and oligodendrocyte functioning following isolation during juvenile and adolescent phases of

rodent development (Makinodan et al., 2012), with impacts on learning and goal-directed behaviors (Hinton et al., 2019).

Summary

The absence of species-typical social experience results in profound changes to behavior and neurobiology in animal models, with the bulk of studies examining rodents. Some studies have identified developmentally-specific effects during periods analogous to adolescence, but a wide range of isolation timings and durations are employed across this literature and often assess the effects of isolation across broader phases of development. Social experience via resocialization in adulthood can ameliorate some, but not all, effects of juvenile/adolescent isolation, and the quality of the social experiences and underlying plasticity may interact to support this amelioration following isolation. While mapping this work onto our understanding of human development is an ongoing challenge, this research provides insight into which behaviors and circuits may be impacted by social experiences in adolescent-like phases of development across species.

Peer Influences on Adolescent Development

Navigating and making sense of increasingly complex social environments among peers is an important aspect of adolescent development. As children get older, they spend more time with their peers, and one study of American children of European ancestry found that time with peers reaches a peak in adolescence (Lam et al., 2014). During this transition, youth also begin to characterize peer relationships as having greater importance; compared to preadolescents, older adolescents tend to attribute greater depth of meaning and value to peer groups and group identities (O'Brien & Bierman, 1988). Much research has sought to understand how peer interaction engages neural and

cognitive systems during adolescence, and what implications this has for real world behaviors (especially those related to health risks). We touch upon this literature here, through the lenses of identifying evidence for heightened sensitivities and/or sensitive periods.

Peer Susceptibilities

The mere presence of peers has been found to elicit developmentally-unique effects in adolescents (largely in cross-sectional studies). Believing that they are being watched by a peer induces heightened feelings of autonomic arousal and embarrassment in adolescents (Somerville et al. 2013). The presence of peers tends not to impact (Smith et al., 2018) or can even improve (King et al., 2018) "cold" cognitive control involving more emotionally neutral stimuli and outcomes. For example, peer observation and feedback during the Flanker task increased early adolescents' effort (Barker et al., 2018) and improved task performance, with changes to medial frontal theta power and connectivity that were consistent with greater error monitoring and proactive control (Buzzell et al., preprint). However, the presence of peers can diminish "hot" cognitive control involving more affectively laden stimuli and outcomes (King et al., 2018). In one cross-sectional study, the presence of peers diminished inhibitory control (performance on the Go/No-Go task) in response to positive social cues in the context of potential monetary reward for adolescents (ages 13-17) as compared to young adults (ages 18-21) or adults (over 21; Breiner et al., 2018).

Social contexts can powerfully modulate cognitive processes supporting learning and decision-making. Peer rejection, as compared to acceptance, can impact persistence on frustrating tasks and sensitivity to loss in a decision-making context (King et al.,

2018). Compared to adults, adolescents experience stronger affective responses to negative social evaluations (Sebastian et al., 2010). Meta-analyses indicate that one region—the ventral striatum— is more reliably recruited in neuroimaging studies of children and/or adolescents than adults (Vijayakumar et al., 2017; developmental effect also seen in Cheng et al., 2020). The ventral striatum plays a role in affective processing (Knutson et al., 2000; Sescousse et al., 2013) and may facilitate emotion regulation (Wager et al., 2008) and specifically positive reappraisal (Doré et al., 2017) when faced with negative or aversive stimuli. In adolescents, ventral striatal responses to social stimuli have been associated with reduced peer susceptibility (Pfeifer et al., 2011). On the other hand, neural responses to social exclusion in regions associated with mentalizing/social cognition have been associated with greater risk-taking on subsequent laboratory tasks simulating driving behavior (Peake et al., 2013; Falk et al., 2014; Wasylyshyn et al., 2018). However, studies relating social exclusion to subsequent risk-behaviors have typically examined adolescent-only samples, making it difficult to assess whether such phenomena are developmentally specific.

Roles of Adolescent Social Motives and Pubertal Hormones in Organizing Behavior

Although adolescents tend to conform to their peers' perceptions of risk (Knoll et al., 2015; Knoll et al., 2017), it is not the case that peers exclusively drive adolescents toward impairment and risk. For example, studies have found that adolescents exhibit greater conformity to prosocial rather than antisocial attitudes espoused by peers (Do et al., 2020), as well as greater conformity to safe rather than risky peer choices compared to young adults on an economic decision-making task (they notably did not conform to computer-generated choices; Braams et al., 2019). These studies suggest that adolescents

adopt a wide range of both positive and negative behaviors and attitudes modeled by peers. It is also not the case that adolescents overwhelmingly or exclusively favor peers across contexts. In one study that employed a risk-taking task with emotional face stimuli, adolescents did not indiscriminately focus on peers over adults but were able to attend to social feedback in a strategic, goal-directed manner (McCormick et al., 2018). Furthermore, in a separate study that employed a card-based decision-making task, adolescents were more likely to make decisions in a manner that would result in greater simulated rewards for their parents over their peers (Guassi Moreira et al., 2018).

One overarching theory focuses on understanding adolescents' propensity for pursuing health-risking behaviors in terms of how such behaviors strategically align with their social motivations, including perceived social risks and benefits (Andrews et al., 2020a; Blakemore, 2018; Ellis et al., 2012). In line with this theory, one study found that adolescents' beliefs about the social desirability of health-risking behaviors impacted their anticipated involvement in such behaviors, especially for youth that had experienced peer victimization (Andrews et al., 2020b). Compared to young adults, adolescents demonstrate a greater willingness to exert physical effort in order to obtain social feedback, suggesting a motivation to learn about themselves from others in order to reduce uncertainty about the self (Bos et al,. 2021). These perspectives highlight how adolescents may be driven by self and/or socially-oriented motivations and perceptions in a manner that might rationally drive their behaviors.

Adolescents' shifting social motivations may be modulated by hormonal changes. Testosterone is related to motivation to learn about and seek social status (Eisenegger et al., 2011) and is associated with greater conformity to high-status behaviors across social

contexts (Rowe et al., 2004). According to the dual hormone hypothesis (Mehta & Josephs, 2010), testosterone is more strongly associated with status-seeking behaviors when cortisol levels are low, but this research has largely been conducted in adults. Consistent with this theory, recent work in early adolescents found that those with high levels of testosterone and low levels of cortisol tended to exhibit the greatest conformity to prosocial behaviors espoused by peers (Duell et al., 2021). This study found that, when making pro-social decisions after viewing peer behavior, individuals high in testosterone and low in cortisol exhibited greater signal in a number of brain regions associated with prosocial decision-making (including posterior superior sulcus/TPJ, orbitofrontal cortex, insula, and caudate).

Long-Term Influences of Loneliness and Social Connectedness in Adolescence

One area of social relationships research that bears on sensitive period theories of adolescence is the degree to which such relationships have an outsized long-term impact. Some studies indeed find that social connectedness has a lasting influence during adolescence, with close friendship quality during this period being related to physical (Allen et al., 2015) and mental (Narr et al., 2019) health over a decade later. Loneliness, or perceptions of social isolation, tend to increase during adolescence (Qualter et al., 2015) and may mediate the relationship between social connectedness and depressive symptoms for adolescents (Nangle et al., 2003; Witvliet et al., 2010). One three-year longitudinal study found that positive social support buffered against future depressive symptoms for adolescents with a history of childhood adversity (van Harmelen, et al., 2016). However, there are conflicting findings as to whether supportive friendships lead to more resilient functioning (van Harmelen et al., 2017) or whether resilient functioning

and supportive friendships change together over time (van Harmelen et al., 2020; authors note that age differences across study samples might be related to this discrepancy). Adolescent friendship quality is related to individual differences in the structural development of the mPFC and TPJ, suggesting that neurodevelopmental trajectories within social cognitive regions exhibit changes relevant to the quality of social relationships across adolescence (Becht et al., 2020).

Summary

Adolescents respond uniquely to peers in a variety of ways, including, e.g., heightened autonomic arousal to the presence of peers, reduced cognitive control in affective decision-making contexts, and heightened sensitivity to peer rejection. It was not a goal of this article to comprehensively review advancements in the area of peer influence, and we highlight theories that adolescents' social motivations and perceptions may strategically drive their choices and that increases in social motivation may be sensitive to changes in pubertal hormones. A few studies of peer susceptibilities used cross-sectional designs with wide age spans that point to developmentally-specific effects. Generally, this area has identified heightened sensitivity effects and has focused on predicting behavior in the short term (especially risk-taking). A greater empirical understanding of how such sensitivities support social learning and/or long-term outcomes might better inform our understanding of sensitive periods.

Social Cognition

Social cognition encompasses a vast number of subprocesses and subfields. This review selectively examines two major areas (theory of mind and face processing) with respect to how they relate to sensitive period theories of adolescence.

Theory of Mind

Understanding associations between social experiences, neurodevelopment, and theory of mind may clarify debates about not only theory of mind development (Mahey et al., 2017), but also adolescent sensitive periods. Longitudinal research confirms previous cross-sectional findings that theory of mind tends to unfold in a particular sequence from preschool through middle childhood (Peterson & Wellman, 2018). Neuroimaging studies examining brain networks supporting theory of mind, including bilateral TPJ, precuneus, and areas of the mPFC, find evidence that these social brain regions are distinct in preschool aged children and exhibit protracted changes (specifically, stronger within-network correlations and weaker between-network correlations) into adolescence (Richardson et al., 2018; replicated in Richardson, 2019). Additionally, cross-sectional lifespan research with large samples suggests that theory-of-mind performance on more challenging tasks does not reach ceiling until the 20s (Klindt et al., 2017). Previous findings that adults were better able to take the perspective of another individual into account for communicative purposes (compared to both children and adolescence) have been replicated in separate samples (Dumontheil et al., 2010; Symeonidou et al., 2016; Tamnes et al., 2018).

Face Processing

Face perception exhibits protracted development into adolescence (Fuhrmann et al., 2016; Rodger et al., 2015; Thomas et al., 2007). Recent research suggests that some of these advancements may be tied to pubertal development. Puberty is associated with a dip in the recognition of adult faces (across gender; Scherf et al., 2012) that is accompanied by an improved recognition of peer faces across adolescence (Picci &

Scherf, 2016). In addition to shifts in *who* is recognized, adolescence may be a period in which there are changes in *what* is recognized. For example, one study identified enhanced discrimination of facial expressions conveying complex social emotional states (sexual interest and contempt) but not basic emotional states (happiness, anger) with pubertal development (Motta-Mena & Scherf, 2017).

The transition into adolescence may also be associated with the loss of plasticity in earlier-developing aspects of face perception (Pascalis, 2020). The classic "other-race" effect finds that children that have more experience with faces from their own race tend to better recognize those faces as compared to faces belonging to those from other races (Kelly et al., 2005). While this effect emerges early in infancy, one study suggests that it can be reversed with extended experience up until approximately 12 years of age (McKone et al., 2019), indicating the transition into adolescence as an endpoint, rather than a starting point, for this type of perceptual narrowing.

Summary

Research on social cognition in the area of theory-of-mind suggests ongoing and deepening specialization, with little evidence for abrupt developmental discontinuities during the transition to adolescence. Face processing studies suggest the possibility of an puberty-related transition from caregivers and toward understanding complex socioemotional expressions in peers, but adolescence may also be a period in which there is a loss of plasticity. Across both domains, the role of experience during this transition might be tested more explicitly to connect sensitive period theories.

Calibration to Social Environments

Mathematical Modeling Approaches

Mathematical modeling approaches that explore environmental pressures on sensitive period evolution may improve our understanding of what patterns of plasticity may be adaptive and theoretically more likely under certain conditions than others. This line of research considers that, from an evolutionary perspective, sensitive periods evolved because developmental systems with differing abilities to adapt to environmental change also differed in their evolutionary fitness (Frankenhuis & Fraley, 2017). One modeling study in this vein found that sensitivity to social information might increase "mid-ontogeny," (i.e., in middle childhood or adolescence) because information with a greater likelihood to impact reproductive fitness may be more available and reliable in conveying information about mating value toward the ages of likely reproductive capacity (Frankenhuis & Walasek, 2020).

Empirical Evidence for Calibration of Psychobiological Systems

The pubertal stress recalibration hypothesis is one line of research that considers the possibility that psychobiological systems calibrate to the environment. This hypothesis suggests that the hypothalamic-pituitary adrenal (HPA) axis adapts to the environment during pubertal development (DePasquale et al., 2018). Recent work found that as children adopted following early-life institutionalization progress through puberty, their previously blunted cortisol stress reactivity is restored to patterns more typically seen in non-institutionalized youth (cross-sectional analysis in DePasquale et al., 2018; longitudinal analysis in Gunnar et al., 2019). A study employing a similar design found that as previously institutionalized children undergo adrenal development, they recover

hormone-coupling patterns (positive cortisol-DHEA coupling) that typically follow stressors in non-adopted youth (Howland et al., 2020).

There is also evidence that the caregiving environment may sculpt the development of the HPA axis in non-adopted adolescents. This additional evidence is important because species-atypical caregiving may itself influence sensitive period timing and previously institutionalized youth may not be a representative population. One study found that parent-child synchrony in cortisol hormone levels extends into adolescence (Saxbe et al, 2014) and is moderated by the amount of time spent together (Papp et al., 2009). Another study of bicultural Mexican-American youth suggested that cultural orientation to either Mexican and/or Anglo cultures shape patterns of cortisol responsivity to acute stressors (Gonzales et al., 2018).

Outside of the HPA axis and adolescent stress responses, caregiving and cultural environments may sculpt the development of cognitive systems more broadly. In one study of post-institutionalized youth, caregiving quality impacted reward processing, executive functioning, and psychopathology during adolescence (Colich et al., 2020). Importantly, the latter two effects of caregiving quality were stronger when assessed during adolescence (ages 12 and 16) than at age 8, which suggests an adolescent-specific effect.

Acculturation following immigration might provide an important model for studying plasticity and sensitive periods (Qu et al., 2021). A previous study found that immigrants from Hong Kong to Canada exhibited greater acculturation at younger ages of immigration (Cheung et al., 2010), suggesting that childhood may be a sensitive period for acculturation; however, this finding was not replicated in a separate sample of

immigrants to the United States by the same research group (Chudek et al., 2015). There are few neuroscience studies of acculturation. One set of studies examined differences in gray matter volume between Asian-born East Asians residing in the United States who varied by whether they carried gene variants associated with greater sensitivity to cultural influences (allele variants of the dopamine-4 receptor gene). East Asians who carried these variants exhibited TPJ (Kitayama et al., 2020) and OFC (Yu et al., 2019) gray matter volumes that were more similar to Americans of European descent who had been raised in the United States. For the OFC only, East Asian participants' OFC volumes only were related to the number of years spent in the United States (Yu et al., 2019). Although these studies did not specifically target adolescents, they recruited young adult East Asians that had spent less than a decade residing in the United States, making it possible that acculturation occurring during adolescence might explain the pattern of results (although this is a weak form of evidence for developmental specificity).

Summary

Mathematical modeling approaches suggest that it might be evolutionarily advantageous for adolescents to calibrate to their environments, and empirical studies point to specific psychobiological systems in which this might be the case. These empirical studies implicate the quality of the adolescent caregiving environment in biopsychosocial and cognitive development. Such studies have tended to use broad environmental indices such as, for example, the quality or context of caregiving, or length of time spent immersed in another culture. As these may be related to many aspects of the social environment, it may not be clear as to which aspects of the environment or culture are driving developmental change.

Discussion

Here, we discuss how the studies reviewed contribute to our understanding of adolescence as a potential sensitive period for sociocultural learning. We address progress and gaps in terms of developmental and domain specificity, as well as in specifically relating experience to sociocultural development.

Progress and Gaps in Understanding Developmental Specificity

A majority of the studies reviewed were cross-sectional and/or used adolescent-only samples. Although such work can be more or less consistent with sensitive period accounts of adolescence, it remains difficult to conclusively establish evidence for sensitive periods hypotheses without comparisons across wide age ranges of children, adolescents, and adults (Blakemore & Mills, 2014; Fuhrmann, Knoll, Blakemore, 2015).

Despite this ongoing challenge, there have also been several promising developments in the field. For example, team science efforts involving large replication efforts with longitudinal samples across wide age ranges have paved the way toward deeper and more robust understandings of developmental trends (e.g., Mills et al., 2016; Tamnes et al., 2017). Targeted study designs with small to medium-sized samples optimized to capture pubertal processes in adolescence have also been informative. For example, face perception studies comparing children and adults to same-age adolescents early and late in their pubertal development strongly implicate puberty in perceptual specialization to peer versus adult faces (Picci & Scherf, 2016) and to understanding complex social emotional facial expressions (Motta-Mena & Scherf, 2017). This strategy circumvented common challenges in disentangling the effects of puberty and age (Herting & Sowell, 2017). The area of pubertal research also faces challenges pertaining

to interpreting effects across numerous physical and hormonal measures associated with puberty (see Barendse et al., preprint for an approach to resolving this difficulty).

Beyond Heightened Sensitivities: Experience as a Driver of Developmental Change

Relatively few studies specifically assess the role of experiences in driving change, which is a critical aspect of understanding sensitive periods. For example, as discussed above, contemporary research that rigorously characterizes adolescent-specific developmental trends has identified replicable patterns of global and regional changes in brain structure. While these studies suggest that adolescence is a period of significant neural remodeling, they do not identify how concurrent experience drives this change. Recent twin studies suggest that genetics explain sizable variation in measures of brain structure, including in the speed of changes in cortical thickness and grey matter density during adolescence (Brouwer et al., 2021), and in structural covariance indices in adults (reflecting correlations between structural metrics across the brain; Valk et al., 2021). Another study examining the spatial distribution of genetic profiles developed from post-mortem tissue also found a substantial genetic contribution to patterns of structural development during adolescence (Whitaker et al., 2016). Early life experience is associated with changes in certain brain structures during adolescence (e.g., Hodel et al., 2015), suggesting that cascading epigenetic, molecular, and circuit-level effects due to experiences earlier in life may causally impact adolescent structural brain development. However, a few studies have attributed regional patterns of gray matter density to experience in childhood (specifically, in the TPJ in development from 7-9 years of age; van der Meulen et al., 2020) and in early adolescence (Brouwer et al., 2015). Although

this example focuses on structural brain development, similar critiques apply to our understanding of functional neurodevelopment.

However, evidence for sensitive periods does not require that all neural changes occurring during adolescence are driven by concurrent experiences. Relationships between genes, experience, and behavior over development are complex, particularly when considering that sensitive periods themselves may reflect the unfolding of genetic programs for acquiring experience. As just one example, a pair of studies reviewed earlier suggest that certain genetic variants heighten the influence of the cultural environment on structural brain development (Kitayama et al., 2020; Yu et al., 2019). As one way of resolving this tension, a translationally-relevant approach might strive to consider the degree to which experiences occurring during adolescence, relative to other factors, tend to drive neural changes in a manner that is relevant to specific aspects of cognition and/or behaviors for a target population and developmental context.

Where's the "Cultural" in "Sociocultural Processing"?

One major limitation in our understanding of adolescence as a sensitive period for sociocultural processing has to do with the relative paucity of studies addressing culture. Notably, an estimated 99% of samples from publications in the field of adolescent developmental neuroscience are from Western countries, reflecting a serious blow to claims of representativeness (Qu et al., 2021) and quite possibly biasing estimates from the literature reviewed here. This reflects a broader issue whereby the majority of human psychology and neuroscience research has taken place among Western, educated, industrialized, rich and democratic (WEIRD) societies and samples (Henrich et al., 2010). In short, it is not an understatement to say that discussions of the claim that

adolescence is a sensitive period for sociocultural learning within developmental cognitive neuroscience have often focused on the "social" and less so the "cultural." A nascent area of developmental cultural neuroscience examines the processes whereby culture shapes adolescent neurodevelopment (for a review, see Qu et al., 2021), and several studies pertaining to culture and acculturation were integrated throughout, when appropriate. Questions regarding sensitive periods fundamentally reflect the interplay between the environment and developmental mechanisms, such that approaches integrating culture might be valuable for understanding not only generalization, but the nature of plasticity itself. Therefore, it is not only ethically critical but also scientifically rigorous to consider environmental variability from wider, cross-cultural and anthropological lenses.

Conclusions

This review identified areas of progress in understanding adolescence as a sensitive period for sociocultural processing, including more robust characterizations of behavioral and neurodevelopmental trends in some domains, as well as greater integration of such trends with study designs that might elucidate the roles of experience and timing in explaining developmental change. A number of weaknesses continue to impede theory-building, including a number of studies in the field that are not necessarily designed to assess whether effects are developmentally specific to adolescence, specific to the social domain, or driven by experience. Furthermore, while research identifying developmental trends of heightened sensitivities may suggest the plausibility of sensitive periods, there are ambiguities as to how heightened sensitivities specifically support the

development of sociocultural processing in a manner that is sensitive to developmental timing.

CHAPTER II

DEVELOPMENTAL TRAJECTORIES OF FRONTOSTRIATAL CONNECTIVITY ACROSS TWO FUNCTIONAL STATES

Introduction

The quality of social relationships influences mortality to a degree comparable to well-established risk factors such as smoking, excessive alcohol consumption, and obesity (Holt-Lunstad et al., 2010). Given this comparability, it has been argued that improving social relationships should be a public health priority (Holt-Lunstad et al., 2017). Social connections may be particularly important during adolescence, a phase of life that may be a sensitive period for sociocultural processing (Blakemore & Mills, 2014). Consistent with this theory, aspects of close social relationships in adolescence are related to physical (Allen et al., 2015) and mental (Narr et al., 2019) health over a decade later, for reasons not entirely known.

The research presented in these three empirical chapters is centrally engaged with the question as to how adolescent girls' social relationships might become "neurally embedded" in a manner that influences their long-term brain functioning. In this first empirical chapter, we aimed to characterize developmental trajectories of functional connectivity within a neural circuit that may be sensitive to social experience in adolescence by age and pubertal development.

Significance of the Nucleus Accumbens and Ventromedial Prefrontal Cortex

We focus on developmental trajectories of functional connectivity between two critical nodes of a mesocorticolimbic circuit for reward, value, and incentive processing:

the nucleus accumbens (NAcc) and the ventromedial prefrontal cortex (vmPFC). Research in animal models suggests that these regions are among several that are sensitive to the effects of adolescent social experience. For example, isolating rats during their peri-adolescent period results in altered fear learning and increased dopaminergic receptor expression in both the NAcc and in medial prefrontal regions, relative to group-reared rats (Han et al., 2012; Shao et al., 2009). Due to ethical issues, empirical research employing similarly extended manipulations of social isolation cannot be directly replicated in humans. However, observational studies can inform our understanding of how and when this circuitry develops, with longitudinal studies potentially informing our understanding of what drives its development.

The NAcc is a ventral subregion within the ventral striatum that is functionally implicated in processing value and emotion across different states of valence. Studies suggest that the NAcc is engaged when processing rewards and in positive prediction error (see Secousse et al., 2013 for a meta-analysis), but also during the regulation of negative affect (Wager et al., 2008) and in prediction error associated with aversive learning (e.g., Delgado et al., 2008). Furthermore, meta-analyses suggest its involvement with emotion processing across valence (Lindquist et al., 2016). On the other hand, the vmPFC is a fairly large swath of cortex encompassing several anatomically-defined regions. It is broadly thought to process and integrate value in a manner that supports decision-making. Prior research has found that blood-oxygen-level-dependent (BOLD) signal from functional magnetic resonance imaging (fMRI) in both the NAcc and vmPFC track with reward value across social and non-social tasks (Haber & Behrens, 2014;

Sescousse et al., 2013) and are elicited during learning from social exchanges (Jones et al., 2011).

Functional coordination between the NAcc and vmPFC regions is anchored in both direct and indirect anatomical connections. In particular, the functionally-defined anterior vmPFC subregion examined in this study densely innervates a narrow portion of the ventral striatum including the shell of the NAcc (Haber et al., 2016). Because of its structural and functional connections with both limbic (e.g., NAcc) and higher-order social cognitive regions, the vmPFC is well-positioned to facilitate the integration of value-related and social cognitive information. The NAcc receives information via direct cortical projections from various subregions of the vmPFC, as well as other subcortical regions including the amygdala, hippocampus, and ventral tegmental area (Haber & Behrens, 2014). However, the NAcc also provides indirect feedback to ventral prefrontal regions via intermediaries (Haber & Knutson, 2010).

Summary

Changes to adolescents' social motivations and social learning are central to conceptualizations of adolescence as a sensitive period for sociocultural processing. Evidence from animal models suggests that the NAcc and vmPFC are key nodes of mesocorticolimbic circuit that support social motivation and learning, and that these regions may be sensitive to social experience. In coordination with other brain regions, the vmPFC and NAcc support the integration of value-related processing and the processing of social information. Understanding patterns of developmental change in NAcc and vmPFC functioning are foundational to understanding adolescent socio-

affective neurodevelopment and may shed insight into the nature of adolescent sensitive periods for social development.

Frontostriatal Connectivity Two Ways: Resting-State and Task-Based Signal

Resting-state and task-based functional connectivity are two different measures that address the degree of cross talk between neural regions. Both measures index the functional organization of the brain through scans taken via MRI, and are important complements to univariate measures of BOLD signal that primarily characterize functional localization/specialization rather than integration (Friston, 2011). Resting-state functional connectivity captures the structure of low-frequency correlations in BOLD signal during a scan with no stimulus presentation (Fox et al., 2005; Gordon et al., 2016; Greicius et al., 2003; Power et al., 2014; Spronk et al., 2018). In contrast, task-based functional connectivity assesses the coordination of different neural regions in a manner that is attuned to the nuances of task condition and context (Cisler et al., 2014). Intriguingly, while these two types of functional connectivity typically differ in both the timescales they operate on and in the mental states that they evoke, brain mapping often finds that they converge on the same regions spatially (Bolt et al., 2018).

With regard to our circuit of interest, studies employing resting-state functional connectivity suggest that linear negative correlations during rest become stronger with both age and testosterone levels (Fareri et al., 2015; van Duijvenvoorde et al., 2014; Parr et al., preprint). Prior studies have not been conclusive in identifying whether task-based functional connectivity between the vmPFC and ventral striatum (of which the NAcc is a part of) is increasingly coordinated across adolescence; they have found increasing connectivity with age (Christakou et al., 2011; van den Bos et al., 2012), decreasing

connectivity with age (Parr et al., preprint), or no differences with age (van Duijvenvoorde et al., 2014).

Summary

Examining resting-state functional connectivity provides opportunities to consider how the NAcc and vmPFC change in their coordination of putatively intrinsic signal, while examining task-based functional connectivity provides opportunities to consider how these regions change in their coordination to facilitate self-disclosure. Task-based connectivity of this circuit has previously primarily been examined in learning and/or decision-making tasks. Considerations of the developmental trajectories of both types of functional connectivity are a contribution to the literature and lay the groundwork for understanding potential developmental mechanisms of change (see Chapter 3).

Adolescent Self-Disclosure

This study examines task-based functional connectivity while adolescents engage in decisions to self-disclose to a close (and ideally, best) friend. Self-disclosure is the sharing of personal thoughts and feelings, and reciprocity in self-disclosure plays a role in the formation and maintenance of close social bonds (as in the interpersonal process model; Reis & Shaver, 1988; Kanter et al., 2020). Studies using self-report measures suggest an increased tendency to self-disclosure to peers in early adolescence (Valkenburg et al., 2011). Changes in the targets of self-disclosure may reflect social reorientations toward peers and romantic partners (Vijayakumar & Pfeifer, 2020) that are characteristic of this developmental period (Nelson et al., 2005; Nelson et al., 2016).

There are several parallels between the adolescent self-disclosure paradigm employed in this study and reward- or value-guided decision-making tasks in which

NAcc-vmPFC connectivity has previously been examined. First, both types of paradigms elicit value-related processes. Researchers have been able to quantify the intrinsic value of self-disclosure in adults by adapting monetary choice tasks (Tamir & Mitchell, 2012). Like adults, adolescents will, on average, forgo monetary incentives for opportunities to self-disclose to a close friend (Vijayakumar et al., 2020). Cross-sectional research with this paradigm suggests that the intrinsic value of self-disclosure is indeed in flux during adolescence, with mid-adolescents valuing opportunities to self-disclose to unfamiliar peers as compared to parents and friends (Mobasser et al., preprint).

Prior research with this paradigm also suggests that self-disclosure decisions, like other reward- and value-guided decision-making tasks, elicit changes in univariate signal across the vmPFC and NAcc (Vijayakumar et al., 2020). Furthermore, neural signal within these regions was found to be sensitive to adolescents' preferences to disclose on the task itself, as well as self-reported friendship quality and feelings of being supported. Adolescent self-disclosure also engages social cognitive regions, which may be because disclosure decisions involve weighing the value of hypothetical choices in complex social contexts, for example, against the risks of embarrassment, or in consideration of a friend's beliefs.

Summary

Adolescent self-disclosure is a developmentally relevant process that, like other reward- and value-guided decision-making tasks, elicits signal in the NAcc and vmPFC. Empirical work suggests that behavioral and neural indices of self-disclosure during a laboratory task can capture the processing of value and social cognitive information in a manner that reflects tendencies toward intimacy and affiliation within close friendships.

Considering functional connectivity during this task captures vmPFC-NAcc coordination to support complex, affectively engaging, and ecologically meaningful social decision-making in the context of a real-world friendship.

Sex and/or Gender-Related Differences in Developmental Processes

The present study solely recruited adolescent girls, as both sex and gender may influence relevant aspects of social and neurobiological maturation. With regard to relevant social behaviors, trajectories of increasing self-disclosure to peers tend to occur earlier in girls than in boys (Valkenburg et al., 2011), and adolescent girls' intrinsic valuation of self-disclosure tends to be higher than that of same-age boys (Mobasser et al., preprint). Associations between the value of self-disclosure to unfamiliar peers and self-reported engagement in health-risking behaviors differed by gender (with effects seen in boys only; Mobasser et al., preprint). Sex-related mechanisms may differentially drive relevant aspects of neurodevelopment, as structural measures of both nucleus accumbens volume (Herting et al., 2018) and the mPFC (Mills et al., 2014) show unique trajectories across adolescence by sex. However, pubertal sex hormones may also have similar effects across sex; a study by Fareri and colleagues (2015) found that levels of testosterone mediated negative associations between age and mPFC-ventral striatum functional connectivity across both males and females.

By limiting our focus to adolescent girls, we increase our power to examine sex-specific pubertal effects. Puberty is composed of multiple and distinct (yet temporally co-occurring) hormonal processes—the adrenal, gonadal, and growth axes—that each propel specific changes in physical development. Puberty has been theorized to drive sex-specific neurodevelopmental changes via both organizational (permanent changes to

neural structure) and activational (temporary changes in neural activity) effects (Sisk & Foster, 2004). Sex-specific changes related to the effects of gonadal hormones on prefrontal development (e.g., Piekarski et al., 2017; Schultz & Sisk, 2016) may impact vmPFC-NAcc connectivity. Measures of puberty may capture variability in maturation that is not detected by measures of chronological age, particularly early in adolescence.

Summary

While sex and gender are not strictly binary (Ainsworth, 2015), they reflect meaningful variation in the unfolding of neurodevelopment and social relationships in adolescence. To reduce sex and gender-related heterogeneity in social behaviors, neurodevelopment, hormones, and mental health problems (covered more extensively in Chapter 4), the present study targeted recruitment toward girls.

Goals of the Current Analysis

Changes to NAcc and vmPFC connectivity are proposed to support social learning during adolescence and may be sensitive to social experience. However, few studies have characterized changes to functional connectivity between the NAcc and vmPFC using longitudinal data and/or in consideration of aspects of maturation other than chronological age (to the best of our knowledge, the following four published studies have done one or both: Fareri et al., 2015; Porter et al., 2015; van Duijvenvoorde et al., 2014, van Duijvenvoorde et al., 2019). Presently, the field lacks a clear understanding of how both resting-state and task-based functional connectivity between the NAcc and vmPFC change across development as measured by age and pubertal development. Therefore, the current analyses use longitudinal data to characterize developmental trajectories of both resting-state and self-disclosure-elicited functional

connectivity between the NAcc and a sub-region of the vmPFC in adolescent girls. As the vmPFC is a large area, we consider NAcc connectivity with a functionally-defined anterior subregion identified from meta-analyses as being elicited widely in task-based studies of social cognitive and socio-affective processes *and* in coordination with other "social brain" regions during rest (Alcalá-López et al., 2018; see next section).

Methods

Data used in these analyses were from the Transitions in Adolescent Girls Study. A complete description of sample details and study procedures can be found in a protocol paper (Barendse et al., 2020).

Participants

This study examined three time points of data (T1-T3) from an ongoing prospective longitudinal study of adolescents (initial ages 10.0-13.0 years, 18 mos. between time points). Study inclusion criteria at T1 were i) fluency in English, ii) no developmental disabilities (except attention disorders), iii) no diagnoses of psychotic disorders, iv) no MRI contraindications, and v) a lower age limit of 10.0 years and an upper age limit of 13.0 years at study entry. By including adolescents between 10-16 years of age (i.e., covering all pubertal stages as well as the peak of pubertal change for females), this study was designed to support inferences about changes due to pubertal development. While recruitment targeted girls, 1.7% of sample identified as non-binary and was confirmed to have been assigned female at birth at baseline. Because of this, I use the term "adolescent(s)" throughout, except where referring to putatively sex or gender-specific processes.

The racial/ethnic distribution of the sample at T1 was 66.1% non-Hispanic/Latinx white, 8.6% white Hispanic/Latinx, 0.6% Asian and Hispanic/Latinx, 0.6% African-American and Hispanic/Latinx, 2.9% not further specified Hispanic/Latinx, 0.6% American Indian/Alaskan Native, 0.6% Asian, 0.6% African American, and 19.5% multiracial. The sample is predominantly non-Hispanic white but also exhibits higher racial and ethnic diversity relative to the overall population of Lane County, Oregon. At T1, 1.7% of participating parents/guardians had less than high school education, 13.8% had completed high school or GED, 8.2% had done some college but without a degree, 5.2% had completed trade, technical or vocational training, 18.4% had an associate's degree, 25.3% had a bachelor's degree, 23.0% had a master's, professional or doctoral degree, and 3.4% did not report their education level.

Recruitment

Participants were largely recruited through letters distributed by schools, and letters were sent to families with children in grades 5 or 6 that were registered as female by the school in the greater Eugene and Springfield area of Lane County, Oregon, USA. We additionally recruited from secure databases of people who registered their interest in our lab's or department's research, recruitment flyers posted around the community or disseminated at community events, and through snow-balling efforts.

Study Retention and Impact of Covid-19

The second time point of the study had 93% retention. As a result of the covid-19 pandemic, T3 data collection was suspended in March 2020 after the first 93 participants. Data collection resumed in November 2020, but only data from sessions prior to the suspension of data collection were included in these analyses. This was out of concern

that neurodevelopmental processes of interest might be sensitive to pandemic-related social deprivation and stress.

Sample Size Across Time Points

The sample size of this analysis was determined by the parent grant of this study, which aimed to enroll 170 adolescents based on Monte Carlo simulations identifying an 80% chance to detect standardized direct effects of >.235 and moderating effects of >.15 with 10% attrition per wave. Data collection was terminated after slightly exceeding the original enrollment target due to budget and time constraints.

Initially, 189 participants were recruited, but 7 failed to meet inclusion/exclusion criteria and 8 withdrew before completing assessments, leading to 174 participants at T1. Of these 174 participants, 10 elected not to participate in the MRI portion of the protocol. This left a total of 164 participants with processed MRI data at T1.

At T2, 12 participants were withdrawn from the study (4 were unresponsive, 6 elected to withdraw, and 2 indicated that they had moved away from the area), 17 participants elected not to participate in the MRI portion of the study, and 1 participant elected not to participate in T2 but did not withdraw. Additionally, 2 participants' MRI scans were excluded due to severe image quality issues (orthodontia-related artifacts). This left a total of 142 participants with processed MRI data at T2.

At T3, 93 participants completed a second session prior to pausing data collection due to covid-19. Of these, 16 elected not to participate in the MRI portion of the protocol, and 1 elected not to participate in the MRI portion of the protocol after beginning the scan. This left a total of 76 participants with processed MRI data at T3.

Protocol

Following phone screening for eligibility, participants were invited to the University of Oregon for two sessions spaced roughly 1 month apart. At the first session, a parent or guardian provided written informed consent, and children provided written assent. At this first session, participants completed a structured diagnostic interview, questionnaires, and received instructions for saliva sample collection at home. At the second session, participants completed an MRI scan, remaining questionnaires, a hair sample, a video task, and anthropometric measures.

Measures

Maturation

Each participant's chronological age at the time of the scan was calculated. To additionally assess pubertal development, participants completed the Pubertal Development Scale (Petersen et al., 1988), which consisted of text-based questions that assess height, body hair and skin changes, as well as breast development and menarche. Participants also indicated which of five line drawings best reflected their current development; line drawings were based on Tanner staging, with one rating for breast development, and a separate one for pubic development (Morris & Udry, 1980).

Scores on the PDS were converted into a 1-5 rating that is intended to be more comparable with Tanner stages (as described in Shirtcliff et al., 2009) and then averaged with self-ratings from the line drawings, resulting in a composite pubertal development score ranging from 1 (prepubertal) to 5 (postpubertal). Analyses of developmental trends treated pubertal stage as an ordinal variable with five equally spaced levels; participants

were grouped into those whose composite scores were between 1-1.8 (approximate stage 1), 1.8-2.6 (stage 2), 2.6-3.4 (stage 3), 3.4-4.2 (stage 4), and 4.2-5 (stage 5).

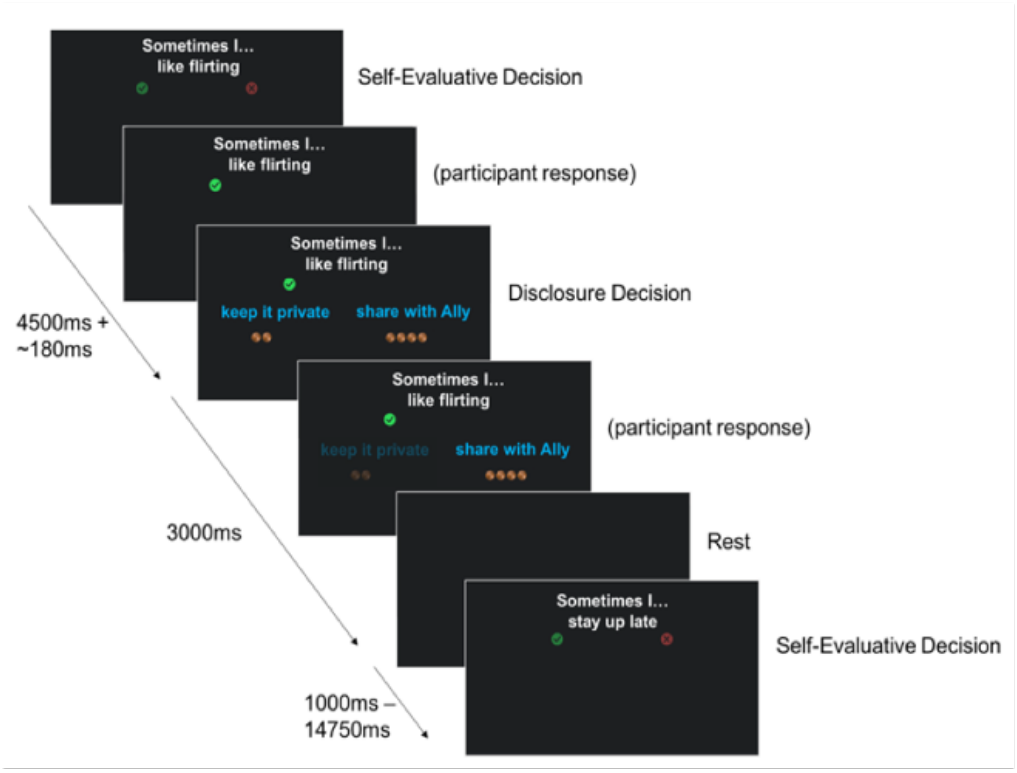
Task-Based Functional Connectivity

Self-Disclosure Task. In each trial of the Self-Disclosure Task, adolescents were presented with either an intimate (e.g. "Sometimes I worry about kissing") or superficial (e.g. "Sometimes I carry chapstick") statement. Adolescents first reported whether or not the statement describes them. They next decided whether or not to share this information with a close friend chosen prior to the scan. They were encouraged to choose a best friend of the same sex and similar-age, when possible, but some chose to share with a parent, sibling, partner, or opposite-sex friend. The "keep private" or "share with friend" options were displayed with two to four coins worth one cent ($0.01) each. Participants complete 82 trials in two runs. Task presentation was optimized to maximize contrast detection between statement depth (intimate vs. superficial) and disclosure value. The self-evaluative phase lasted 4.5 s and was separated from the disclosure phase by 0.02–0.70 s (jittered). Trials were separated by presentation of a blank screen of variable length (1-15 s). In total, each of the two runs lasted 8 minutes.

To improve the task's ecological validity, participants agreed beforehand to share one of the responses with their chosen friend in real life. Following the MRI scan, they were presented four statement options (a randomly chosen subset of items including both superficial and intimate items) from among the statements they chose to share within the task, and were asked to disclose one of the statements of their choice. Participants were also informed that they would receive the sum of all coins from their selections, and received up to a few extra dollars for completing this task. (For more details about this

Figure 2.1

Self Disclosure Task Paradigm



Note. Figure reproduced from publications by Barendse and colleagues (2020) and Vijayakumar and colleagues (2020).

task, see Vijayakumar et al., 2020).

Data Acquisition. Data were acquired on a 3T Siemens Skyra MRI scanner at the Lewis Center for Neuroimaging at the University of Oregon. High-resolution T1-weighted structural images were collected with the MP-RAGE sequence (TE = 3.41 ms, TR = 2500 ms, flip angle = 7°, 1.0 mm slice thickness, FOV = 256 mm, 176 slices, duration = 5:59 min:sec). Two self-disclosure task functional runs of T2*-weighted BOLD-EPI images were acquired with a gradient echo sequence (TE = 25 ms, TR = 2000 ms, flip angle = 90°, 2.0 mm slice thickness, FOV = 208mm, 72 slices, multiband acceleration factor = 3, in-plane factor = 2, duration = 2 x 8 mins). To correct for local

magnetic field inhomogeneities, a field map was also collected (TE = 4.37 ms, TR = 639.0 ms, flip angle = 60°, 2.0 mm slice thickness, FOV = 208 mm, 72 slices).

Data Pre-processing. To facilitate reproducibility, both task and resting-state data were organized into the Brain Imaging Data Structure (BIDS; http://bids.neuroimaging.io/), an emerging standard that facilitates the use of fully-contained analysis pipelines called BIDS Apps (Gorgolewski et al., 2017). Data were processed using the fmriprep BIDS App (v20.2.1; https://github.com/poldracklab/fmriprep). The authors of fMRIPrep strongly recommend the verbatim use of the following language to describe the pre-processing pipeline (https://fmriprep.org/en/latest/citing.html):

> Results included in this manuscript come from preprocessing performed using FMRIPREP version latest (Esteban et al., 2018; Esteban et al., 2020, RRID:SCR_016216), a Nipype (Gorgolewski et al., 2011; Gorgolewski et al., 2017, RRID:SCR_002502) based tool. Each T1w (T1-weighted) volume was corrected for INU (intensity non-uniformity) using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using antsBrainExtraction.sh v2.1.0 (using the OASIS template). Brain surfaces were reconstructed using recon-all from FreeSurfer v6.0.1 (Dalet et al., 1999; RRID:SCR_001847), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (Klein et al., 2017; RRID:SCR_002438). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c

(Fonov et al., 2009; RRID:SCR_008796) was performed through nonlinear registration with the antsRegistration tool of ANTs v2.1.0 (Avants et al., 2008; RRID:SCR_004757), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (Zhang et al., 2001) (FSL v5.0.9, RRID:SCR_002823).

Functional data was motion corrected using mcflirt (FSL v5.0.9; Jenkinson et al, 2002). Distortion correction was performed using an implementation of the TOPUP technique (Andersson, Skare, Ashburner, 2003) using 3dQwarp (AFNI v16.2.07 (Cox, 1996). This was followed by co-registration to the corresponding T1w using boundary-based registration (Greve et al., 2009) with six degrees of freedom, using bbregister (FreeSurfer v6.0.1). Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0) using Lanczos interpolation.

Physiological noise regressors were extracted applying CompCor (Behzadi et al., 2007). Principal components were estimated for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). A mask to exclude signal with cortical origin was obtained by eroding the brain mask, ensuring it only contained subcortical structures. Six tCompCor components were then calculated including only the top 5% variable voxels within that subcortical mask. For aCompCor, six components were calculated within the intersection of the subcortical mask and the union of CSF and WM masks calculated in T1w space, after their projection

to the native space of each functional run. Framewise displacement (Power et al., 2013) was calculated for each functional run using the implementation of Nipype.

Many internal operations of FMRIPREP use Nilearn (Abraham et al., 2014; RRID:SCR_001362), principally within the BOLD-processing workflow. For more details of the pipeline see https://fmriprep.readthedocs.io/en/latest/workflows.html.

Longitudinal images were processed separately within each time point, and pipeline outputs used in subsequent analyses had been normalized to the non-linear, asymmetrical MNI 152 2009 atlas (MNI152NLin2009cAsym).

Beta-Series Analysis. Task data that had been normalized to the MNI atlas were further smoothed using a 2 mm Gaussian kernel in Statistical Parametric Mapping software (SPM12). A fairly small smoothing kernel was used because results averaged across voxels within regions. We then used beta-series correlation methods to obtain estimates of task-based functional connectivity. For these analyses, each trial of the Self-Disclosure Task (collapsed across the self-evaluation and disclosure phases) was convolved with a hemodynamic response function and modeled as a separate regressor.

First-Level Models. Models also included regressors for four motion parameters (Euclidean distance/rotation and their first derivatives), as well as a regressor that flagged volumes for extreme motion ("trash volumes", based on motion estimates and signal intensity; Cosme, Flournoy, & Vijayakumar, 2018). Runs with greater than 20% of volumes coded as trash were excluded from analyses (T1: 33 runs; T2 18 runs, T3 6 runs). Runs with 15-20% of trash volumes (T1: 15 runs; T2: 6 runs, T3: 1 run) were visually inspected and trash volumes were manually identified. Following manual

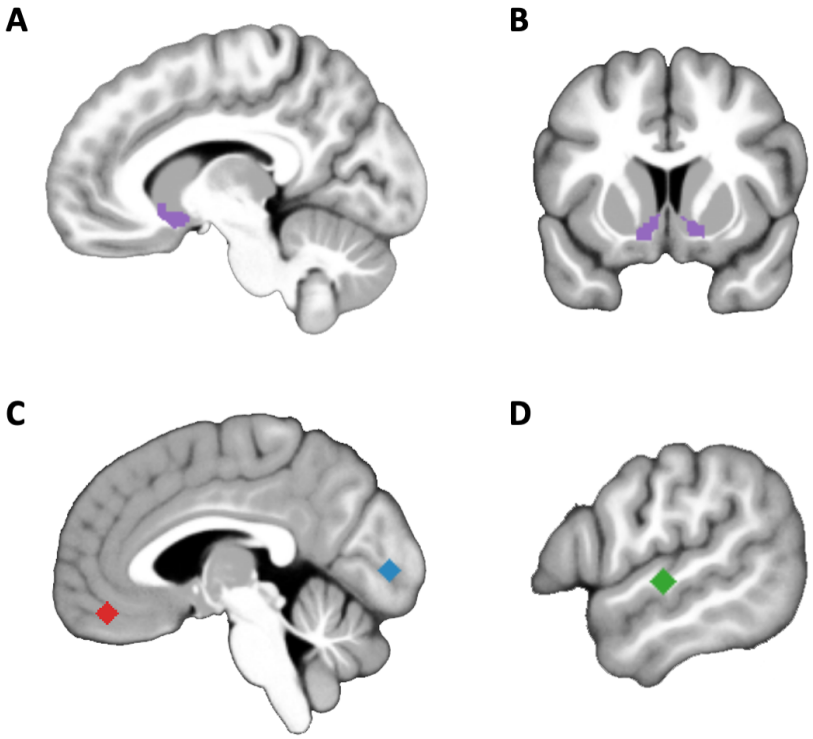
inspection, if the percentage of trash volumes exceeded 20%, then the run was excluded (T1: 2 runs; T2: 1 run; T3: no runs); otherwise, the run was included and regressors for manually identified trash volumes were used in place of the automated ones. This followed procedures in Vijayakumar et al., 2020 with one major difference: here, thresholds and manual quality assessment were per *run* rather than per *participant,* as this was a trial-level analysis where participants with only a single run of available data were still included.

Regions-of-Interest and Control Regions. For each trial, a spatially averaged beta-estimate was extracted for both the vmPFC and NAcc (Figure 2). The vmPFC was defined by a cluster from a meta-analysis of the social brain network identified in this meta-analysis was constrained to be a maximum of 200 contiguous voxels (https://neurovault.org/images/45339/) (Alcalá-Lopez et al., 2018). This constraint resulted in a small, irregular shape that was more narrow at the midline and extended bilaterally, yet had spatial discontinuities. Using AFNI 3dROIMaker, this region was inflated/padded by two voxels to maintain the overall structure of the region-of-interest while increasing its size and improving its continuity. The bilateral anatomical NAcc region-of-interest was defined using the Harvard-Oxford probabilistic atlas (set to a 75% probability threshold; this region was also used in Op de Macks et al., 2018).

The left primary auditory cortex and visual cortex were selected as control regions, reflecting basic sensory processes that are (visual system) and are not (auditory system) explicitly engaged in the task; both sensory systems are thought to have largely reached developmental maturity. The auditory region was a sphere with a 4 mm radius

Figure 2.2

Defining Regions Within Connection of Interest and Control Connections



Note. Panel A and B depict sagittal (x = -10) and coronal (y = 11) views of the NAcc region-of-interest (in purple). Panel C depicts the vmPFC (in red) region-of-interest and a control region in the primary visual cortex (blue; x = -2). Panel D depicts a control region in the primary auditory cortex (in green; x = -56).

around the MNI coordinates -56, -16, 0, and the visual region was a sphere with the same dimensions around the coordinates -4, -88, 4. These coordinates were visually identified as being among peak coordinates resulting from association tests across the literature of the terms “primary auditory” and “primary visual” (NeuroSynth; https://neurosynth.org/).

Calculating Beta-Series Connectivity Estimates. Trials were excluded if averaged first-level beta-parameter estimates exceeded the mean +/- 3 standard deviations for either of the two regions forming the connection-of-interest (the vmPFC or the NAcc) across runs. On average, 1.2 trials (SD = 1.1; range = 0-5 volumes) were excluded per

participant, per time point. Next, averaged beta-parameters for the vmPFC were regressed on averaged beta-parameters for the NAcc in separate models to obtain second-level beta-series connectivity estimates. This procedure was repeated to obtain estimates of NAcc connectivity with the primary auditory and primary visual control regions.

Resting State Functional Connectivity

Data Acquisition. In addition to the scans described above, participants completed a resting-state scan. Prior to this scan, they were instructed to keep their eyes closed while a fixation cross was displayed on the screen. Additionally, two resting-state functional runs of T2*-weighted BOLD-EPI images were acquired with a gradient echo sequence (TE = 32 ms, TR=780 ms, flip angle = 55°, 2.5 mm slice thickness, FOV = 210 mm, 60 slices, multiband acceleration factor = 6, duration = 2 x 5:16 min:sec). The number of volumes per run collected for the resting-state scan was increased from 270 (duration = 2 x 3.51 min:sec) to 395 late in T1/early in T2 data collection (August 2017) to increase the likelihood of obtaining sufficient high-quality resting-state data.

Data Pre-Processing. Data were processed as described above using fMRIPrep (v. 20.2.1). Only participants with >5 minutes of low-motion data (defined by a framewise displacement < 0.2 mm) were included in analyses. This pre-registered criteria sought to balance considerations that (a) resting-state functional connectivity estimates become more reliable with increasing scan length (Birn et al., 2013), and (b) that requiring too high of a threshold would increase the amount of missing data.

Data were additionally denoised using an adapted version of the 36p-spkreg pipeline (Satterthwaite et al., 2013) using xcpEngine (Ciric et al., 2019). This pipeline reduces correlations between subject motion and edge strength (an index from graph

theory suggesting connectivity with a greater number of other regions) and further reduces—but does not entirely eliminate— distance-dependent effects of motion (Ciric et al., 2017). Both the time series and the nuisance regressors were filtered using a first order Butterworth filter with a pass-band ripple of 0.5 and a stop-band ripple of 2, as well as a bandpass filter to 0.009-0.08 Hz, prior to residualization. Denoising within this pipeline included confound regression with three translational and three rotational motion parameters, their temporal derivatives, their first power, and their quadratic expansion, as well as mean white matter, mean cerebrospinal fluid, and global signal. Frames with greater than 0.2 mm framewise displacement per second were censored from the time course (> 0.256 mm displacement per frame, given the 0.78 s TR). Outputs were smoothed using a 2 mm Gaussian kernel and normalized to the non-linear, asymmetrical MNI 152 2009 atlas (MNI152NLin2009cAsym).

Deriving Indices of Resting-State Functional Connectivity. To obtain estimates of resting-state functional connectivity that were independent of participants' tendencies toward higher motion, 5 minutes of data (385 frames) were randomly sampled from the denoised and censored time course. Fisher's Z-transformed correlations between the averaged truncated time courses were calculated for each connection.

Statistical Analyses

The current analyses aimed to characterize developmental trajectories of both resting-state and self-disclosure-elicited functional connectivity between the NAcc and a sub-region of the vmPFC in adolescent girls. By using multilevel/hierarchical linear modeling with longitudinal data, this approach accounted for nesting within participants. Multilevel models were estimated using maximum likelihood methods in *lme4* (v 1.1-21)

with complete observations only, statistical comparisons were evaluated using *lmerTest* (v. 3.1-0) with the Satterthwaite approximation for degrees of freedom with multilevel models), and tables were generated using *sjPlot* (v. 2.8.8); all of these packages are in *R.*

Examining Beta-Series Estimates by Condition

In the self-disclosure task, we manipulated statement depth such that some of the items adolescents were asked about in the task were superficial statements, while other items reflected relatively more intimate and personal information. We first predicted NAcc-vmPFC beta-series connectivity estimates from statement depth, while accounting for nesting within participants using random intercepts. These analyses did not suggest that beta-series connectivity estimates differed by condition (see Results), and subsequent analyses using beta-series estimates collapsed across statement depths.

Developmental Models with Age

To assess the effects of age on both task-based and resting-state functional connectivity across early adolescence, we tested both linear ($Connectivity_{it} = \beta_{0i} + \beta_1(Age) + e_{it}$) and quadratic ($Connectivity_{it} = \beta_{0i} + \beta_1(Age) + \beta_2(Age^2) + e_{it}$) age models. Models included a random intercept per participant (β_{0i}). Model fit was assessed via both likelihood ratio tests and Akaike Information Criteria (AIC). Linear and quadratic age models were first compared to one another, and the best-fitting model of the two was compared to a null model containing random intercepts and residuals per participant.

Developmental Models with Pubertal Stage

To assess effects of puberty on both types of functional connectivity, I compared models including pubertal stage to null models using the same criteria above. As pubertal stage is an ordinal variable with five levels, models examined four polynomial contrasts

(the number of levels minus one; i.e., linear, quadratic, cubic, and quartic effects).

The pubertal composite score was derived from questionnaire measures assessing participant's perceptions of their own pubertal development. With measures of this type, it is typical for some adolescents to regress on scores of pubertal stage over time (Peterson et al,. 1988). Analyses were repeated for all participants and in sensitivity analyses that censored scores contributing to pubertal stage regression as follows: for participants whose T1 pubertal composite scores were higher than their T2 scores, T1 scores were censored. For participants whose T2 pubertal composite scores were higher than their T3 scores, T3 scores were censored. This procedure removed scores relatively earlier and later in development because prior research suggests that indices of self-perceived pubertal development are systematically biased when compared to clinician ratings such that relatively less advanced adolescents tend to overestimate their development, while more advanced adolescents tend to underestimate (Shirtcliff et al., 2009; Schlossberger et al., 1992).

Developmental Models with Both Age and Pubertal Stage

To evaluate whether age and pubertal stage independently predicted neural connectivity, age was added to each of the puberty models (if the linear age model was the better fit, then a linear term was added; if the quadratic age model was the better fit, then linear and quadratic age terms were added). Although this permitted model comparisons between puberty models and models containing both puberty and age, separate models containing puberty and age were not compared directly as these models were not nested and included slightly different participants (due to missing pubertal data).

Post-hoc analyses

Visual inspection of results suggested that the quartic effect of pubertal development on task-based beta-series connectivity was driven by a particular pubertal stage transition. To investigate this possibility, post-hoc statistical comparisons were conducted with custom contrasts using the emmeans (v 1.4) package in R.

Results

Participant Inclusion

See Table 2.1 for a summary of participant inclusion across task and rest modalities.

Self-Disclosure Task

The self-disclosure task has two runs. At T1, 9 participants did not complete either run (2 had technical issues, 2 had vision impairments that could not be corrected with available MRI-compatible glasses, and 5 ended the protocol early by participant or researcher choice). Another 11 participants completed a single run of the task (2 had technical issues, 1 did not complete the first run of the task correctly, and 8 ended the scan early by participant or researcher choice). An additional participant completed the second run of the task twice (for a total of three runs), but was considered as having completed only the first run due to a lack of documentation about which repetition to retain. Motion contamination is a major concern in neuroimaging analyses. Runs of the task were excluded from analyses if >20% of volumes exhibited motion artifacts (see Methods for more information on how artifacts were identified). Of the 143 participants with two runs of data, 11 participants were excluded because both runs exceeded the

motion threshold, while another 20 were included with only a single run of data that had not exceeded the threshold. Of the 12 participants with a single run of task data, 4 were excluded due to exceeding the motion threshold. This left a total of 140 of 164 participants with task-based functional connectivity estimates: 112 whose estimates were calculated from both runs of data and 28 whose estimates were calculated from a single run only.

At T2, 9 participants did not complete either run of the task (4 had technical issues and 5 ended the protocol early by participant or researcher choice). Another 7 completed only a single run of the task (2 did not complete the first run of the task correctly and 5 ended the scan early due to participant or researcher choice). Of the 126 participants with two runs of data, 5 were excluded because both runs exceeded the motion threshold, 1 was excluded due to reported sleepiness, and 10 were included with only a single run of data (of these, 9 exceeded the motion threshold and 1 was removed due to visual inspection revealing that the field map was not successfully applied to one of the runs only). Of the 7 participants who completed a single run of the task, 2 were excluded due to motion. This left a total of 125 of 142 participants with task-based functional connectivity estimates: 110 whose estimates were calculated from both runs of data and 15 whose estimates were calculated from a single run only.

At T3, 2 participants did not complete either run of the task (1 had technical errors and 1 elected to end the protocol early). Another 2 only completed a single run of the task. Of the 72 participants with two runs of data, 2 were excluded because both runs exceeded the motion threshold and 2 were included with only a single run of data that had not exceeded the threshold. Of the 2 participants who initially completed only a single

run, 1 was excluded due to exceeding the motion threshold. This left a total of 71 of 76 participants with task-based functional connectivity estimates: 68 whose estimates were calculated from both runs of data and 3 whose estimates were calculated from a single run only.

Resting-State Functional Connectivity. At each time point, participants with less than five minutes of data not exceeding a motion threshold of 0.2 mm framewise displacement were excluded from analyses. Substantially more resting-state scans were excluded from T1 in large part because the length of the run was changed from 3.51 to 5.14 minutes per run (there were two runs in total) partway through the longitudinal study to increase the likelihood of obtaining sufficient high-quality data. Before implementing this change, 137 participants at T1 and four participants at T2 underwent the protocol with shorter resting-state scans.

At T1, 3 participants only completed a single run of the two resting state scans, while a fourth participant had one run excluded because they fell asleep. After applying motion thresholding, 52 participants were excluded on the basis of not having sufficient resting-state data. This left 112 of 164 participants with resting state data at T1.

At T2, neither run of resting state data was collected for 2 participants, and 2 participants skipped a single run (one had a technical issue, and for the other the researcher opted to end the protocol early). After applying motion thresholding, 10 participants were excluded. An additional participant was excluded for falling asleep across both runs. This left 128 of 142 participants with resting state data at T2.

At T3, neither run of resting state data was collected for 2 participants. After applying motion thresholding, 5 participants were excluded. This left 69 of 76 participants with resting state data at T3.

Descriptive Statistics

Functional Connectivity

Examining descriptive statistics (Table 2.1) for each time point suggested that mean task-based connectivity was higher for the NAcc-vmPFC and NAcc-primary visual cortex connections than for the NAcc-primary auditory cortex. Additionally, mean resting-state connectivity was higher for the NAcc-vmPFC than for either the NAcc-primary auditory or NAcc-primary visual connections.

Comparison of Task-based Functional Connectivity Across Superficial and Intimate Disclosures. The self-disclosure task was designed to include statements that differed by their depth or intimacy. Linear mixed models identified no significant fixed effect of statement depth on NAcc-vmPFC connectivity across waves, accounting for nesting by participant with a random intercept (b = 0.02, SE = 0.02, $t(506.57)$ = 0.75, p = 0.46). Therefore, subsequent analyses with task-based functional connectivity were collapsed across both superficial and intimate trials of the task. See Figure 2.3 for a comparison of NAcc-vmPFC connectivity by statement depth across waves.

Maturation

See Table 2.2 for descriptive statistics pertaining to age and pubertal stage in our sample. Age and pubertal stage (composite score) were moderately correlated across time points (T1: r = 0.50; T2: r = 0.53; T3: r = 0.36).

Table 2.1

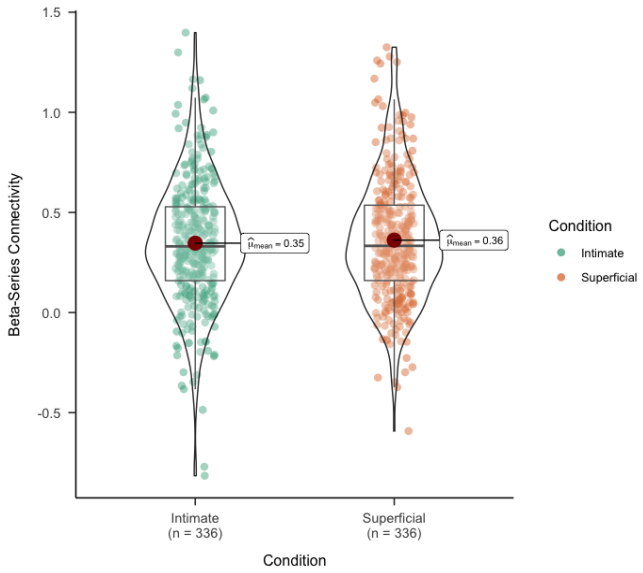
Task-Based and Resting-State Functional Connectivity Across Time Points

Modality	Connection	Metric	T1	T2	T3
Task	NAcc-vmPFC	Mean (SD)	0.38 (0.29)	0.34 (0.28)	0.33 (0.25)
	NAcc-auditory	Mean (SD)	0.13 (0.17)	0.12 (0.19)	0.07 (0.16)
	NAcc-visual	Mean (SD)	0.3 (0.29)	0.28 (0.31)	0.2 (0.25)
	All	N missing (%)	24 (15%)	17 (12%)	5 (7%)
Rest	NAcc-vmPFC	Mean (SD)	0.17 (0.24)	0.13 (0.2)	0.16 (0.17)
	NAcc-auditory	Mean (SD)	0.05 (0.17)	0.01 (0.17)	0.01 (0.15)
	NAcc-visual	Mean (SD)	0.02 (0.19)	-0.02 (0.19)	-0.03 (0.15)
	All	N missing (%)	52 (32%)	14 (10%)	7 (9%)

Note. Task-based functional connectivity values are second-level beta estimates relating averaged signal between regions across disclosure trials. Resting-state functional connectivity values are Z-scored time series correlations.

Figure 2.3

Task-Based NAcc-vmPFC Connectivity Across Statement Depth and Time



Note. Examination of task-based beta-series connectivity estimates did not identify average differences by statement depth condition.

Table 2.2

Age and Pubertal Stage Composite Scores Across Time Points

Variable	Metric	T1	T2	T3
Age	Range	10 - 131	11.5 - 151	13.2 - 161
	Mean (SD)	11.62 (0.83)	13.19 (0.84)	15.02 (0.68)
	N Missing (%)	0 (0.00)	0 (0.00)	0 (0.00)
Puberty Composite	Range	1-4.75	1.25-5	3-5
	Mean (SD)	2.95 (0.90)	3.9 (0.78)	4.53 (0.45)
	N Missing (%)	8 (0.05)	2 (0.01)	0 (0.00)

Note. The percentage of missing data was calculated out of the total number of participants with available task and/or resting-state data at each time point.

Pubertal Stage Regressions. Seven participants exhibited stage regression across waves, with 4 exhibiting a higher pubertal stage composite score at T1 compared to T2, and 3 exhibiting a higher score at T2 compared to T3. A sensitivity analysis found that censoring values contributing to pubertal stage regression had a minimal impact on results. Results presented below are from the sensitivity analysis with censored data (i.e., contain no stage regressions).

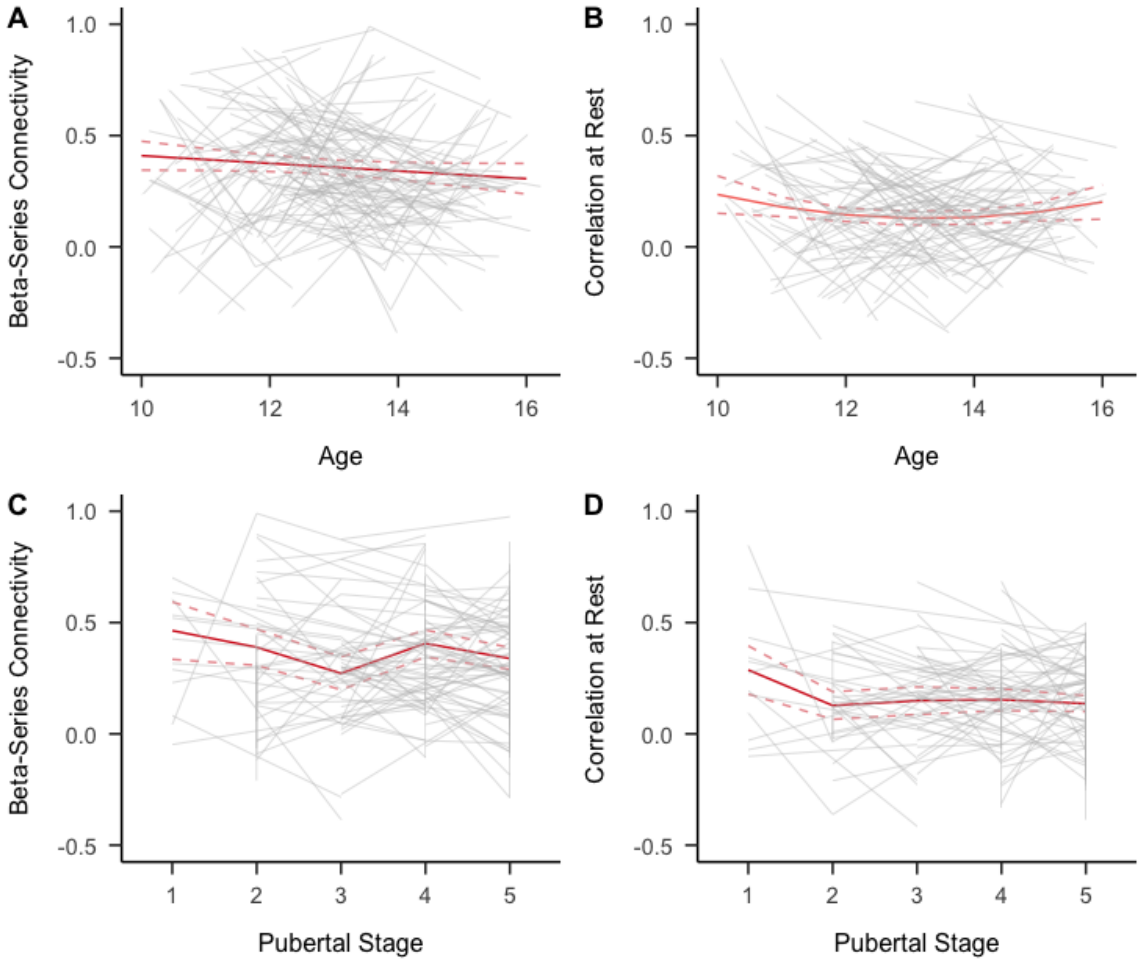
Developmental Models

Developmental Trends by Age

Task-Based Functional Connectivity. We first identified the best-fitting age model of task-based NAcc-vmPFC connectivity. As including a quadratic age term in the linear age model did not improve model fit (ΔAIC = 1.86, $\Delta\chi^2(1) = 0.14$, $p = 0.71$), we preferred compared a model with just a linear effect of age to the null model, and found

Figure 2.4

Task-Based and Resting-State NAcc-vmPFC Connectivity Across Development



Note. This figure displays the functional connectivity of the NAcc-vmPFC by age and pubertal stage for task-based and resting-state functional connectivity. Solid red lines depict trajectories as predicted by the models. Dashed red lines reflect conservative estimates of uncertainty (akin to 95% confidence intervals, but calculated from the standard deviation rather than standard error). Gray lines reflect individual trajectories by participant. Solid red lines in Panels A and B reflect the best fitting or simplest age models, which were linear for task-based and quadratic for resting-state connectivity. Solid red lines in Panels C and D reflect models with polynomial effects of pubertal stage.

Table 2.3

Models Predicting Beta-Series Connectivity During Disclosure Decisions by Age and Pubertal Stage

	Model 1: Age			Model 2: Puberty			Model 3: Puberty + Age		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.58 ***	0.33 – 0.83	<0.001	0.37 ***	0.33 – 0.41	<0.001	0.67 ***	0.33 – 1.02	<0.001
Age	-0.02	-0.04 – 0.00	0.084				-0.02	-0.05 – 0.00	0.085
Pubertal Stage (Linear)				-0.06	-0.16 – 0.03	0.172	-0.01	-0.12 – 0.11	0.922
Pubertal Stage (Quad)				0.06	-0.03 – 0.14	0.184	0.07	-0.01 – 0.16	0.100
Pubertal Stage (Cubic)				-0.05	-0.13 – 0.02	0.188	-0.05	-0.13 – 0.02	0.179
Pubertal Stage (Quartic)				-0.09 **	-0.17 – -0.02	0.009	-0.09 *	-0.16 – -0.02	0.012
Random Effects									
σ^2	0.06			0.06			0.06		
τ_{00}	0.01 $_{participant}$			0.02 $_{participant}$			0.01 $_{participant}$		
ICC	0.15			0.22			0.20		
N	159 $_{participant}$			158 $_{participant}$			158 $_{participant}$		
Observations	336			319			319		
Marginal R^2 / Conditional R^2	0.009 / 0.160			0.036 / 0.245			0.044 / 0.230		

Note. Only the best-fitting or simplest age model is shown. * *p<0.05* ** *p<0.01* *** *p<0.001*

Table 2.4

Models Predicting Resting-State Connectivity by Age and Pubertal Stage

	Model 1: Age			Model 2: Puberty			Model 3: Puberty + Age		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	1.89 *	0.33 – 3.45	0.018	0.17 ***	0.14 – 0.20	<0.001	1.68	-0.02 – 3.37	0.053
Age (Linear)	-0.26 *	-0.51 – -0.02	0.031				-0.24	-0.49 – 0.02	0.073
Age (Quad)	0.01 *	0.00 – 0.02	0.033				0.01	-0.00 – 0.02	0.065
Pubertal Stage (Linear)				-0.09 *	-0.16 – -0.01	0.025	-0.08	-0.17 – 0.02	0.106
Pubertal Stage (Quad)				0.07	-0.00 – 0.14	0.052	0.06	-0.01 – 0.13	0.116
Pubertal Stage (Cubic)				-0.06 *	-0.13 – -0.00	0.039	-0.07 *	-0.14 – -0.01	0.020
Pubertal Stage (Quartic)				0.02	-0.04 – 0.08	0.453	0.02	-0.04 – 0.08	0.424
Random Effects									
σ^2	0.04			0.04			0.04		
τ_{00}	0.00 $_{participant}$			0.00 $_{participant}$			0.00 $_{participant}$		
ICC	0.02			0.03			0.03		
N	159 $_{participant}$			158 $_{participant}$			158 $_{participant}$		
Observations	309			298			298		
Marginal R^2 / Conditional R^2	0.015 / 0.032			0.024 / 0.054			0.036 / 0.062		

Note. Only the best-fitting or simplest age model is shown. * *p<0.05* ** *p<0.01* *** *p<0.001*

that this only marginally improved model fit (ΔAIC = -0.98, $\Delta\chi^2(1) = 2.98$, $p = 0.08$). Linear age models suggested that there was a non-significant negative effect of age on task-based NAcc-vmPFC connectivity ($b = -0.02$, SE = 0.01, $t(332.19) = -1.74$, $p = 0.08$, Table 2.3, Model 1: Age, Figure 2.4A).

Resting-State Functional Connectivity. When predicting resting-state NAcc-vmPFC functional connectivity, a model including a quadratic age effect fit better than one with linear age only (ΔAIC = -2.55, $\Delta\ \chi^2(1) = 4.55$, $p = 0.03$). In this model, both linear ($b = -0.26$, SE = 0.12, $t(271.28) = -2.17$, $p = 0.03$) and quadratic ($b = 0.01$, SE = 0, $t(268.73) = 2.14$, $p = 0.03$) age effects were significant predictors of resting-state connectivity (Table 2.4, Model 1: Age; Figure 2.4B). However, this quadratic model exhibited only marginally better fit when compared to a null model (ΔAIC = -0.82, $\Delta\ \chi^2(2) = 4.82$, $p = 0.09$).

Developmental Trends by Pubertal Stage

Task-Based Functional Connectivity. There was a significant quartic effect of pubertal stage on task-based NAcc-vmPFC functional connectivity ($b = -0.09$, SE= 0.04, $t(305.41) = -2.61$, $p = 0.01$), and this model was better fitting when compared to the null model (ΔAIC = -4.23, $\Delta\chi^2(4) = 12.23$, $p = 0.02$; see Table 2.3, Model 2: Puberty).

Visual inspection of Figure 2.4C suggested that the quadratic effect was driven by increases in beta-series connectivity between stages 3-4 of pubertal development. Greater beta-series connectivity for stage 4 versus stage 3 of pubertal development was confirmed via post-hoc statistical comparison (t(*297.2*) = 2.97, p = 0.003). See Appendix Figure A.1 for a visualization of beta-series estimates and confidence intervals by pubertal stage.

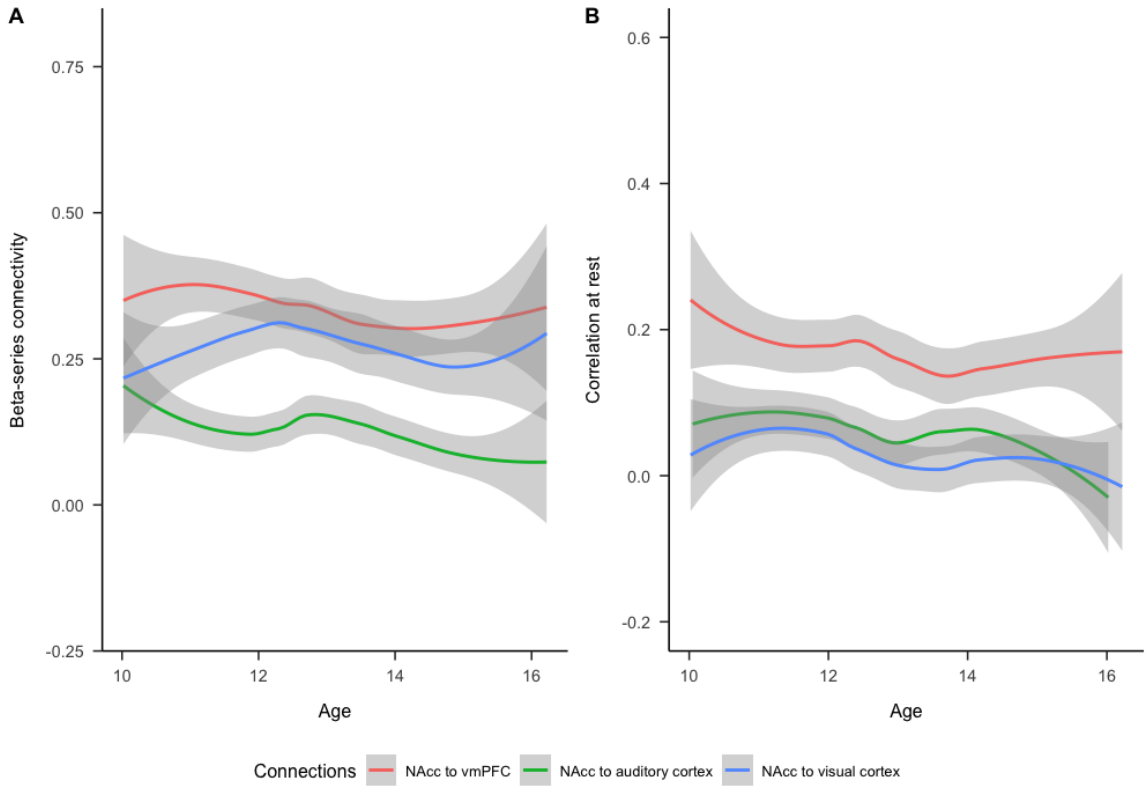
Prior models identified a weak linear age effect on task-based connectivity. Adding this linear age term into a model already containing pubertal stage as a predictor only marginally improved model fit (ΔAIC = -0.88, $\Delta\chi^2(1) = 2.88$, $p = 0.09$; Table 2.3, Model 3: Puberty + Age). Examination of variance inflation factors did not suggest an issue with multicollinearity between age and puberty (VIF = 2.14).

Resting-State Functional Connectivity. NAcc-vmPFC resting-state functional connectivity was predicted by linear (b = -0.09, SE= 0.04, $t(297.95) = -2.26$, $p = 0.02$), non-significant quadratic (b = 0.07, SE= 0.04, $t(278.45) = 1.96$, $p = 0.05$), and cubic (b = -0.09, SE= 0.04, $t(297.95) = -2.26$, $p = 0.02$) effects of pubertal stage (See Table 2.4 Model 2: Puberty; Figure 2.4D). However, models incorporating pubertal stage did not improve model fit when compared to the null model (ΔAIC = 0.74, $\Delta\chi^2(4) = 7.26$, p = 0.12).

Prior models predicting NAcc-vmPFC functional connectivity identified significant linear and quadratic effects of age (See Table 2.4 Model 3: Puberty + Age). Adding these terms to the model did not improve model fit (ΔAIC = 0.28, $\Delta\chi^2(2) = 3.72$, $p = 0.16$). Evidence for multicollinearity between puberty and age was low (VIF = 2.34). ICC values for both neural measures were fairly low (Tables 2.3 and 2.4), with ICC values for resting-state functional connectivity being particularly low and indeed near zero. Lower ICC values indicate higher within-subject and lower between-subject variability, and such scores reflect low within-subject homogeneity across time points in our sample.

Figure 2.5

Task-Based and Resting-State Connectivity Across Connections



Note. Panel A displays task-based beta-series connectivity estimates by age across three connections; Panel B displays resting-state connectivity estimates by age for the same three connections. Solid lines were generated via locally weighted scatterplot smoothing (lowess) and do not reflect developmental models as in Figure 2.4.

Developmental Trends in Control Connections

Developmental trajectories of control connections were not the focus of this investigation, but information about these models are in Appendix A. As a reference for research presented in future chapters, Figure 2.5 displays trajectories by age.

Discussion

This chapter aimed to examine how functional connectivity between the NAcc and vmPFC changed across adolescence in two distinct mental states: during self-

disclosure decisions and during rest. We built and compared multilevel models incorporating linear and nonlinear effects of age and pubertal stage. Task-based connectivity was best explained by quartic effects of pubertal stage that appeared to be driven by increases between stages 3 and 4. Trajectories of resting-state functional connectivity exhibited nonlinear declines (linear and quadratic effects of age; linear, quadratic, and cubic effects of pubertal stage) that appeared to be driven by changes early in maturation. However, developmental models of resting-state functional connectivity did not exhibit improved model fit when compared to a null model.

Trajectories of Task-Based Functional Connectivity during Self-Disclosure

As there were no differences in NAcc-vmPFC connectivity across self-disclosure statement depths (intimate vs. superficial disclosures), all models examining task-based connectivity collapsed across conditions. Age models identified non-significant negative linear effects of age, while a puberty model identified significant negative quartic effects of pubertal stage. Only the pubertal stage model exhibited improved fit when compared to a null model, and additionally including age into the puberty model did not improve model fit. Overall, findings suggested that task-based NAcc-vmPFC functional connectivity during self-disclosure was better characterized by puberty than age.

No other study has examined trajectories of NAcc-vmPFC connectivity during adolescent self-disclosure, to the best of our knowledge. However, a number of studies have examined developmental changes in NAcc (or ventral striatum, of which the NAcc is a part of) connectivity with medial and ventromedial PFC regions during reward, learning, and/or decision-making tasks across adolescence. One study employing a temporal discounting task found that greater ventral striatal connectivity with the vmPFC

was associated with a tendency to more heavily weigh long-term benefits (relative to immediate rewards) and that connectivity increased with age (in 11-32 year old males; Christakou et al., 2011). Another study employing a probabilistic feedback learning task found greater ventral striatum connectivity with the mPFC for positive as compared to negative feedback trials; this context-modulated connectivity difference both predicted learning and increased with age (across ages 8-22 years; van den Bos et al., 2012). A third study employing a risky decision-making task found greater NAcc-vmPFC connectivity for reward as compared to loss outcomes, but found that this effect did not vary with age (ages 10-25 years; van Duijvenvoorde et al., 2014). More recently, a longitudinal study employing a reward learning task identified age-related decreases in connectivity between the NAcc and other vmPFC subregions that did not overlap with the region selected in our study (ages 12-31; Parr et al., preprint).

Overall, prior studies provide mixed evidence for developmental changes in task-based connectivity across reward, learning, and decision-making tasks in adolescence. Methodological differences may be at play; while the first study used partial time series correlations (Christakou et al., 2011), the next two studies employed psychophysiological interaction approaches (McLaren et al., 2012) to examine how positive versus negative task contexts modulated connectivity (van den Bos et al., 2012; van Duijvenvoorde et al, 2014), and the last study used a background connectivity approach (Salvador et al., 2005) to assess sustained connectivity across the scan (with a focus on removing task-evoked signals; Parr et al., preprint). In contrast, this analysis used a beta-series correlation approach, which is consistent with contemporary recommendations considering the timing of our event-related design (Cisler, 2014). While the use of different task designs

and analysis approaches makes inconsistencies less surprising, they also underscore needs for standardization and replication in the field.

While the present analyses identified weak linear effects of age, trajectories of NAcc-vmPFC connectivity during self-disclosure were better explained by non-linear effects of pubertal stage than age. This trajectory exhibited a notable mid/late pubertal increase in connectivity between stages 3-4. Shifts in female development between Tanner stages 3 to 4 include a decrease in height velocity as well as substantial changes to breast and pubic hair development (Emmanuel & Bokor, 2020). The onset of menarche is typically associated with entry into stage 4. While few studies have focused on identifying normative shifts in peer relationships by pubertal status, one study found increases in social emotion understanding in a group of adolescent girls characterized as being late in puberty by the onset of menstruation (Burnett et al., 2011). Additionally, this particular stage transition has also been identified as a time when depression increases among girls (Angold et al., 1998, replicated in Conley & Rudolph, 2009). As a caveat, we note that the measures employed in the study fundamentally differ from Tanner staging by clinician assessment due to their focus on adolescents' perceptions of their own bodies. Overall, findings point to an increase in NAcc-vmPFC connectivity during self-disclosure in mid/late puberty that is not identified when examining development in terms of age only.

Trajectories of Resting-State Functional Connectivity

Trajectories of resting-state functional connectivity between the NAcc and vmPFC identified non-linear effects of age and pubertal stage, and visual inspection of the trajectory suggested that changes were predominantly early in development

(measured by either age or pubertal stage). However, resting-state functional connectivity appeared to be fairly stable across adolescent girls in this sample, and models including age and/or pubertal stage did not fit better than the null model.

An earlier cross-sectional study identified age-related linear decreases in ventral striatal resting-state functional connectivity across subregions of the medial prefrontal cortex (across ages 4.5-23 years; Fareri et al.; 2015). A similar age-related decrease was observed between the NAcc and vmPFC (in a subregion extending rostrally from the subgenual anterior cingulate cortex) in another study (across ages 8-25; van Duijvenvoorde et al., 2015). Longitudinal analyses found similar age-related decreases in connectivity between these regions, which may be a part of a broader pattern of weaker subcortical-cortical connectivity across adolescence (ages 8-28 years; van Duijvenvoorde et al., 2019). However, one study did not identify age-related connectivity changes between the ventral striatum and vmPFC, except in a very caudal and dorsal region of the anterior cingulate cortex (ages 9-44; Porter et al., 2015). One possibility explaining discrepancies in our findings is that developmental changes in resting-state functional connectivity may be more pronounced and notable in samples with larger age ranges than employed in our sample.

Limitations

The findings of these analyses should be interpreted in light of certain limitations. First, there were not enough time points to fit higher-order polynomial trends with true separation of within- and between-subjects effects, although examining intra-class correlations suggested that variability in both task-based and resting-state functional connectivity, but especially the latter, was largely between-subjects. Furthermore,

interpretations of the shapes of longitudinal trajectories should be made with caution because they can be influenced by the age ranges included in a study (Fjell, 2010). While our sample included participants from all pubertal stages, there were fewer participants in the earliest stages of pubertal development as well as a restricted age range (by design).

Task-based metrics presented here were calculated from beta-series analyses across the entire trial of a self-disclosure task, which included both self-evaluation and self-disclosure decision phases. Because of the task timing, it was not possible to fully disentangle signals from both task phases. Additionally, from a psychological process perspective, it was quite possible that adolescents were anticipating their disclosure decisions from the trial onset, rather than only once the disclosure prompt appeared on screen. However, prior research with this paradigm in the first wave of this sample identified differing neural responses to the self-evaluation and self-disclosure phases, including in NAcc and vmPFC (Vijayakumar et al., 2020). When modeled separately, differing effects for superficial and intimate statement depths also emerge. Future analyses might consider developmental effects of all aspects (task phase: self-evaluation and self-disclosure; statement depth: intimate and superficial) of the task design.

Another limitation of this study is related to the presence of substantial missing data across waves. The majority of data excluded from T1 can be attributed to insufficient high quality resting-state data that was remedied by collecting a greater volume of data at later time points. A number of participants also did not have three waves of data because the final wave was interrupted by the covid-19 pandemic. While these were the two main sources of missing data, a number of other factors, including difficulty comfortably staying still enough for the full length of the scan, contributed to

missing data in both task and rest modalities. Because of the difficulty in collecting reliable data from high-motion participants, it is challenging to ascertain whether the data were missing not at random (i.e., if the ask or resting-state functional connectivity values themselves differed between those from whom data could and could not be collected); if so, estimates may be biased.

Conclusions

Analyses identified a non-linear effect of pubertal stage on task-based NAcc-vmPFC connectivity during self-disclosure that was not captured in trajectories that used age as the sole measure of maturation. This effect was driven by increases in task-based functional connectivity occurring around stages 3-4. Analyses identified non-linear decreases in NAcc-vmPFC resting-state connectivity with age and pubertal stage, but models containing these predictors did not exhibit significantly improved model fit when compared to the null model. The identification of stronger effects of puberty on task-based but not resting-state functional connectivity may be more consistent with activational rather than organizational effects of puberty on neurodevelopment, and the next chapter specifically considers potential developmental mechanisms relating task and rest modalities over time.

CHAPTER III

DEVELOPMENTAL MECHANISMS RELATING SOCIAL RELATIONSHIPS TO NEURAL CHANGE

Introduction

Close friendships play a significant role in shaping thoughts and behaviors during adolescence, and aspects of friendship quality during this period play an outsized role in health and well-being that lasts until decades later (Allen et al., 2015; Narr et al., 2019). The empirical chapter centrally engages with the questions as to *how* and *when* close friendships might exert this influence via changes to NAcc and vmPFC connectivity. By becoming "neurally embedded", these experiences might influence the long-term functioning of neural circuits for processing value and social cognition. As in the previous chapter, I consider both chronological age and pubertal development as indices of maturation that may influence the degree of this putative embedding.

Long-term Phasic Modeling as a Neurodevelopmental Mechanism of Change

Long-term phasic modeling posits that, for developing circuits, transient or phasic connectivity will predict resting-state functional connectivity over time. Resting-state functional connectivity indexes the brain's functional architecture while participants are exposed to minimal stimuli (e.g., Fox et al., 2005; Grecius et al., 2003). Although nascent organization is present from infancy (Fransson et al., 2007), little is known about the remodeling that results in stable (Gratton et al., 2018) and individually distinct (Finn et al., 2015; Miranda-Dominguez et al., 2014) features within adult architecture that are associated with psychopathology (e.g., Xia et al., 2017).

Very few empirical studies have examined longitudinal task- and resting-state associations in the human developmental cognitive neuroscience literature. In a two-wave longitudinal study of children ages 4 to 18, evidence for the long-term phasic modeling hypothesis was found in an amygdala-mPFC circuit (Gabard-Durnam et al., 2016). Specifically, amygdala-mPFC connectivity elicited by emotional face stimuli was associated with resting-state connectivity two years later, but not vice versa. This association (task predicts rest) suggests that phasic patterns of connectivity elicited over the course of development may shape resting-state connectivity, and that this can be measured despite differences in the signal timescales captured by task-based and resting-state connectivity measures. Additionally, the magnitude of this effect declined across childhood and was no longer present after early adolescence, providing a rough timing estimate for the potential conclusion of a sensitive period for sculpting this circuit.

In contrast, a second study found that resting-state signal (as measured by source-localized EEG alpha current density) within the dorsal mPFC at age 4 predicted selectivity of these same regions to mental state reasoning (as measured by fMRI) during a theory of mind task at ages 7 and 8. This association (rest predicts task) suggests that early, task-independent maturation of the brain may provide foundational scaffolding supporting functional specialization (Bowman et al., 2019). This preliminary work was carried out in a fairly small sample (N=12), and researchers were unable to test or rule out the long-term phasic modeling hypothesis because task-based functional connectivity measures were not available at the earlier wave of data collection (age 4), and resting-state functional connectivity measures were not available at the later wave (ages 7-8).

Summary

The long-term phasic modeling hypothesis suggests that phasic patterns in functional connectivity during earlier experiences sculpt the brain's emerging functional architecture. Preliminary evidence for long-term phasic modeling has been identified in one circuit, suggesting that this mechanism may be at play in developing circuitry supporting socio-affective processing. Examining longitudinal relationships between task-based and resting-state functional connectivity across development can help us to understand the neural embedding of experience and/or the nature of functional specialization across development, although very few studies have done so.

Adolescent Self-disclosure as a Potential Driver of Phasic Modeling

Psychological science can advance candidate processes that might be sufficiently *frequent*, *socio-emotionally salient*, and *developmentally significant* as to be drivers of phasic modeling. Self disclosure, or the sharing of personal thoughts and feelings, may be one such driver. With respect to the criteria of frequency, self-disclosure is a normative behavior that reflects a large proportion of speech in the real world (Dunbar et al., 1997) and online (Naaman et al., 2010). Reciprocal and deepening self-disclosures are socio-emotionally salient as a primary means of developing intimacy in friendships (Berndt, 2002). As reviewed in the previous chapter, studies using self-report measures identify greater self-disclosure to peers during early adolescence (Valkenburg et al., 2011) and behavioral task paradigms suggest changes to the intrinsic value of peer disclosures in adolescence (Mobasser et al., preprint). These behavioral changes in the targets of self-disclosure may reflect changes that are consistent with social reorientation (Vijayakumar

& Pfeifer, 2020), a major theory of adolescent development (Nelson et al., 2005; Nelson et al., 2016).

Additionally, candidate processes for driving phasic modeling critically must also elicit neural signal within circuits of interest. Prior research with this paradigm finds that adolescent self-disclosure engages key nodes within a fronto-striatal circuit in a manner that tracks with preference to disclose, friendship quality, and feelings of being supported (Vijayakumar et al., 2020). However, task-based connectivity metrics are not a direct indicator of close friendship experiences, and the degree to which they are related to friendship quality is empirically investigated in Chapter 4.

Summary

An examination of the features of self-disclosure from the perspectives of developmental psychology and neurobiology suggests that this process may be a candidate for driving phasic modeling.

Puberty May Regulate Sensitive Periods in the Transition into Adolescence

The transition into adolescence is a particularly formative period of cognitive, affective, and physical change. In the social domain, this transition is accompanied by increased motivation for peer acceptance (O'Brien & Bierman, 1988) and sensitivity to social exclusion (Sebastian et al., 2010). Furthermore, the heightened salience of social experiences may be adaptive for learning from and about complex social environments, ultimately supporting a species-typical transition into sexual maturity (Crone & Dahl, 2012). In part because of these transitions, adolescents have been theorized to undergo a sensitive period for sociocultural learning (although see Chapter 1 for a more nuanced discussion of the relationships between heightened sensitivities and sensitive periods).

Developmental timing mechanisms are likely to vary across adolescence, as it is a prolonged period potentially spanning beyond a decade. The onset and conclusion of adolescence are not sharply defined. Biological perspectives on adolescence have marked its onset with puberty, but puberty itself is multi-faceted and unfolds over time. Meanwhile, sociocultural perspectives find that entry into adolescence in most societies is defined partly by puberty but also via initiation ceremonies (Worthman & Trang, 2018). Aspects of puberty, especially increases in pubertal sex hormones, organize the brain and behavior (Schultz & Sisk, 2016) and have been theorized to play regulatory roles in sensitive period timing, including both opening and closing sensitive periods during the transition to adolescence (Byrne et al., 2017; Piekarski et al., 2017).

Summary

The transition into adolescence may reflect the onset of a sensitive period for sociocultural development. This sensitive period may also be related to increases in pubertal hormones, as puberty is accompanied by tremendous hormonal, physical, neural, and social developmental change.

Goals of the Current Analysis

The core aim of the current chapter is to evaluate long-term phasic modeling as a neurobiological mechanism by which close friendship experiences may influence the development of brain systems for processing value and social cognition. Although evidence suggests that this process occurs in other circuits during development, it is not known whether this is the case for vmPFC-NAcc circuitry, which may play roles in integrating value-related and social cognitive processes. In a circuit undergoing long-term phasic modeling, phasic task-based connectivity would predict later resting-state

connectivity; i.e., resting-state connectivity between regions reflects their history of coactivation. Consistent with this hypothesis, I predict that earlier phasic NAcc and vmPFC connectivity during self-disclosure will predict later connectivity at rest. The reverse pattern (rest predicts task) would suggest that connectivity is predominantly driven by the unfolding of cumulative antecedent effects, e.g. early adversity or pubertal hormones directly organize a circuit in a manner that influences its functioning during specific social processes.

The secondary aim of this chapter is to explore whether maturation moderates associations across states of functional connectivity. Pubertal development is of particular interest in the context of theories positing pubertal processes as drivers of sensitive periods. If identified, moderating effects of maturation, defined in terms of chronological age or as pubertal development, would provide evidence for timing windows in which aspects of how adolescents process their relationships with their close and/or best friends more strongly influence neurodevelopment.

Methods

For the core aim of this chapter, structural equation modeling was used to evaluate the long-term phasic modeling (LTPM) hypothesis and an alternative hypothesis as mechanisms of developing NAcc-vmPFC connectivity. For the secondary aim of this chapter, the structural equation modeling was extended to test whether time-lagged effects varied across time points. Hierarchical generalized additive models were additionally used to explore moderating effects of maturation with more precision (i.e., at the level of age and pubertal stage, rather than by study time point). The same

participants and measures were used as described in Chapter 2. Because this chapter focuses on relationships between neural measures across time, matrices of Pearson correlation coefficients were provided to better characterize bivariate associations among these measures.

Statistical Approach

Testing Long-Term Phasic Modeling and Alternative Neurodevelopmental Mechanisms

Developmental hypotheses were examined using structural equation modeling. In the model testing the LTPM hypothesis, time-lagged task-based and resting-state connectivity predicted later resting-state connectivity (Figure 1A). In the model testing an alternative hypothesis, time-lagged task-based and resting-state connectivity predicted later task-based connectivity (Figure 1B). These models are not mutually exclusive and it is *not* a fundamental aim of this work to pit them against one another. Constructing two separate models (as compared to using a cross-lagged panel model) allowed for investigating the dependence of time-lagged x on y and time-lagged y on x using a less restricted model specification, which can simplify estimation difficulties and reduce misspecification issues (Allison et al., 2017).

Across models specified to test the LTPM and alternative hypotheses, *alpha* was included as a latent variable to capture unmeasured individual differences causing endogenous variables. Here, endogenous variables are somewhat akin to outcomes and are modeled as being caused by other variables in the model, while exogenous variables are somewhat akin to predictors and are modeled as causes. In the model testing the LTPM hypothesis, resting-state connectivities at T2 and T3 were endogenous while other

variables were exogenous; in the model testing the alternative hypothesis, task-based connectivities at T2 and T3 were endogenous while other variables were exogenous.

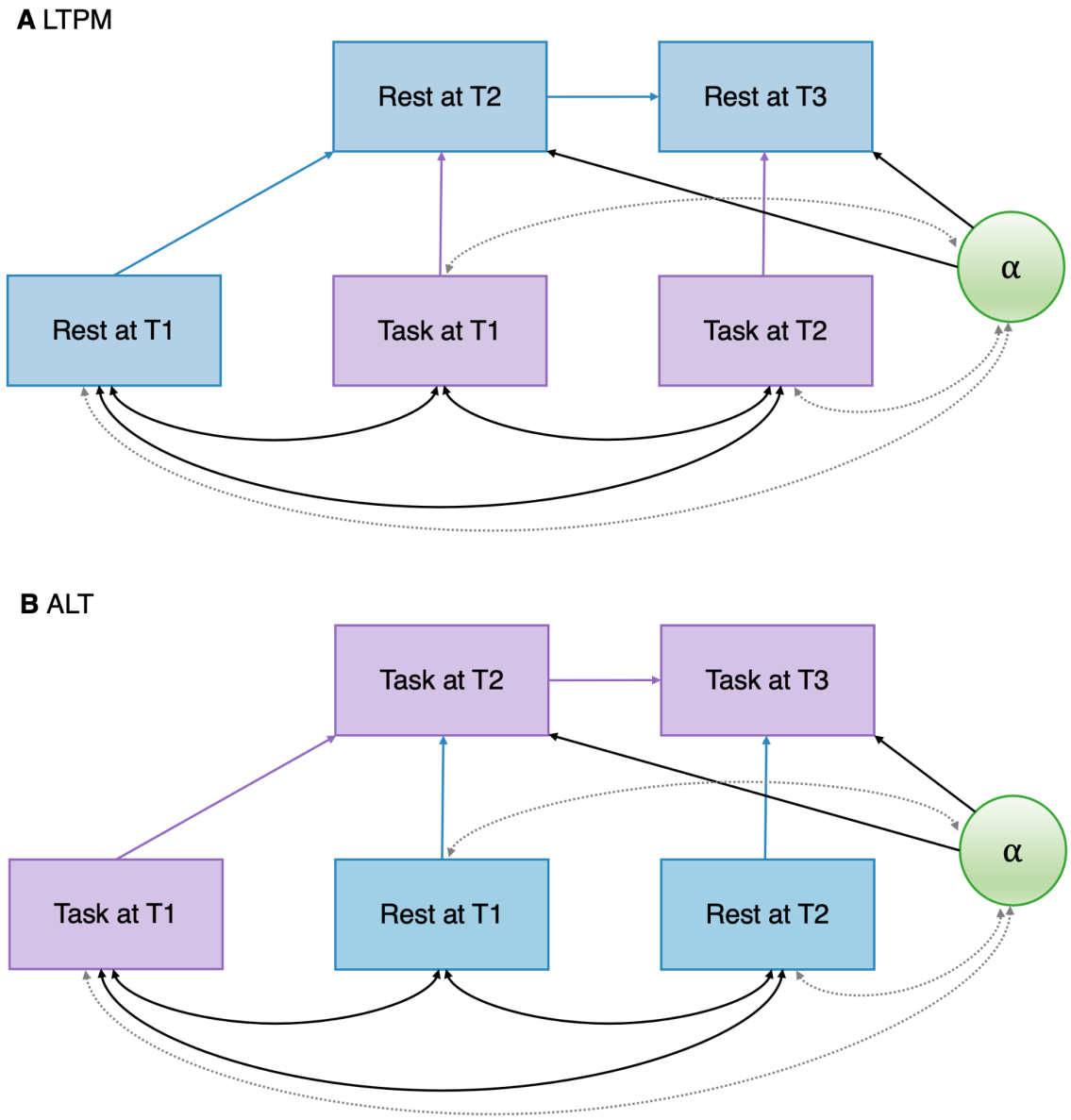
A structural equation modeling approach was chosen over a multilevel modeling approach. Within a structural equation modeling framework, *alpha* can co-vary with exogenous variables (fixed effects model; Allison et al., 2017) in a model that separates between and within-person effects (Hamaker & Muthén, 2020). In contrast, *alpha* is commonly modeled as a random intercept when using multilevel modeling (random effects model), and in such regression models *alpha* and all other predictors are assumed to be independent. Separation of between and within-person effects in multilevel models requires the use of difference scores, centering, and/or the addition of other parameters.

When models faced estimation difficulties (indicated by impossible solutions such as negative estimated variances) and when examination of estimated model parameters suggested that it was appropriate, models were simplified by moving from fixed to random effects models (i.e., no longer freely estimating covariances between alpha and other exogenous variables). If problems persisted and when examination of estimated model parameters suggested it was appropriate, models were further simplified by removing *alpha* altogether, resulting in a path model with no latent variables (Figure 3.1).

All structural equation models were constructed and estimated using the *sem* function within the *lavaan* package (v. 0.6-5) for *R*. Models were estimated using maximum likelihood estimation, and full information maximum likelihood estimation was used to handle missing data. Models examined both the connection-of-interest (NAcc-vmPFC) and two control connections (NAcc-primary auditory cortex and NAcc-primary visual cortex).

Figure 3.1

Structural Equation Models for Long-Term Phasic Modeling and Alternative Hypotheses



Note. Full (fixed effects) structural equation models testing the long-term phasic modeling (LTPM) and alternative (ALT) hypotheses. Task = beta-series connectivity estimated during self-disclosure decisions; Rest = resting-state functional connectivity. Some models were simplified due to estimation issues. In the random effects model, gray dotted lines representing covariances between α and exogenous variables were removed. In the path model, α and its associated paths were removed.

Metrics of Interest. Models were evaluated based on the χ^2 test, Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Standardized Root Mean Square Residual (SRMR) as global fit indices (following recommendations from Klein, 2016). The χ^2 test evaluates a null "exact-fit" hypothesis that the model predicts the data such that rejecting the null hypothesis ($p < 0.05$) leads the researcher to reject the model. The RMSEA is an absolute, one-sided badness-of-fit statistic typically reported with its 90% confidence interval; zero is the best result. The CFI is an incremental goodness-of-fit statistic comparing the model to the null model, where 1.0 is the best result. The SRMR is an absolute badness-of-fit statistic where larger values suggest greater discrepancies between observed and predicted correlations, and values >0.1 suggest poor model fit. Overall, global fit indices provide information about average model fit, but cannot determine whether models are correct, as models may still be misspecified.

To evaluate the LTPM hypothesis, the estimated effect of time-lagged task-based connectivity on resting-state connectivity was presented alongside its standard error. To evaluate the alternative hypothesis, the estimated effect of time-lagged resting-state connectivity on task-based connectivity was also presented. Effects were evaluated with a null-hypothesis significance testing approach at an uncorrected threshold of *alpha* = 0.05.

Assessing Effects of Developmental Timing

The secondary aim of this chapter was to examine evidence for sensitive periods. Specifically, we evaluated whether time-lagged effects across task-based and resting-state functional connectivity varied by adolescent maturation via both structural equation modeling and hierarchical generalized additive modeling.

Extending the Structural Equation Model to Assess Effects of Study Time Point. The structural equation models presented in the prior section were extended to test whether time-lagged effects across states of task and rest varied by time point. Because adolescents become older across time points, this tests the possibility that time-lagged effects might be stronger relatively earlier or later in development across the sample. The model testing the LTPM hypothesis was altered by estimating unique parameters for the effect of time-lagged task-based connectivity on resting-state connectivity between T1-T2 and T2-T3, rather than constraining these paths to be equal. Relative model fit was examined using likelihood ratio tests and Akaike Information Criterion (AIC). This procedure was repeated for the model testing the alternative hypothesis such that the effect of time-lagged resting-state connectivity on task-based connectivity was specified as varying between T1-T2 and T2-T3 rather than being constrained to be equal; this procedure was further repeated across not only the connection of interest (NAcc-vmPFC) but also the control connections (NAcc-primary auditory cortex and NAcc-primary visual cortex).

Using Hierarchical Generalized Additive Models to Assess Effects of Age and/or Pubertal Stage. Due to the study's semi-accelerated longitudinal design, the ages of participants at different time points overlapped (e.g., ages 10, 11, 12 at the first session of T1, ages 11, 12, 13, and 14 at the first session of T2). Considering whether effects varied by time point therefore only coarsely tested the possibility that effects varied depending on participants' degree of maturation. Hierarchical generalized additive modeling was used to explore possible effects of more fine-grained measures of maturation. Advantages to this approach are that it can estimate smooth functional

nonlinear relationships while accounting for nesting. Structural equation modeling was not used because adding additional variables with interactions would have dramatically increased model complexity to a degree that could not be estimated with the available sample size. Furthermore, it is not straightforward to account for non-linear trajectories within a structural equation modeling framework, and evidence from analyses of developmental trajectories in the previous chapter suggests that non-linear changes might be at play.

Hierarchical generalized additive models took the form of$y_{it} = \beta_0 + \beta_1 y_{it-1} + f(m_{it-1})x_{it-1} + \varsigma_i + \varepsilon_{it}$. In the LTPM formulation of this model, y was resting-state connectivity, *x* was task-based connectivity, i was the participant, t was time point, $\beta_0$was the intercept, $\beta_1$was the lagged effect of the dependent variable, $\varsigma_i$was a smoothed random intercept, and$\varepsilon_{it}$was the residual. Maturation (*m)* was examined in separate models both in terms of chronological age and as composite pubertal stage scores. The term $f(m)$ was a smoothed function of maturation *m* (tensor product smooth using *te* within the *mgcv* package (v. 1.8-28) for *R*). In the alternative formulation of this model, task-based connectivity was examined as the outcome variable and time-lagged resting-state connectivity was the predictor.

Hierarchical generalized additive models were constructed and estimated using the *gam* function within the *mgcv* package (v. 1.8-28) for R. The number of basis functions (*k*) was set to 5; model parameters and residuals were also inspected with larger *k*, and doing so did not suggest that using a larger set of basis functions would alter the pattern of statistical findings. Models were estimated using maximum-likelihood with complete observations only. Models examined both the connection-of-interest (NAcc-

vmPFC) and two control connections (NAcc-primary auditory cortex and NAcc-primary visual cortex).

Results

Bivariate Correlations Among Neural Measures

Examination of bivariate correlations among measures of NAcc-vmPFC functional connectivity suggested that task-based beta-series connectivity values were typically positively correlated across consecutive time points, while resting-state functional connectivity values were not (Figure 2). However, both task-based and resting-state functional connectivity values were negatively correlated with themselves across T1 and T3. For additional descriptive statistics of the variables used in these analyses, please refer to Chapter 2.

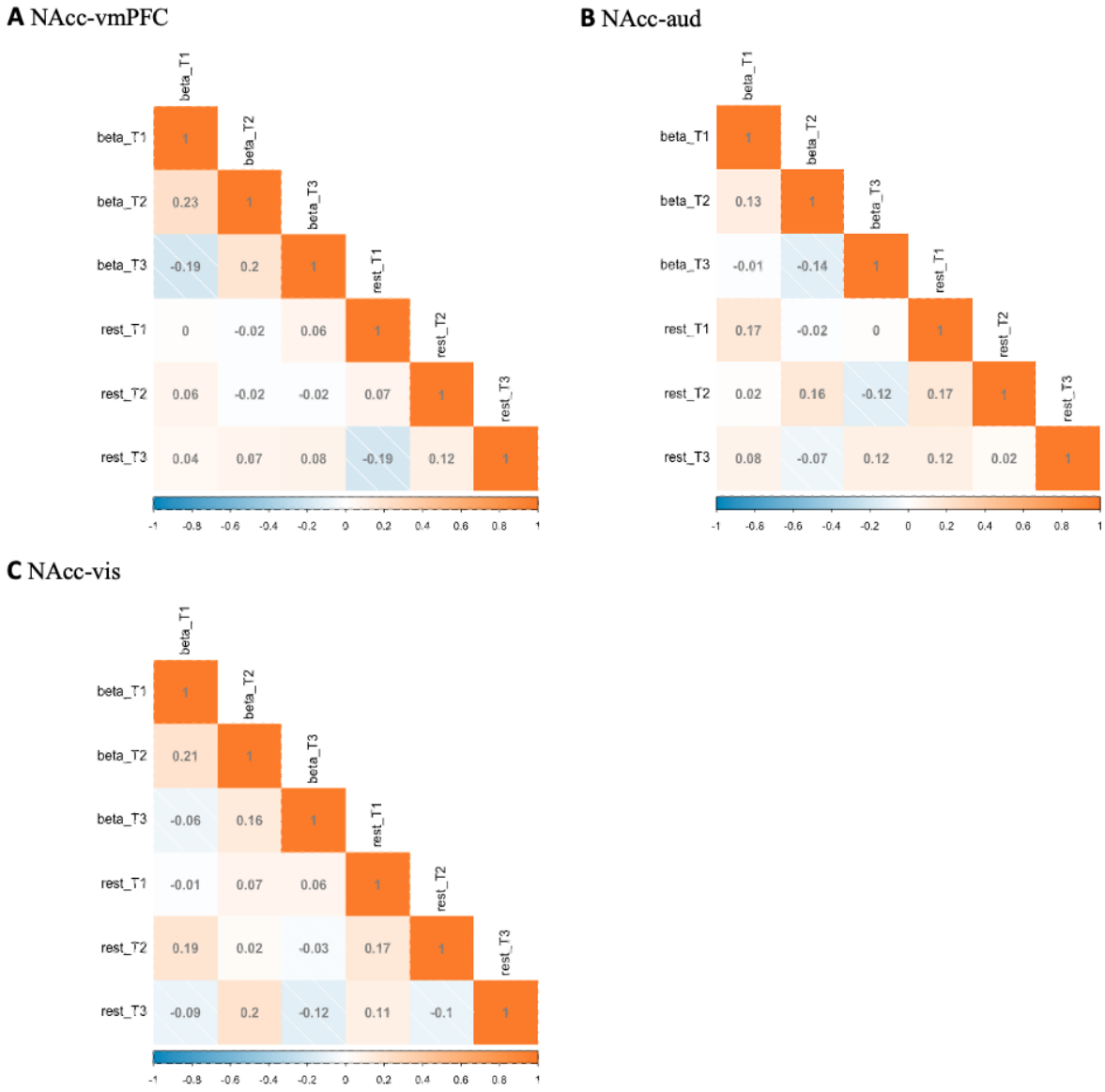
Time-Lagged Effects Across Modalities

Structural Equation Modeling

Long-Term Phasic Modeling Hypothesis of NAcc-vmPFC Connectivity. We first examined evidence for the long-term phasic modeling hypothesis for NAcc-vmPFC connectivity using a structural equation modeling approach. When examining the model as pre-specified, some estimated variances were negative, which is often a sign of model misspecification. Inspection of the estimated parameters suggested that negative variances were between α and exogenous variables. We therefore re-specified the model as a random effects model, which assumed that α and the exogenous variables did not covary. This resulted in a model whereby all estimated variances were positive. Examination of possible modifications to the model did not suggest that reintroducing the

Figure 3.2

Correlations Between Neural Measures Across Time Points



Note. Beta = Task-based beta-series connectivity, Rest = Resting-state connectivity

removed covariance specifications would improve model fit. Therefore, parameters presented here are from random effects models; in such models α is included but does not covary with the exogenous variables (Hamaker & Muthén, 2020).

Examination of the random effects model testing the long-term phasic modeling hypothesis identified adequate global fit (see Figure 3.3 LTPM-C; $\chi^2(4) = 1.48$, $p = 0.83$; SRMR = 0.04, RMSEA = 0, 90% CI [0, 0.07], CFI = 1).[1] This model did not identify significant time-lagged relationships of task-based functional connectivity on resting state functional connectivity (standardized effects are presented throughout; task at T1 predicting rest at T2: $b = 0.07$, $SE = 0.07$, 95% CI = [-0.08, 0.21], $Z = 0.92$, $p = 0.36$; task at T2 predicting rest at T3: 0.08, $SE = 0.09$, 95% CI = [-0.09, 0.25], $Z = 0.92$, $p = 0.36$). (Note that while unstandardized estimates were constrained to be equal, standardized values presented both in the text and figures appear to vary slightly across waves because standard errors varied.)

Allowing Time-Lagged Estimates to Vary by Time Point. The random effects version of the model describing the long-term phasic modeling hypothesis specified the effect of task-based connectivity on resting-state connectivity to be equal for the time lagged paths between both T1 to T2 and T2 to T3. To test a sensitive periods hypothesis, we allowed time-lagged effects between states of task and rest to vary across waves (Figure 3.3 LTPM-U). Comparative fit indices suggested that a model where time-lagged effects varied across waves did not better fit the data (ΔAIC = 1.91, $\Delta\chi^2(1) = 0.09$, $p = 0.77$). Therefore, the simpler model where time-lagged, cross-modal effects were constrained to be equal was retained.

Alternative Model of NAcc-vmPFC Connectivity. A model was estimated for the alternative hypothesis of NAcc-vmPFC connectivity with time-lagged effects of

[1] The Tucker-Lewis Index was -80.93, and this is unusual because the typical range of TLI values is from 0 to 1. While this can be truncated to zero (and a zero value would indicate poor model fit), this index can be unreliable when sample size/degrees of freedom are small and is not interpreted further in this report.

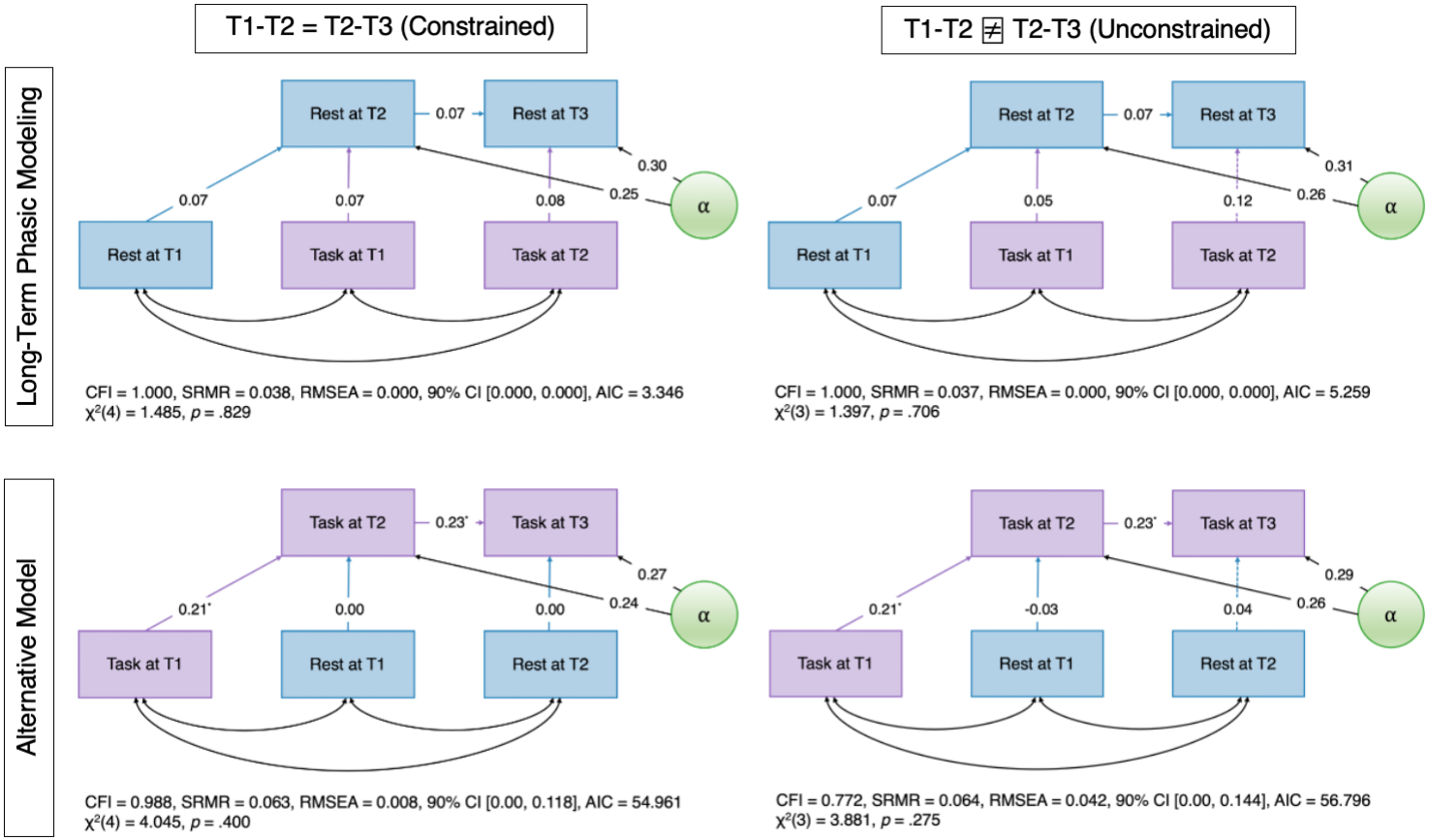
resting-state connectivity predicting task-based connectivity (Figure 3.3 ALT-C). The original specification of the alternative model resulted in the same challenges with model estimation that were described above regarding the long-term phasic hypothesis model; estimated variances were negative until covariances between α and the exogenous variables were constrained (to zero) rather than freely estimated, and examination of modification indices did not suggest that allowing those variables to covary would improve model fit. The random effects model is therefore presented for the alternative hypothesis, as well.

Examination of the random effects model testing the alternative hypothesis (Figure 3.3 ALT-C) indicated adequate global fit ($\chi^2(4) = 4.05$, $p = 0.40$; SRMR = 0.06, RMSEA = 0.01, 90% CI [0, 0.12], CFI = 0.99), but these metrics were generally slightly worse than those for the model of the long-term phasic modeling hypothesis. The alternative model did not identify time-lagged effects of resting-state functional connectivity on task-based functional connectivity (rest at T1 predicting task at T2: b = 0.00, SE = 0.08, 95% CI = [-0.17, 0.16], Z = -0.02, p = 0.99; rest at T2 predicting task at T3: b = 0.00, SE = 0.08, 95% CI = [-0.16, 0.16], Z = -0.02, p = 0.99). Task-based functional connectivity positively predicted itself over time (from T1 to T2: b = 0.21, SE = 0.08, 95% CI = [0.05, 0.37], Z = 2.59, p = 0.01; from T2 to T3: b = 0.23, SE = 0.10, 95% CI = [0.04, 0.42], Z = 2.42, p = 0.02).

Allowing Time-Lagged Estimates to Vary by Time Point. A separate model was estimated where time-lagged effects between states of task and rest were allowed to vary across waves (Figure 3.3 ALT-U). Comparative fit indices suggested that a model of the alternative hypothesis where time-lagged effects varied across waves did not better fit the

Figure 3.3

Structural Equation Models of NAcc-vmPFC Connectivity



Note. LTPM = model of the long-term phasic modeling hypothesis, ALT = model of the alternative hypothesis.

data (ΔAIC = 1.84, $\Delta\chi^2(1) = 0.16$, $p = 0.69$); the simpler model where time-lagged, cross-modal effects were constrained to be equal was retained.

Control connections. Connectivity between the NAcc and both control regions was first examined using random effects models (for comparability with the models of NAcc-vmPFC connectivity). In both of these models, some estimated variances were negative, and inspection of the models suggested that negative variances were attributed to α. When α was removed entirely, leaving a path model only, all model variance estimates were positive. Parameters presented here are from path models with no latent variables (see Limitations for a discussion of how this affected parameter estimates).

Connectivity Between the NAcc and Primary Auditory Cortex. Global fit statistics of a model testing the long-term phasic modeling hypothesis (Figure 3.4A) in explaining connectivity between the NAcc and the primary auditory cortex suggest acceptable average fit between the model and the data ($\chi^2(5) = 5.86$, $p = 0.32$; SRMR = 0.06, RMSEA = 0.03, 90% CI [0, 0.12], CFI = 0.74), but global fit indices were generally slightly worse than in the equivalent model of NAcc-vmPFC connectivity. There were no significant time-lagged relationships of task-based functional connectivity on resting-state functional connectivity (task at T1 predicting rest at T2: b = -0.01, SE = 0.07, 95% CI = [-0.15, 0.13], Z = -0.13, p = 0.89; task at T2 predicting rest at T3: b = -0.01, SE = 0.09, 95% CI = [-0.20, 0.17], Z = -0.13, p = 0.89). A model allowing time-lagged cross-modal associations to vary by time point did not better fit the data (ΔAIC = 1.84, $\Delta\chi^2(1) = 0.23$, $p = 0.63$), and a simpler model with constrained paths was retained.

Global fit statistics of a model testing the alternative hypothesis for NAcc-primary auditory cortex connectivity identified slightly worse fit between the model and the data

($\chi^2(5) = 6.53$, $p = 0.26$; SRMR = 0.06, RMSEA = 0.04, 90% CI [0, 0.12], CFI = 0.52) as compared to the LTPM model. There were no significant time-lagged relationships of resting-state functional connectivity on task-based functional connectivity (rest at T1 predicting task at T2: $b = -0.04$, $SE = 0.10$, 95% CI = [-0.23, 0.15], $Z = -0.43$, $p = 0.67$; rest at T2 predicting task at T3: $b = 0.04$, $SE = 0.09$, 95% CI = [-0.15, 0.22], $Z = 0.39$, $p = 0.70$). Unlike when modeling NAcc-vmPFC connectivity, task-based functional connectivity did not positively predict itself over time (from T1 to T2: $b = 0.03$, $SE = 0.07$, 95% CI = [-0.11, 0.17], $Z = 0.43$, $p = 0.66$; from T2 to T3: $b = 0.04$, $SE = 0.10$, 95% CI = [-0.14, 0.23], $Z = 0.44$, $p = 0.66$). A model allowing time-lagged cross-modal associations to vary by time point were only a marginally better fit to the data (ΔAIC = 1.80, $\Delta\chi^2(1) = 0.20$, $p = 0.65$), and a simpler model with constrained paths was retained.

Connectivity Between the NAcc and Primary Visual Cortex. Global fit statistics of a model testing the long-term phasic modeling hypothesis (Figure 3.4B) in explaining connectivity between the NAcc and the primary visual cortex suggested adequate fit between the model and the data ($\chi^2(5) = 4.15$, $p = 0.53$; SRMR = 0.06, RMSEA = 0, 90% CI [0, 0.10], CFI = 1). This model identified time-lagged relationships of task-based functional connectivity on resting-state functional connectivity (task at T1 predicting rest at T2: $b = 0.17$, $SE = 0.07$, 95% CI = [0.04, 0.31], $Z = 2.47$, $p = 0.01$; task at T2 predicting rest at T3: $b = 0.22$, $SE = 0.09$, 95% CI = [0.05, 0.39], $Z = 2.49$, $p = 0.01$). A model allowing time-lagged cross-modal associations to vary across waves not better fit (ΔAIC = 2.00, $\Delta\chi^2(1) = 0.00$, $p = 0.99$).

Global fit statistics of a model testing the alternative hypothesis for NAcc-primary visual cortex connectivity also suggested adequate fit between the model and the data

($\chi^2(5) = 1.32$, $p = 0.93$; SRMR = 0.03, RMSEA = 0, 90% CI [0, 0.03], CFI = 1). This model did not identify significant time-lagged relationships of resting-state functional connectivity on task-based functional connectivity (rest at T1 predicting task at T2: b = 0.01, SE = 0.08, 95% CI = [-0.14, 0.16], Z = 0.13, p = 0.90; rest at T2 predicting task at T3: b = 0.01, SE = 0.09, 95% CI = [-0.17, 0.19], Z = 0.13, p = 0.90). As with the NAcc-vmPFC, task-based functional connectivity positively predicted itself over time (from T1 to T2: b = 0.17, SE = 0.07, 95% CI = [0.04, 0.30], Z = 2.50, p = 0.01; from T2 to T3: b = 0.21, SE = 0.09, 95% CI = [0.04, 0.38], Z = 2.48, p = 0.01). A model allowing time-lagged cross-modal paths to vary across waves did not better fit the data (ΔAIC = 1.41, $\Delta\chi^2(1) = 0.59$, p = 0.44), and a simpler model with constrained paths was retained.

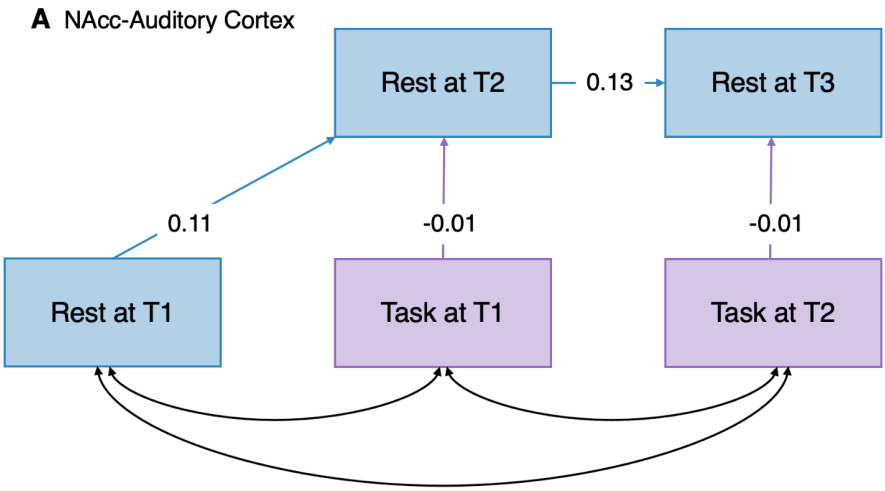
Hierarchical Generalized Linear Modeling Approach

Augmented Long-Term Phasic Modeling Hypothesis for NAcc-vmPFC Connectivity. To test sensitive period theories, hierarchical generalized additive models augmented models of the LTPM hypothesis to investigate whether time-lagged and cross-modal effects might vary with maturation. This modeling approach was used to examine nonlinear interactions between time-lagged beta-series connectivity and time-lagged maturation (age or pubertal stage in separate models) in predicting resting-state functional connectivity within the NAcc-vmPFC (Table 1, LTPM-Age and LTPM-Puberty models). Examination of omnibus statistics for the joined spline terms did not identify significant interactions between beta-series connectivity and age ($F(2) = 0.69$, p = 0.50) or puberty ($F(2) = 0.62$, p = 0.54) that predicted resting-state connectivity.

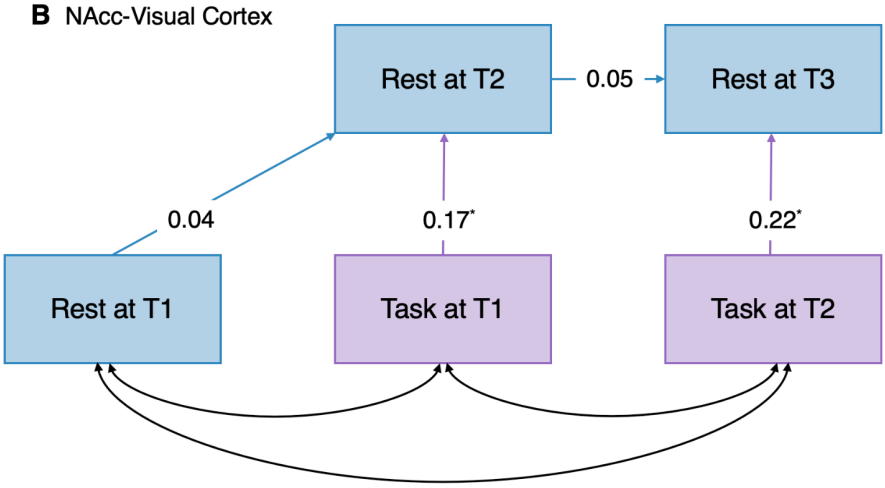
Augmented Alternative Hypothesis for NAcc-vmPFC Connectivity. A similar approach was employed to examine how maturation might augment effects specified by

Figure 3.4

Structural Equation Models of NAcc Connectivity with Primary Sensory Regions



CFI = 0.744, SRMR = 0.063, RMSEA = 0.032, 90% CI [0.000, 0.117], AIC = -364.945
$\chi^2(5) = 5.859$, $p = .320$



CFI = 1.000, SRMR = 0.054, RMSEA = 0.000, 90% CI [0.000, 0.099], AIC = -53.746
$\chi^2(5) = 4.151$, $p = .528$

Note. All models reflect the long-term phasic modeling hypothesis.

the alternative hypothesis. We examined nonlinear interactions between time-lagged resting-state connectivity and time-lagged maturation (Table 1, ALT-Age and ALT-Puberty) on task-based connectivity. Omnibus test statistics for the joined spline terms did not identify significant interactions between resting-state connectivity and age ($F(2) = 0.13$, $p = 0.88$) or puberty ($F(2) = 1.46$, $p = 0.24$) predicting connectivity during self-disclosure in the NAcc-vmPFC.

Control Connections. Hierarchical generalized additive models similarly augmented models of the LTPM and alternative hypotheses for control connections. Omnibus test statistics for the joined spine terms did not identify significant interactions predicting connectivity between the NAcc and primary auditory or visual cortices (see Appendix B). The LTPM was supported for NAcc-visual cortex only, so we visualized the following effects on resting-state NAcc-visual cortex connectivity: (A) linear effects of time-lagged age and time-lagged beta-series connectivity, (B) the non-linear interaction between time-lagged age and time-lagged beta-series connectivity, and (C) the non-linear interaction between time-lagged pubertal stage and time-lagged beta-series connectivity (Figure 3.5). Visual inspection suggested that time-lagged cross-modal effects might be driven by older, more pubertally mature adolescents (although not statistically significant).

Discussion

This chapter primarily aimed to evaluate LTPM and alternative neurobiological mechanisms of frontostriatal development and secondarily aimed to explore evidence for sensitive period effects of such mechanisms. Using structural equation modeling, we

Table 3.1

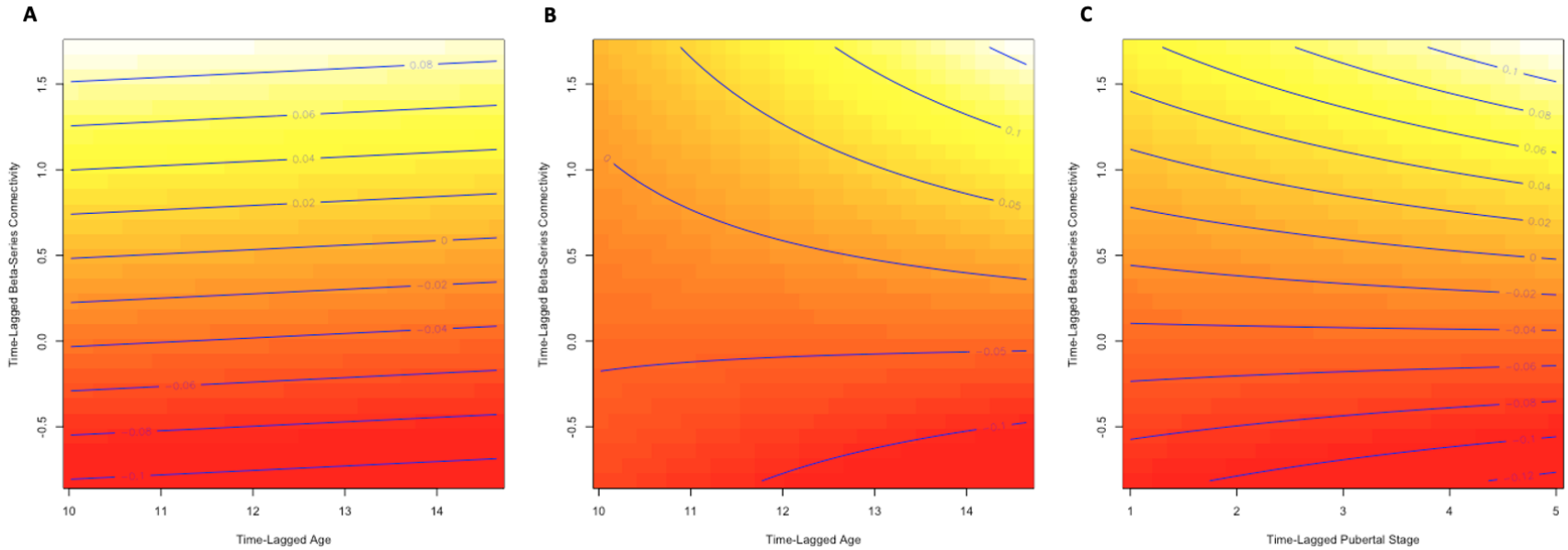
Hierarchical Generalized Additive Models Examining Neural Predictor by Maturation Interactions for NAcc-vmPFC Connectivity

	LTPM - Age			LTPM - Puberty			ALT - Age			ALT - Puberty		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.10 **	0.04 – 0.16	0.002	0.09 **	0.03 – 0.15	0.005	0.30 ***	0.22 – 0.39	<0.001	0.28 ***	0.20 – 0.37	<0.001
RSFC	0.07	-0.08 – 0.22	0.342	0.08	-0.08 – 0.23	0.328						
Beta							0.10	-0.07 – 0.28	0.242	0.18	-0.00 – 0.35	0.054
		F(2)	*p*		*F*(2)	*p*		*F*(2)	*p*		*F*(2)	*p*
Beta by age		0.691	0.503									
Beta by puberty					0.618	0.541						
RSFC by age								0.129	0.879			
RSFC by puberty											1.463	0.236
Observations	130			124			137			130		
R^2	0.017			0.017			0.028			0.052		

Note. * *p*<0.05 ** *p*<0.01 *** *p*<0.001; RSFC = resting-state functional connectivity; Beta = beta-series, task-based connectivity; LTPM = Long-Term Phasic Model; in LTPM models, the interaction between task-based beta-series connectivity and maturation predicted resting-state functional connectivity; ALT = Alternative model; in ATL models, the interaction between resting-state connectivity and maturation predicted task-based functional connectivity. All predictor variables were time-lagged by one time point. Omnibus tests evaluated the null hypothesis for the joined spline terms.

Figure 3.5

Resting-State NAcc-Visual Cortex Connectivity Predicted by Time-Lagged Maturation, Beta-Series Connectivity, and Their Interaction



Note. Models predicted resting-state connectivity of the NAcc-visual cortex. Panel A visualizes additive linear effects of time-lagged age and time-lagged beta-series connectivity and are presented for comparison/context only. Panel B visualizes the non-significant interaction between time-lagged age and time-lagged beta-series connectivity afforded by the hierarchical generalized additive modeling approach (Model LTPM - Age). Panel C visualizes the non-significant interaction between time-lagged pubertal stage and time-lagged beta-series connectivity using the same approach (Model LTPM - Puberty). Plots were created using the *vis.gam* function of the *mgcv* package in R.

identified patterns consistent with the LTPM hypothesis in NAcc connectivity with the primary visual cortex rather than with the vmPFC (or with primary auditory cortex). Across structural equation modeling and hierarchical generalized additive modeling approaches, we did not identify evidence of sensitive period effects.

Evaluating Models of the Long-Term Phasic Modeling and Alternative Hypotheses

Global model fit indices (chi squared, RMSEA, SRMR, and CFI) suggested moderate to good fit across structural equation models of both the LTPM and alternative hypotheses following model adjustments to facilitate estimation. Across the connection-of-interest and control connections, indices generally suggested better global fit in models of the LTPM hypothesis as compared to models of the alternative hypothesis. However, there were no significant time-lagged cross-modal paths in models of the LTPM or alternative hypotheses describing NAcc-vmPFC connectivity such that there is not good evidence that the inclusion of core hypothesized paths were centrally responsible for improved global fit. If both the LTPM and alternative hypotheses are not true for this circuit, it might be that resting-state and task-based connectivity develop independently of one another and/or are more substantively driven by factors including genetic programming, early life experience, and/or aspects of concurrent experience that are not well-captured by the self-disclosure task.

One important consideration in interpreting these findings is that the vmPFC is a functionally-defined region that lacks strict and agreed-upon anatomical boundaries and thereby includes a large swath of cortex encompassing multiple subregions. The fairly small subregion of the vmPFC examined in this study was also functionally rather than anatomically defined; it was chosen for being strongly implicated in socio-affective

processing networks in meta-analyses considering findings from both the task-based and resting-state literature (Alcalá-Lopez et al., 2018). In addition to anatomical connections with this subregion of the vmPFC, the NAcc also has connections with more caudal (e.g., anterior cingulate cortex) and ventral regions (e.g., orbitofrontal cortex) of the vmPFC. Prior longitudinal studies have identified heterogeneous effects of NAcc connectivity across the extent of the vmPFC. One study systematically examined parcels across the extent of the vmPFC and identified connectivity decreases across three other vmPFC subregions (ventral anterior cingulate cortex, subgenual anterior cingulate cortex, and posterior medial orbitofrontal cortex), but not in an anterior vmPFC region more similar to the one that was the focus of this investigation (Parr et al., 2021). Another longitudinal study of only resting-state connectivity identified age-related decreases in a region of fronto-medial cortex that partly overlapped the vmPFC region that we examined, as well as in a subcallosal subregion of the vmPFC (van Duijvenvoorde et al., 2019). These studies examined developmental trajectories and not the LTPM or alternative hypotheses; however, they highlight the heterogeneity of the vmPFC and suggest that additional exploratory research across the extent of this region may be warranted.

Within a modality, task-based NAcc-vmPFC connectivity predicted itself over time. This is notable in light of the fact that (as detailed in the next chapter), the majority of participants chose a different friend to disclose to at each wave. It suggests that NAcc-vmPFC connectivity during self-disclosure at least partly reflects a stable individual difference across adolescence. However, we identified low stability of resting-state connectivity between the NAcc and our vmPFC subregion across adolescence. Some studies suggest that resting-state connectivity is stable in adulthood (Gratton et al., 2018),

and prior studies examining resting-state connectivity between NAcc and vmPFC subregions during adolescence have also identified greater stability than in this study (ICC values of 0.21-0.31 in van Duijvenvoorde et al., 2019, compared to values close to zero in these analyses). Low within-person stability suggests that the NAcc's resting-state connectivity with the target region may be particularly sensitive to factors that vary by session, such as what participants are thinking about, and/or because individual factors dominate more when samples are drawn from a limited age span.

The LTPM hypothesis was supported in NAcc connectivity with the primary visual cortex. For this circuit, task-based connectivity unexpectedly predicted resting-state connectivity 18 months later, even when visual stimuli were absent (as participants' eyes are closed during the resting-state scans). We identified better global fit of models of the LTPM hypothesis as compared to the alternative hypothesis, as well as statistically significant time-lagged cross-modal paths suggesting that task-related connectivity during self-disclosure predicted resting-state connectivity across waves (Figure 3.4B). This association was observed in the raw correlations, suggesting that it is not an artifact of the model (Figure 3.2C). This pattern was not observed in NAcc connectivity with the primary auditory cortex, which suggests that it is not a feature of NAcc connectivity with primary sensory regions in general, but with task-relevant modalities. Connectivity between the NAcc and primary visual cortex during self-disclosure trials may reflect basic affective salience of the stimuli themselves. Previous studies have identified that reward value modulates neuronal activity in the primary visual cortex of non-human primates (Stănişor et al., 2013), as well as within an extended ventral visual pathway in humans (Hickey & Peelen, 2017). While there may be some afferent connections from

visual and somatosensory regions to the striatum (Salgado & Kaplitt, 2015), the NAcc and primary visual cortex are not part of a major circuit and their coordinated signal may be a result of indirect anatomical connections, as is the case for other regions that exhibit correlated signal at rest.

The unexpected finding of evidence for the LTPM hypothesis in NAcc connectivity with the primary visual cortex raises a new set of questions. First, the visual system has a well-understood hierarchical structure, and additional analyses might consider how "high up" and along what visual system pathway(s) this effect is seen. Understanding the degree to which this developmental pattern extends to regions involved in reading, semantic understanding, and/or social cognition might implicate higher-order cognitive processes, whereas greater specificity of this developmental pattern to primary visual cortex might suggest that the finding is grounded in a more basic sensory responses to the stimuli themselves. Second, analyses separately examining the two phases of self-disclosure trials (self-evaluation and self-disclosure decision phases) might additionally identify whether this pattern is driven by the self- and/or other-oriented aspects of the task, as both may be salient. However, it would be important to acknowledge that the two phases of the task do have overlapping time courses such that their signal can only be partly disentangled. Finally, follow-up analyses might seek to understand the extent to which task-based shifts in NAcc-primary visual connectivity reflect the unfolding of processes such as normative increases in reward approach during adolescence that tend to be associated with pubertal development (e.g., Igenogle et al., 2017), or whether they might be driven by experience. Compared to a few decades ago, adolescents' self-disclosure decisions are increasingly mediated by digital technologies

involving greater engagement of visual and text-based modalities when interacting with friends outside of the laboratory. Future analyses might consider whether changes between NAcc and visual system connectivity during self-disclosure are related to changes in technology use, particularly regarding technology that mediates social interactions.

Evaluating Sensitive Period Hypotheses

Results did not identify support for sensitive period hypotheses. Structural equation models in which time-lagged cross-modal effects were constrained to be equal tended to fit the data better than those that estimated different paths for T1 to T2 and T2 to T3. Additionally, hierarchical generalized additive models did not identify significant interactions between time-lagged predictors and maturation as measured by either age or pubertal stage. These findings suggest that null effects in models testing LTPM and alternative hypotheses were not the result of varying effects over time that cancelled one another out. Furthermore, we did not identify statistical evidence that the effect of task-based connectivity on resting-state connectivity identified in one control connection (NAcc-primary visual cortex) varied by maturation. Visual inspection of the interaction plots suggests that this effect might be stronger at later ages and pubertal stages (Figure 3.5), which might be explored with later waves of data from the Transitions in Adolescent Girls Study. If sensitive period hypotheses are not true for this circuit, it might be that its development is cumulatively informed by genetics and experience across childhood and into adulthood. Additionally, changes seen in adolescence may be transient, such as those reflecting, activational effects of puberty.

Limitations

First, a major limitation is that analyses can only speak to a form of causality grounded in temporal precedence that is typical of observational studies. Experimental manipulations that provide more certainty regarding causal mechanisms, such as those involving social deprivation in animal models, are unlikely to be feasible or ethical in children and adolescents. However, randomized intervention studies geared toward improving adolescent social connections may be one future avenue for experimental research. Second, resting-state functional connectivity scans were collected after separate runs of a self-evaluative task, and it is not possible with these data to rule out the possibility that effects may be related to carry-over of cognitive processes and/or thought patterns from those scans (Grigg & Grady, 2010). Third, we encountered estimation difficulties requiring the use of simpler models that either did not account for correlations between exogenous variables and a latent factor α (representing unmeasured causes of endogenous variables; this was the case in models of NAcc-vmPFC connectivity) or that eliminated α altogether (this was the case in models of NAcc-auditory and NAcc-visual connectivity). Eliminating α in models for the control connections tended to impact estimates of the within modality time-lagged effect, but minimally impacted the cross modality time-lagged effects that were of central interest in evaluating the LTPM and alternative hypotheses. Finally, robust missing data methods have not yet been developed for hierarchical generalized additive models (including those that would facilitate pooling parameters from multiple imputation), and these estimates may have been biased if the data were not missing completely at random. However, structural equation models

incorporated full-information maximum likelihood methods for producing unbiased estimates and standard errors when data are missing at random or completely at random.

Conclusions

We did not identify evidence for the LTPM or alternative hypotheses as developmental models of NAcc-vmPFC connectivity. Instead, we identified evidence for the LTPM hypothesis in NAcc connectivity with the primary visual cortex only. While follow-up analyses are needed to understand the specificity and extent of this effect, this finding complements prior work suggesting that LTPM effects can be identified despite differences in the timescales and analytic approaches employed across modalities (Gabard-Durnam et al., 2016). Exploratory analyses found that time-lagged cross-modal effects were not stronger at certain time points, ages, or pubertal stages, providing no evidence of sensitive period effects in the connections examined.

CHAPTER IV

IMPLICATIONS FOR SOCIAL RELATIONSHIPS AND MENTAL HEALTH IN ADOLESCENT GIRLS

Introduction

Despite epidemiological links between puberty and adolescent mental health, relatively little is known about how neural and social changes explain or mediate this association (Pfeifer & Allen, 2021). This chapter examined associations between neural connectivity and behavioral measures related to the self-disclosure task, as well as measures of adolescent friendship quality and mental health (with a focus on internalizing symptoms and especially depression). In doing so, we aimed to guide interpretations of our prior models of developmental change (Chapters 2 and 3) and to inform future research linking biopsychosocial processes during adolescent development to mental health.

Symptoms of psychopathology begin to increase at puberty across genders, and gender discrepancies in the prevalence of internalizing disorders emerge with the onset of puberty (Mendle, 2014). Meta-analyses suggest that early pubertal timing is linked to internalizing symptoms (Ullsperger & Nikolas, 2017), and in the same sample of girls analyzed in this study, the link between early timing and internalizing problems was more pronounced when measured by physical maturation rather than hormone levels (Barendse et al., preprint). A recent large-scale meta-analysis identified developmental differences in the median age of disorder onset, with fear/anxiety disorders typically emerging in childhood/adolescence and mood disorders more typically being diagnosed later in

adolescence and in adulthood (Solmi et al., 2021). However, a sizeable prior body of work has suggested that rates of depressive symptoms emerging in mid-adolescent girls tended to be associated with early puberty, and to persist into adulthood (Mendle et al., 2017), implicating potential sex- and/or gender-specific biopsychosocial mechanisms of developmental psychopathology (Ge & Natsuaki, 2009). These factors ultimately contribute to a sizable gender discrepancy in the prevalence of depression (1.5-3 times greater in women than men) and other internalizing problems worldwide (Mojtabai et al., 2016; World Health Organization, 2017).

A key protective factor that is associated with a reduced likelihood of major depressive disorder is self-disclosure (Santini et al., 2015). One large longitudinal study employing a quasi-causal design identified opportunities for self-disclosure as a robust predictor of depression in adults, even among a wide range of lifestyle factors (e.g., exercise and sleep; Choi et al., 2020). Self-disclosure processes may facilitate opportunities for social connectedness, and Although self-disclosure is normative and in many cases protective, patterns of self-disclosure involving extensive discussion of problems (known as co-rumination) are associated with increases in internalizing psychopathology and may be more pronounced in friendships among adolescent girls (Rose, 2002). When examining the neural processes supporting self-disclosure decisions to a close friend, NAcc and vmPFC engagement has been found to be sensitive to characteristics of that friendship (Vijayakumar et al., 2020). Both regions are part of a mesocorticolimbic system for processing value and reward that has been theorized to change with puberty and to play a central role in adolescent-emergent depression (Forbes & Dahl, 2005).

Goals of the Current Analysis

Considerations of neurodevelopmental processes as potential mediators between pubertal development and mental health is a relatively nascent area (Pfeifer & Allen, 2021). In such emerging areas of research, establishing effect sizes of pairwise relationships via exploratory research emphasizing effect sizes may be an important step toward long-term model- and theory-building (Flournoy et al., 2020). This chapter therefore examined effect sizes of associations between neural measures of functional connectivity and behavioral indices pertaining to aspects of adolescents' friendships and mental health. Between participants, greater NAcc-vmPFC task-based connectivity during self-disclosure was hypothesized to be associated with greater valuation of self-disclosure, as well as intimacy, support, and stability in adolescents' close friendships across time points. Greater NAcc-vmPFC connectivity during both self-disclosure and rest was hypothesized to be associated with fewer depressive symptoms, anxious symptoms, and better well-being (specifically, a connectedness facet of well-being) across time points. Task-based and resting-state connectivity between two additional regions (regions within the primary auditory and primary visual cortices) were also examined to evaluate the specificity of any effects.

Methods

The goal of the present analyses was to estimate the magnitude of effects between neural and behavioral measures across all time points. Three types of behavioral measures were examined: (1) indices related to the Self-Disclosure Task, (2) questionnaire measures related to the adolescents' friendships, and (3) questionnaire

measures related to mental health and well-being. Neural measures of task-based and resting-state connectivity were cleaned and processed as described in Chapter 2.

Additional Measures

Indices Related to the Self-Disclosure Task

Chosen Friend Stability. When completing the self-disclosure task, adolescents made a disclosure decision at every trial about whether to keep information about themselves private, or whether to share this information with a friend. Participants were interviewed prior to the scan to identify this friend and to verify that this was a close, ideally best friend that they would typically share at least some superficial and intimate information with. When possible, participants were encouraged to select a best friend of the same gender, but participants also chose male friends and/or relatives. Participants were informed that they would be asked to share one of their responses with their friend in real life, following the scan. Stability in their chosen friend on the self-disclosure task was coded as a "1" for participants who had listed the same friend across time points for which they had available neural task data, and as a "0" for participants who listed a different friend at any time points for which they had available neural task data. We note that further validation is needed to understand how this relates to the stability of adolescents' friendships in general, and that measuring chosen friend stability by examining friend's names is not an ideal measure, as adolescents' friends (particularly non-binary and/or transgender youth) may change their names over time.

Points of Subjective Equivalence. When choosing to keep information private or to self-disclose, each choice was associated with two to four pennies that translated to real monetary rewards that participants could earn on the task. Points of subjective

equivalence, or PSE values, were identified from cumulative normal curves fit to disclosure data on each increment of difference between the value of the two disclosure options (for more details, see Vijayakumar et al., 2020). Impossible estimates of PSE were calculated when participants had highly skewed behavior (i.e., always or almost always choosing to disclose or not to disclose), and these values were winsorized to a meaningful range based on the study design (e.g., -$0.02 or +$0.02 cents, which was the maximum discrepancy. Negative PSEs indicated a willingness to forfeit monetary reward to share information, reflecting a high intrinsic value of disclosure.

Questionnaire Measures of Adolescent Friendships

Across all questionnaire measures, mean response values were used; adolescents who missed one or more items were included in analyses.

Friendship Quality. The Intimate Friendship Scale (IFS) measured friendship quality via 32 items rated on a 7-point Likert scale, with higher scores reflecting higher friendship quality (Sharabany, 1994). This questionnaire assesses eight dimensions: disclosure, sensitivity, attachment, exclusiveness, giving, imposition, common activities, and trust, and these subscales had previously been found to exhibit adequate internal reliability (Sharabany et al., 1994). This scale was completed in reference to the same close peer chosen for disclosure in the self-disclosure task.

Perceived Support. The Multidimensional Scale of Perceived Social Support (MSPSS) measured perceptions of social support via 12 items rated on a 7-point Likert scale, with higher scores reflecting greater perceived support (Zimet, Dahlem, Zimet, & Farley, 1988). Separate items assessed support from family, friends, and significant

others. As we were interested in peer relationships and as the self-disclosure task focused on a close friendship, analyses here focused on the subscale related to friends.

Co-Rumination. Co-rumination refers to extensive focus and elaboration on negative feelings and problems within the context of a close friendship. Text preceding the questionnaire instructed participants to describe the way that they usually are with their best or closest same-sex friends. The Co-Rumination Questionnaire (CRQ) assessed co-rumination behaviors via 27 items rated on a 5-point Likert scale, with higher scores indicating greater co-rumination (Rose, 2002). These behaviors included the frequency of discussing problems, discussing problems in lieu of engaging in other activities, mutual encouragement of discussing problems, discussing the same problem repeatedly, speculation about the causes, consequences, and poorly understood aspects of problems, and focusing on negative feelings.

Questionnaire Measures of Mental Health

Depressive Symptoms. Depressive symptoms were assessed on the Center for Epidemiologic Studies Depression Scale for Children (CES-DC), a continuous measure developed by the NIMH that emphasizes depressed mood over the past week (Faulstich et al., 1986). The scale contains 20 items rated on a 4-point Likert scale, with higher scores indicating higher levels of depression.

Anxiety Symptoms. The Screen for Child Anxiety Related Emotional Disorders Brief Assessment of Anxiety and Post Traumatic Stress Symptoms was administered to participants to assess their anxiety and post traumatic stress symptoms at the time of assessment (Muris et al., 2000). Designed for children ages 7-18, the questionnaire

includes 10-items each rated on a 3-point Likert scale. As we were interested in general internalizing problems rather than trauma, analyses focused on the anxiety subscale only.

Connectedness as a Facet of Well Being. The Engagement, Perseverance, Optimism, Connectedness, and Happiness (EPOCH) measure of adolescent well-being was adapted from an adult model of well-being to be more developmentally appropriate for youth (Kern et al., 2016). The measure includes 20 items each rated on a 5-point Likert scale. As we were interested in social and especially peer relationships, analyses here focused on the connectedness subscale, which emphasized subjective feelings of closeness, support, and being valued by others. This measure was administered at T3 only.

Statistical Analyses

The current analyses aimed to identify effect sizes of relationships between neural resting-state and self-disclosure-elicited functional connectivity between the NAcc and a sub-region of the vmPFC (as well as two control regions) and behavioral measures in a sample that recruited adolescent girls. By using multilevel/hierarchical linear models, first-level models took the form of $Connectivity_{it} = \beta_{0i} + \beta_1(Behavior_{it} - \underline{Behavior}_i) + e_{it}$, whereas second-level models took the form of $\beta_{0i} = \gamma_{00} + \gamma_{01}(\underline{Behavior}_i) + u_{0i}$. Including mean-centered behavioral variables as first-level predictors and within-person means as second-level predictors allowed for estimation of both within- (β_1) and between- (γ_{01}) person effects. Two of the variables that we examined were time-invariant—there was only one variable assessing chosen friend stability over time, and connectedness as a facet of well-being was measured at T3 only. Time-invariant variables were included as second-level predictors, such that first-level models only estimated the effect of the

random intercept. Multilevel models were estimated using maximum likelihood methods and were specified in *lme4* (v 1.1-21) with complete observations only in *R*. Standardized fixed-effects estimates and their 95% confidence intervals were reported as indicators of effect size.

Results

Bivariate Correlations Between Behavioral Measures

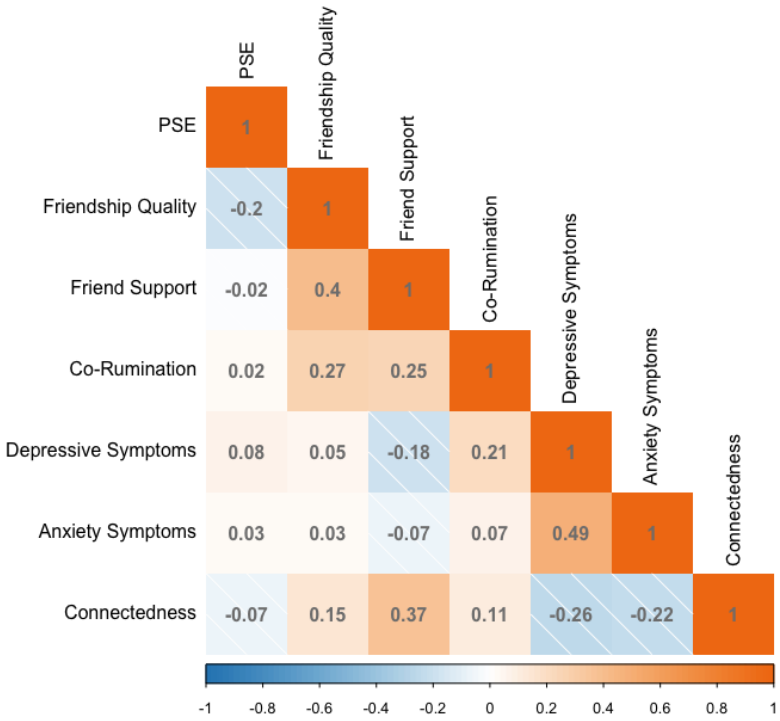
Examination of the Pearson correlation coefficients of disclosure task indices, friendship questionnaire, and mental health variables across waves revealed that the strongest correlations were between symptoms of anxiety and depression (r = 0.49), followed by correlations between friendship support, friendship quality, and social connectedness measures (r = 0.37-0.40). Also notable were negative correlations between social connectedness and symptoms of both depression and anxiety (r=0.26–0.22). Co-rumination was modestly correlated with friendship quality, friendship support, and social connectedness (r=0.15-0.27), but was also positively correlated with depressive symptoms (r=0.21). Finally, PSE only exhibited weak correlations with all other variables, except for friendship quality (r = -0.2); this suggested that adolescents with better friendship quality tended to place greater value on self-disclosure. (See Figure 4.1.)

Associations Between Self-Disclosure Task Indices and Neural Connectivity

Across measures of behavioral variables on neural connectivity, we characterize effects for which estimates with standardized effect sizes of greater than 0.1 whose confidence intervals did not include zero; however, some effects below that threshold are discussed when part of a broader pattern of effects.

Figure 4.1

Correlations Between Behavioral Measures, Collapsed Across Time Points



Note. PSE = Point of subjective equivalence

Table 4.1

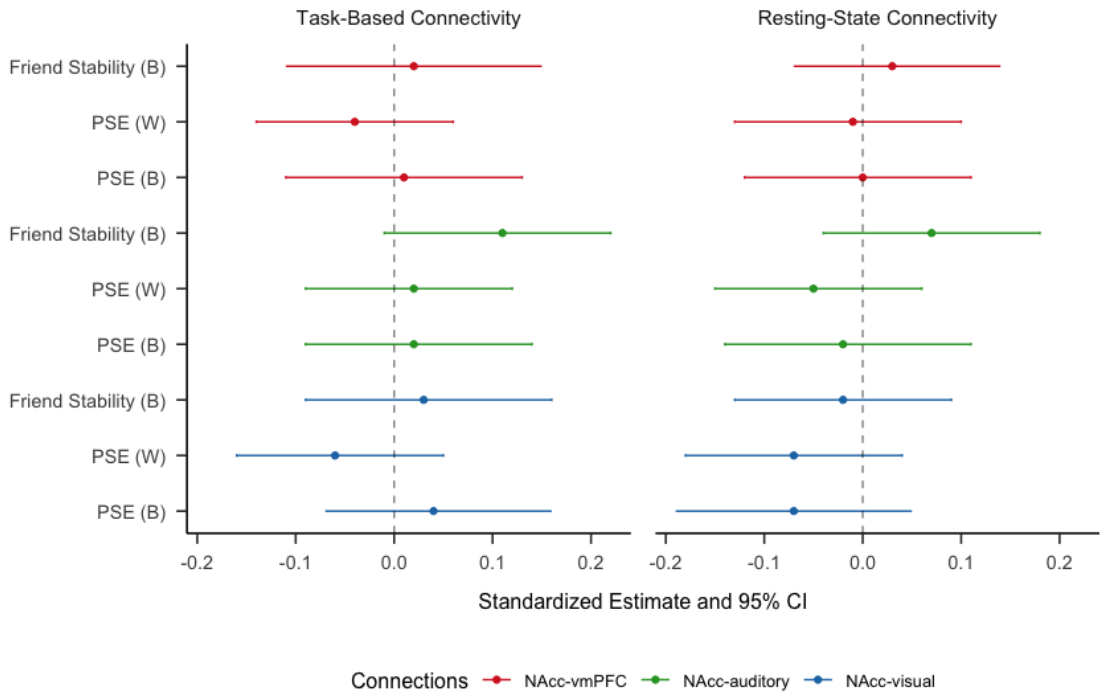
Descriptive Statistics of Self-Disclosure Task Variables Across Time Points

Variable	Metric	T1	T2	T3
Friend Named	N	147	136	72
	N missing (%)	1 (1%)	1 (1%)	1 (5%)
Same Friend as the Wave Prior	N		28	17
Same Friend as Two Waves Prior	N			11
PSE	Mean (SD)	-0.85 (1.46)	-0.46 (1.35)	-0.26 (1.36)
	N missing (%)	1 (1%)	15 (11%)	13 (17%)

Note. PSE = Point of subjective equivalence

Figure 4.2

Effect Sizes of Self-Disclosure Task Variables on Neural Connectivity



Note. PSE = Point of subjective equivalence; W = Within-person effect, B = Between-person effect.

Friendship Stability

An examination of effect sizes from multi-level models did not suggest that stability in the friend selected on the self-disclosure task was strongly related to task-based or resting-state connectivity between the NAcc and vmPFC or any of the control regions (Figure 4.2)

Intrinsic Value of Self-Disclosure

Similarly, examination of effect sizes did not suggest that the intrinsic value of disclosure (quantified as the PSE) that adolescents exhibited in the self-disclosure task

Table 4.2

Descriptive Statistics of Friendship Variables Across Time Points

Variable	Metric	T1	T2	T3
Friendship Quality	Mean (SD)	5.52 (0.77)	5.62 (0.66)	5.52 (0.65)
	N missing (%)	6 (4%)	2 (1%)	2 (0%)
Perceived Support from Friends	Mean (SD)	5.61 (1.16)	5.8 (1.05)	5.68 (1.2)
	N missing (%)	2 (0.01)	2 (0.01)	0 (0)
Co-Rumination	Mean (SD)	2.29 (0.86)	2.54 (0.77)	2.71 (0.81)
	N missing (%)	18 (0.12)	2 (0.01)	0 (0)

was strongly related to task-based or resting-state connectivity between the NAcc and vmPFC or any of the control regions (Figure 4.2)

Associations Between Friendship Questionnaire Measures and Neural Connectivity

Friendship Quality

Within-person changes in friendship quality were negatively associated with task-based NAcc connectivity with the vmPFC (b = -0.11, 95% CI [-0.21, -0.01]).

Perceived Social Support from Friends

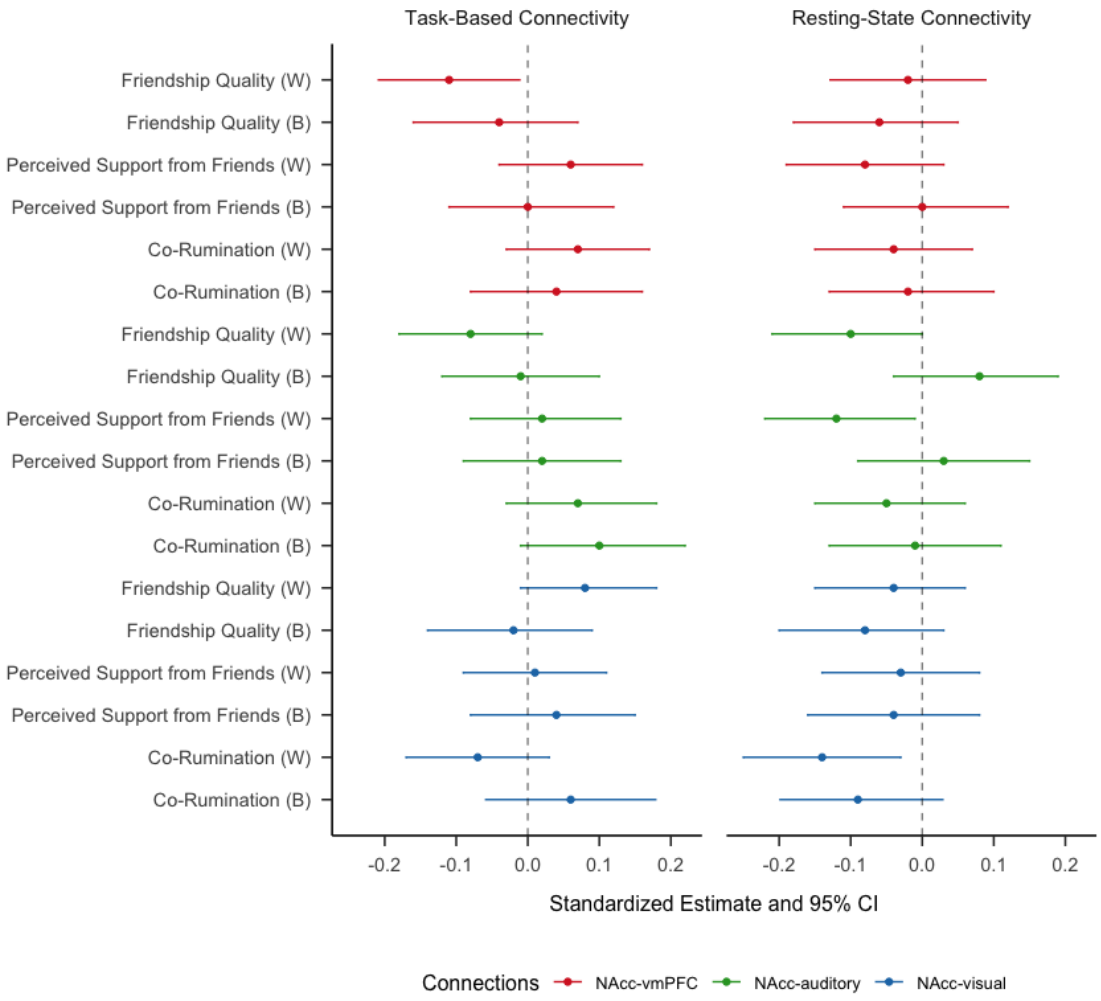
Within-person changes in perceived social support from friends were negatively associated with resting-state NAcc-auditory cortex connectivity (b = -0.12, 95% CI [-0.22, -0.01]).

Co-Rumination

Within-person changes in co-rumination were negatively associated with resting-state NAcc-visual cortex connectivity (b = -0.14 95% CI [-0.25, -0.03]).

Figure 4.3

Effect Sizes of Friendship Variables on Neural Connectivity



Note. W = Within-person effect, B = Between-person effect.

Associations Between Mental Health, Well-Being, and Neural Connectivity

Depressive Symptoms

Examination of effect sizes did not suggest that the depressive symptoms were strongly related to task-based or resting-state connectivity between the NAcc and vmPFC or any of the control regions (Figure 4.4).

Table 4.3

Descriptive Statistics of Mental Health Variables Across Time Points

Variable	Metric	T1	T2	T3
Depressive Symptoms	Mean (SD)	0.64 (0.51)	0.76 (0.59)	0.96 (0.64)
	N missing (%)	6 (4%)	2 (1%)	2 (0%)
Anxiety Symptoms	Mean (SD)	0.36 (0.36)	0.37 (0.37)	0.42 (0.34)
	N missing (%)	11 (0.07)	2 (0.01)	0 (0)
Connectedness	Mean (SD)			3.27 (0.72)
	N missing (%)			17 (0.22)

Anxiety Symptoms

Examination of effect sizes did not suggest that the anxiety symptoms were strongly related to task-based or resting-state connectivity between the NAcc and vmPFC (Figure 4.4). However, anxiety symptoms were negatively related to within-person resting-state connectivity between the NAcc and primary auditory cortex (b = -0.13 , 95% CI [-0.23, -0.02]).

Social Connectedness as a Facet of Well-Being

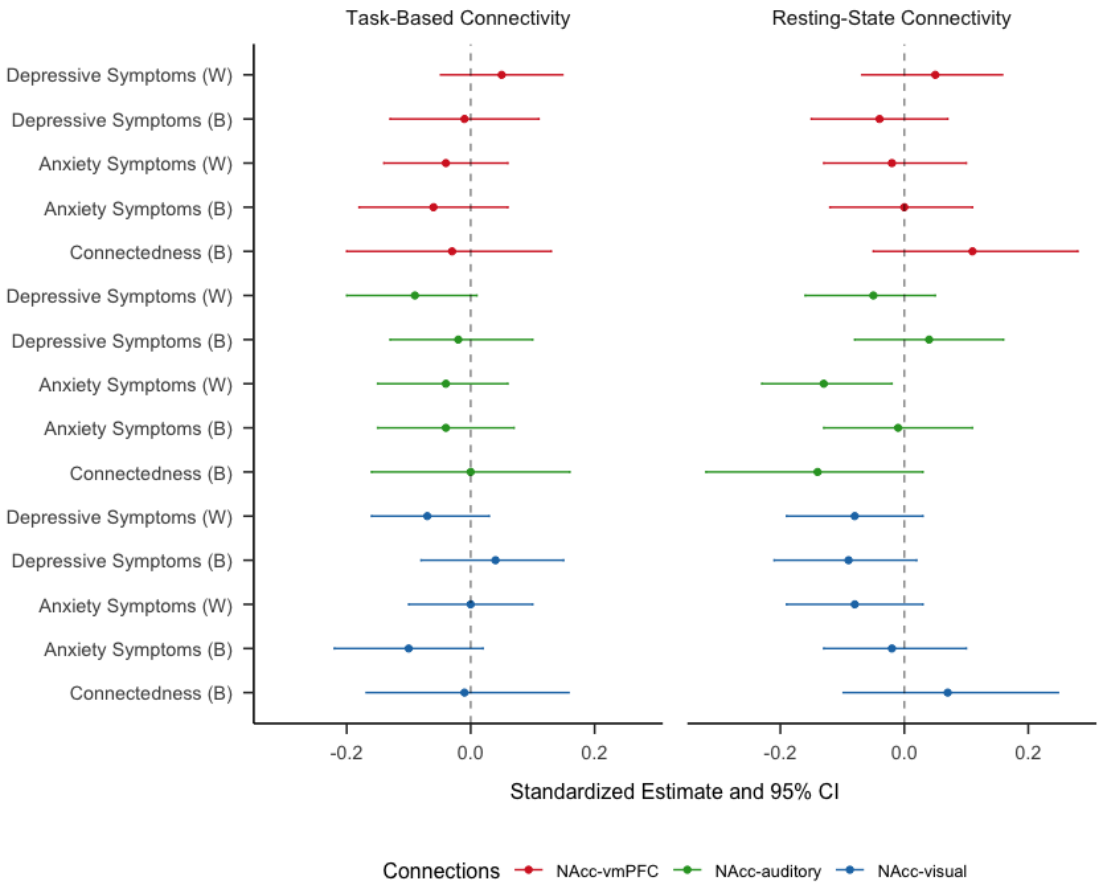
Examination of effect sizes did not suggest that the connectedness facet of well-being was strongly related to task-based or resting-state connectivity between the NAcc and vmPFC or any of the control regions (Figure 4.4).

Discussion

This chapter aimed to examine associations between neural measures of NAcc-vmPFC connectivity and behavioral indices related to the self-disclosure task, adolescent

Figure 4.4

Effect Sizes of Mental Health Variables on Neural Connectivity



Note. W = Within-person effect, B = Between-person effect.

friendships, and mental health. For brevity, we focused on interpreting associations with standardized effect sizes of greater than 0.1 whose confidence intervals did not include zero, although the broader pattern of effect sizes is presented for context (Figures 4.1-4.3, see Appendix C for a table of all values).

Associations with NAcc-vmPFC Connectivity

Examination of standardized effects across multilevel models did not suggest sizable associations between behavioral measures and NAcc-vmPFC connectivity at either task or rest, as effects were largely close to zero/rarely exceeded 0.1 and commonly exhibited wide confidence intervals. One association between a behavioral variable and NAcc-vmPFC connectivity was notable, but was in the opposite direction as hypothesized. This within-person effect suggested that higher levels of friendship quality were associated with lower-levels of task-based connectivity in our circuit of interest. The magnitude of the effect was such that one standard deviation of change in friendship quality (equivalent to roughly ⅔ of a point on averaged responses to a 7-point Likert scale from "Always disagree" to "Always agree" on the IFS) was associated with a tenth of a standard-deviation of change in neural connectivity.

Previous findings from the first wave of data found that univariate signal within the vmPFC and NAcc during disclosure decisions was predicted by the interaction of task condition (superficial versus intimate friendship depth) and friendship quality (Vijayakumar et al., 2020). This suggested that the relationship between NAcc-vmPFC connectivity and friendship quality might be sensitive to the specific types of information shared and in what contexts; additional analyses might clarify this relationship by examining differences between task conditions.

Associations with NAcc Connectivity to Control Regions

Examination of standardized effects across models did not suggest sizable effects between behavioral measures and task-based connectivity between the NAcc and control regions. However, results suggested within-person effects of behavioral variables on

NAcc resting-state connectivity with control regions. Specifically, perceived social support from friends and anxiety symptoms were both related to lower NAcc-auditory cortex resting-state connectivity, while co-rumination was also related to lower NAcc-visual cortex resting-state connectivity. Effect sizes were small; one standard deviation of change in perceived social support (roughly 1 point on averaged responses to a 7-point Likert scale ranging from "Very strongly disagree" to "Very strongly agree" on the MSPSS) or anxiety symptoms (⅓ of a point on averaged responses to a 3-point Likert scale ranging from "Not true or hardly ever true" to "Very often or often true" on the SCARED inventory) was associated with approximately a tenth of a standard-deviation of change in neural connectivity.

Effects involving connectivity with the auditory system suggest that, although participants were putatively "at rest", they were still navigating a unique environment created by the scanner that included MRI sounds commonly regarded as unpleasant. As NAcc signal has been associated with regulating responses to aversive stimuli (Wager et al., 2008; Doré et al., 2017), greater coordination between the NAcc and primary auditory cortex in the presence of these stimuli may reflect greater regulatory capacities or tendencies during exposure to noxious stimuli that appeared to be related to lower anxiety symptoms outside of the scanner. (This pattern would not be observed in task-based connectivity, as such sounds were present both during trials and at baseline and were therefore subtracted out from the signal.)

However, this interpretation does not help to explain why the same pattern of findings was identified for perceived social support from friends, in which greater perceptions of support from friends were also related to lower NAcc-auditory resting-

state connectivity; nor does it help to explain the association between greater co-rumination and lower NAcc-visual resting-state connectivity. Future analyses might systematically examine other voxels or parcels to assess the specificity and strength of these effects in light of broader developmental patterns. The present analyses do not rule out the possibility that negative within-person brain-behavior effects identified here might be due to coinciding with broader developmental trends, such as a tendency for NAcc and other subcortical structures to exhibit increasingly segregated resting-state connectivity with cortical regions across development (van Duijvenvoorde et al., 2019).

Limitations

These analyses should be interpreted in light of limitations discussed in previous chapters, including issues with missing data and collapsing across task conditions (Chapter 2), as well as the possibility of a different pattern of effects in other aspects of the vmPFC (Chapter 3). Associations between behavioral variables and task-based connectivity might be particularly obscured by collapsing across statement depths (superficial and intimate disclosures). However, the aim of the analyses in this chapter was not to verify a specific model of friendship development or psychopathology, but rather to identify effect sizes for future models and to aid in the interpretation of earlier developmental effects or trends (reflected in our decision to examine task-related signal at the same level of granularity employed when examining developmental trends and mechanisms).

Conclusions

Our hypotheses that NAcc-vmPFC task-based connectivity during self-disclosure and resting-state connectivity would be associated with behavioral variables reflecting

self-disclosure task behavior, aspects of friendship quality, and mental health were not supported. Overall, the strongest brain-behavior associations exhibited standardized estimates of around 0.10-0.15), with notable effects tending to be within- rather than between-subjects. These included the finding that within-person increases in friendship quality were associated with lower levels of NAcc-vmPFC task-based connectivity, a result that was in the opposite direction than hypothesized. When examining control regions, we found that NAcc resting-state connectivity with primary sensory regions was associated with anxiety symptoms and perceived social support from friends (auditory cortex), as well as co-rumination (visual cortex). While some of these findings might be interpreted in terms of the presence of unpleasant sensory stimuli (MRI sounds) during the resting-state scan, others are not straightforward and may be artifacts of other developmental processes.

CHAPTER V

DISCUSSION

Sensitive period theories posit that experiences during adolescence may sculpt the development of sociocultural processing by way of neurobiology. From an evolutionary lifespan perspective, the ability to tailor psychobiological systems to the sociocultural environment during adolescence might be adaptive in promoting reproductive success. This dissertation examines the theory that adolescence is a sensitive period and presents empirical work focused on identifying evidence for sensitive periods via a specific mechanism of change.

The first chapter of this dissertation updated and extended a prior review that had both articulated a framework for understanding adolescence as a sensitive period for sociocultural processing and identified significant gaps in the evidence base for this theory (Blakemore & Mills, 2014). As the last decade saw major advances in the field of developmental cognitive neuroscience, this chapter surveyed the literature with a focus on understanding changes to sociocultural processing and its neural underpinnings during adolescence, and how these changes might be driven by experience. Overall, while greater attention has been paid in some domains to the identification of robust developmental trends, an integrated and thorough understanding of experience-driven, developmentally-specific, and domain-specific effects has not yet emerged in most areas.

Sensitive Periods Theories from a Translational Science Lens

Major goals of elucidating developmental theory are not only to understand constructs for their own sake, but to predict behavior and to support or intervene on

systems in a way that can foster healthy youth development. Academic interests in elucidating theory, considering all possible alternative explanations, and generating high-profile findings may be tangential to or at odds with translational aims of policy-makers and youth-serving professionals who seek guidance on how to act within more immediate time frames. Is further research geared toward understanding adolescence as a sensitive period of true practical significance? Despite articulating limitations and gaps in our understanding of adolescence as a sensitive period for sociocultural processing, I suggest that many translational inferences may be adequately supported by heuristic conceptualizations of adolescence as such. For example, social isolation in the form of solitary confinement is detrimental across the lifespan, and may be particularly harmful for adolescents. Such isolation has been noted for inducing symptoms of psychosis as far back as the 19th century (Smith, 2006), and isolating youths in juvenile detention is associated with suicide (Cloud et al., 2014). The social isolation endured as a part of the coronavirus pandemic is thought to be detrimental to adolescent development, on average (Orben et al., 2020). In these cases, a heuristic conceptualization of adolescence as a period that expects rich social experiences to support typical development is well-founded. Significant barriers to adequate mental health care globally include stigma, access, and little preventative care (Wainberg et al., 2017). This heuristic may be useful in countering narratives that only experiences in early childhood are worthy of public focus, thereby highlighting the need for investment in treatment and prevention during adolescence.

Pushing beyond heuristic uses of sensitive periods conceptualizations of adolescence may support additional possibilities for translation. Conceptualizing

adolescence as a period of heightened sensitivity requires less stringent evidence than sensitive period theories, and may also inform useful translational approaches. Knowing that adolescents may be more likely to take certain kinds of risks in the presence of peers, or when motivated by social acceptance may be relevant for public policy aimed toward reducing health-risking behaviors. One framework suggests that harnessing adolescents' desire for status and respect can improve adolescent interventions, especially those targeting risky or antisocial behaviors (Yeager et al., 2018), for example by increasing the status associated with desirable behaviors such as healthy eating (Bryan, et al., 2016) and rejecting cigarettes (Farrelly et al., 2002). An additional possibility is to capitalize on the heightened relevance of highly connected peers to shape values and behavior. In one intervention study, schools were randomly assigned to receive an anti-conflict intervention that invited randomly-selected students to take a more active and public role in opposing school conflict (Paluck et al., 2016). Schools in which more of the randomly-selected students were highly connected "social referents" saw the greatest declines in disciplinary reports of peer conflict.

Another area within the study of sensitive periods seeks to understand their limits and flexibility in a way that may support recovery of plasticity later in development. For example, following social isolation in the juvenile period, resocialization in combination with administration of the antidepressant fluoxetine, but not alone, reduced aggressive behaviors in rodents (Mikics et al., 2018). This effect was dependent on the signaling of brain-derived neurotrophic factor, a widely expressed neural growth factor that supports long-term memory that is up-regulated in response to both antidepressants and exercise (Russo-Neustadt et al., 2001). The authors suggest that behavioral interventions for

childhood adversity (specifically neglect) later in development might have enhanced efficacy when administered in concert with interventions that target plasticity itself (Miskolczi et al., 2019).

Overview of Results

The empirical portion of this dissertation examined functional connectivity within a specific neural circuit, with a focus on its developmental trajectories (Chapter 2), developmental mechanisms (including sensitive period mechanisms; Chapter 3), and relationships with behavioral variables (Chapter 4). We focused on two key nodes of a mesocorticolimbic circuit (the nucleus accumbens (NAcc) and the ventromedial prefrontal cortex (vmPFC). Measures of functional connectivity assessed the degree of putative coordination between these regions across states of rest and task. Resting-state connectivity is commonly thought to reflect the brain's intrinsic connectivity, while task-based connectivity is a window into neural functioning during a specific psychological process. In this case, frontostriatal connectivity during self-disclosure to a close friend was considered as a window into the integration of value-related and social cognitive processes within the context of adolescents' close friendships. However, it is important to note that this measure is not a direct measure of social experiences and environments of adolescents, as suggested by the weak correlations with behavioral variables identified in Chapter 4.

When examining developmental trajectories in Chapter 2, we found that pubertal development, but not age, was associated with non-linear changes in connectivity elicited by self-disclosure decisions. This trend was driven by task-based connectivity increases between pubertal stages 3 and 4 on a scale that is akin to, but not a precise mapping to,

Tanner staging. When examining trajectories of resting-state functional connectivity, models incorporating age and/or pubertal stage did not exhibit improved fit compared to null models; however, a visual inspection of the data suggested possible connectivity decreases occurring at the earliest ages and pubertal stages.

In Chapter 3, we evaluated the long-term phasic modeling hypothesis that in developing circuits, phasic connectivity sculpts resting-state connectivity over long time-scales. Structural equation models of the long-term phasic modeling hypothesis and an alternative hypothesis (that resting-state connectivity predicts task-based connectivity) did not suggest that either process characterized longitudinal changes in connectivity of the NAcc-vmPFC. Evidence consistent with the long-term phasic modeling hypothesis was unexpectedly identified for NAcc connectivity with the primary visual cortex, which was examined as one of two sensory control connections. Additional analyses considered sensitive periods hypotheses by examining whether time-lagged cross-modal effects central to either the long-term phasic modeling hypothesis or its alternative varied by maturation. No evidence for sensitive periods hypotheses was identified across connections when maturation was measured in terms of wave, pubertal stage, or age.

In Chapter 4, we explored brain-behavior associations. Results across task and rest found that, of numerous behavioral variables, NAcc-vmPFC connectivity during task was only weakly negatively associated with friendship quality (within-person effect). Examination of resting-state NAcc connectivity with control regions identified similar negative and within-person associations with co-rumination (visual cortex), as well as anxiety symptoms and perceived social support from friends (auditory cortex).

Summary

Empirical analyses suggested that task-based frontostriatal connectivity (between the NAcc and vmPFC) during self-disclosure exhibits a period of flux around pubertal stages 3-4 (Chapter 2), and within-person increases in connectivity were associated with poorer friendship quality (Chapter 4). Evidence that phasic modeling drives resting-state connectivity in this circuit and/or that sensitive periods sculpt this circuit's development was lacking. Evidence consistent with the long-term phasic modeling hypothesis was instead identified for connectivity between the NAcc and primary visual cortex (Chapter 3), which was unexpected given the relatively early-developing nature of the visual system relative to higher-order cognitive systems. Exploratory analyses suggest resting-state connectivity between these regions was associated with lower self-reported co-rumination (Chapter 4) such that phasic sculpting might be adaptive, although longitudinal mediation models are needed to explore this further.

Limitations

The empirical portion of this dissertation centrally investigated the idea that adolescent girls' social relationships become neurally embedded via NAcc-vmPFC circuitry in a manner that may be relevant to behavior and psychopathology, particularly symptoms of depression. Ultimately, the evidence did not support this framework. This section explores reasons that this might be the case.

Inferences about developmental trajectories are influenced by the age range of participants recruited into a study. There are two possibilities related to not having examined the appropriate age range that would have led us to miss effects consistent with one or more of the developmental models: First, it is possible that we looked too early,

and that the proposed developmental mechanism might be observed later in development. While changes to task-based NAcc-vmPFC functional connectivity occurred fairly late in development (between pubertal stages 3-4), the average pubertal stages at each time point were approximately 3, 4, and 5. This suggests that there was likely adequate sampling of participants at later stages of development in order to identify downstream effects of changes occurring around stages 3-4. Second, it is possible that we looked too late, and that the proposed mechanism might be observed earlier in development. This possibility is consistent with indications that resting-state NAcc-vmPFC functional connectivity was already fairly stable across time points, and that non-linear decreases in NAcc-vmPFC connectivity were present very early in maturation only. As it would not be the case that these early changes to resting-state connectivity were driven by later puberty-related increases in NAcc-vmPFC connectivity, this would thus only have influenced our ability to detect the alternative hypothesis.

Another possibility is that these developmental patterns might be identified in other regions of the vmPFC, a heterogeneous and functionally-defined region (see the discussion in Chapter 3) and indeed in other neural systems entirely. Identification of evidence consistent with the long-term phasic modeling hypothesis in NAcc connectivity with a region in the primary visual cortex suggests that this developmental mechanism may be implicated in more basic processing, and that null findings in the vmPFC may not be entirely attributed to differences, for example, in the time-scales examined across task-based and resting-state connectivity analyses. In these analyses, we focused on overall effects of self-disclosure, collapsed across trial phases (self-evaluative and disclosure) and types (superficial and intimate disclosures). The identification of a finding related to

NAcc connectivity with the visual system, as well as small brain-behavior effects, may be because comparisons of overall self-disclosure trials to baseline/blank screens is more of a "hammer" approach that is not as informative with respect to the nuances of social processing.

The field is lacking in standard analytic formulas for power calculations with multilevel models that account for temporal dependencies (Lafit et al., 2021), and simulations would be needed to account for the type of models used here. While a lack of power can never be ruled out as reasons for null findings, the sample size of the current study was comparable to previous developmental studies of frontostriatal connectivity (particularly when accounting for the focus on girls only in this study) and much larger than previous studies of time-lagged effects across task-based and resting-state modalities.

Finally, effect sizes relating neural measures to behavioral measures identified in Chapter 4 were small. Although the limitations above suggest the possibility of additional exploratory analyses, the immediate practical consequences of this research, based on the present findings, are unclear. Analyses relating human neuroimaging measures to real world behavioral measures have often found such effects to be small and/or difficult to replicate (Masouleh et al., 2020). Furthermore, interpreting the practical relevance and significance of variables based on their effect sizes is an important and evolving issue with newly emerging standards in the psychological sciences (Anvari et al., 2021).

Future Directions

First, additional analyses might explore the unexpected finding of evidence for the long-term phasic modeling hypothesis in the NAcc-primary visual cortex. Follow-up

analyses might consider the extent of this effect along hierarchical pathways of visual processing, and whether the effect varies by trial phase or condition within the self-disclosure task, as well as across different tasks entirely. These analyses might facilitate interpretations of this finding, particularly to parse whether this effect is associated with developmental changes to the intrinsic salience of the self- and/or other related visual stimuli, and/or whether experience with text-based, visual experience with self-disclosure and in digital social environments play a role in this observed developmental shift.

Limitations of the current analyses might be mitigated in future studies examining cross-lagged effects across states of task and rest via a multi-stage strategy employing preliminary data-driven approaches to select connections-of-interest meeting certain criteria. Connections of interest between voxels or parcels might be selected for being developmentally plausible based on trajectories suggesting fluctuations in task-based and/or resting-state connectivity in the earlier time points of a longitudinal studies. They might also be selected for exhibiting sizable associations with behavioral variables of interest, which might improve both utility and interpretability.

Analyses here have focused on functional connectivity across different states of task and rest, specifically testing hypotheses that are aligned with conceptions of resting-state functional connectivity as potentially reflecting histories of co-activation. There is substantial debate, however, as to what "resting-state" truly reflects. Bolt and colleagues (2018) argue that division between evoked (task-based) and intrinsic (resting-state) activity is a false dichotomy, and that large-scale activity patterns observed across states may be better characterized as the brain's way of supporting specific functions within a set of constraints across time. Another challenge to this view comes from recent analyses

suggesting that latent patterns of functional connectivity across a wide range of tasks is more "intrinsic"—stable and predictive of other brain states—than resting-state functional connectivity (McCormick et al., preprint). There are at least two ways of potentially improving tests of long-term phasic modeling hypotheses under this view: (1) by understanding mappings from prior task states to a variety of future task and "rest" states, and (2) by incorporating measures of structural connectivity, at least for connections with clear anatomically-defined direct or indirect paths. Multimodal analyses may shed further light into the role of white matter development in facilitating e.g., long-term phasic modeling or other neurodevelopmental mechanisms. Pubertal sex hormones are another biological measure that, in tandem with knowledge about hormone receptor density, might be informative with respect to understanding what drives developmental change. Gonadal steroids may be of particular interest for future inquiry, as estrogen has been hypothesized to play a role in regulating sensitive periods of prefrontal plasticity in the transition to adolescence (Piekarski et al., 2017), and testosterone levels have been shown to mediate the effects of age on ventral striatal connectivity with ventromedial prefrontal regions during rest (Fareri et al., 2015).

Conclusions

This dissertation reviewed existing evidence for adolescence as a sensitive period for sociocultural development and identified progress and gaps in this literature within the field of developmental cognitive neuroscience. Overall, empirical analyses did not find evidence consistent with a developmental mechanism whereby phasic task-based frontostriatal connectivity during self-disclosure becomes neurally-embedded in a manner that is relevant for behavior and psychopathology. Instead, support for a long-term phasic

modeling mechanism was identified in connectivity between the nucleus accumbens and the primary visual cortex, suggesting extended development of the visual system in a manner that integrates affective information. No effects consistent with sensitive periods were identified, and effects relating neural to behavioral measures were small. Important future directions include elaborating on the specificity (both spatially and in terms of task condition) and translational relevance of these putative developmental mechanisms.

The empirical research described here additionally highlights an analysis strategy that capitalizes on the relative strengths and weaknesses of two major modeling approaches (structural equation modeling and generalized additive modeling) to understand the temporal precedence of changes in variables *and* to assess how those changes may vary with maturation. This strategy might be applied to examinations of developmental and sensitive period mechanisms across longitudinal studies with more than two waves of data in studies of the brain and/or behavior.

APPENDIX A

Table A.1

Models Predicting NAcc-Auditory Cortex Beta-Series Connectivity During Disclosure Decisions by Age and Pubertal Stage

	Model 1: Age			Model 2: Puberty			Model 3: Puberty + Age		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.34 ***	0.18 – 0.50	<0.001	0.13 ***	0.11 – 0.16	<0.001	0.37 **	0.14 – 0.60	0.001
Age	-0.02 **	-0.03 – -0.01	0.006				-0.02 *	-0.04 – -0.00	0.038
Pubertal Stage (Linear)				-0.06 *	-0.12 – -0.00	0.048	-0.02	-0.09 – 0.06	0.624
Pubertal Stage (Quad)				0.02	-0.04 – 0.08	0.450	0.04	-0.02 – 0.09	0.241
Pubertal Stage (Cubic)				-0.02	-0.07 – 0.04	0.550	-0.02	-0.07 – 0.03	0.488
Pubertal Stage (Quartic)				-0.02	-0.06 – 0.03	0.493	-0.01	-0.06 – 0.03	0.554
Random Effects									
σ^2	0.03			0.03			0.03		
τ_{00}	0.00 $_{participant}$			0.00 $_{participant}$			0.00 $_{participant}$		
ICC	0.03			0.04			0.04		
N	159 $_{participant}$			158 $_{participant}$			158 $_{participant}$		
Observations	336			319			319		
Marginal R^2 / Conditional R^2	0.022 / 0.055			0.016 / 0.053			0.029 / 0.072		

Note. Only the best-fitting or simplest age model is shown. * *p*<0.05 ** *p*<0.01 *** *p*<0.001

Table A.2

Models Predicting NAcc-Auditory Cortex Resting-State Connectivity by Age and Pubertal Stage

	Model 1: Age			Model 2: Puberty			Model 3: Puberty + Age		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.19 *	0.03 – 0.36	0.020	0.04 **	0.01 – 0.07	0.002	0.23 *	0.01 – 0.46	0.044
Age	-0.01 *	-0.03 – -0.00	0.040				-0.02	-0.03 – 0.00	0.093
Pubertal Stage (Linear)				-0.06 *	-0.12 – -0.00	0.048	-0.02	-0.10 – 0.05	0.516
Pubertal Stage (Quad)				0.03	-0.02 – 0.09	0.236	0.04	-0.01 – 0.10	0.143
Pubertal Stage (Cubic)				-0.05	-0.10 – 0.00	0.058	-0.05	-0.10 – 0.00	0.058
Pubertal Stage (Quartic)				0.01	-0.04 – 0.06	0.624	0.01	-0.03 – 0.06	0.545
Random Effects									
σ^2	0.02			0.02			0.02		
τ_{00}	0.00 $_{participant}$			0.00 $_{participant}$			0.00 $_{participant}$		
ICC	0.12			0.17			0.17		
N	159 $_{participant}$			158 $_{participant}$			158 $_{participant}$		
Observations	309			298			298		
Marginal R^2 / Conditional R^2	0.013 / 0.129			0.020 / 0.185			0.029 / 0.190		

Note. Only the best-fitting or simplest age model is shown. * *p<0.05* ** *p<0.01* *** *p<0.001*

Table A.3

Models Predicting NAcc-Visual Cortex Beta-Series Connectivity During Disclosure Decisions by Age and Pubertal Stage

	Model 1: Age			Model 2: Puberty			Model 3: Puberty + Age		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.48 ***	0.21 – 0.74	<0.001	0.27 ***	0.23 – 0.32	<0.001	0.54 **	0.16 – 0.91	0.005
Age	-0.02	-0.04 – 0.00	0.125				-0.02	-0.05 – 0.01	0.172
Pubertal Stage (Linear)				-0.02	-0.12 – 0.08	0.735	0.03	-0.09 – 0.15	0.616
Pubertal Stage (Quad)				-0.03	-0.12 – 0.06	0.538	-0.02	-0.11 – 0.08	0.744
Pubertal Stage (Cubic)				0.06	-0.02 – 0.15	0.130	0.06	-0.02 – 0.14	0.139
Pubertal Stage (Quartic)				0.02	-0.06 – 0.10	0.584	0.02	-0.05 – 0.10	0.544
Random Effects									
σ^2	0.07			0.07			0.07		
τ_{00}	0.01 $_{participant}$			0.01 $_{participant}$			0.01 $_{participant}$		
ICC	0.16			0.14			0.14		
N	159 $_{participant}$			158 $_{participant}$			158 $_{participant}$		
Observations	336			319			319		
Marginal R^2 / Conditional R^2	0.007 / 0.161			0.012 / 0.147			0.018 / 0.160		

Note. Only the best-fitting or simplest age model is shown (trends were consistent with a quadratic age model, but this model did not meet thresholds for being considered "best-fitting") * *p<0.05* ** *p<0.01* *** *p<0.001*

Table A.4

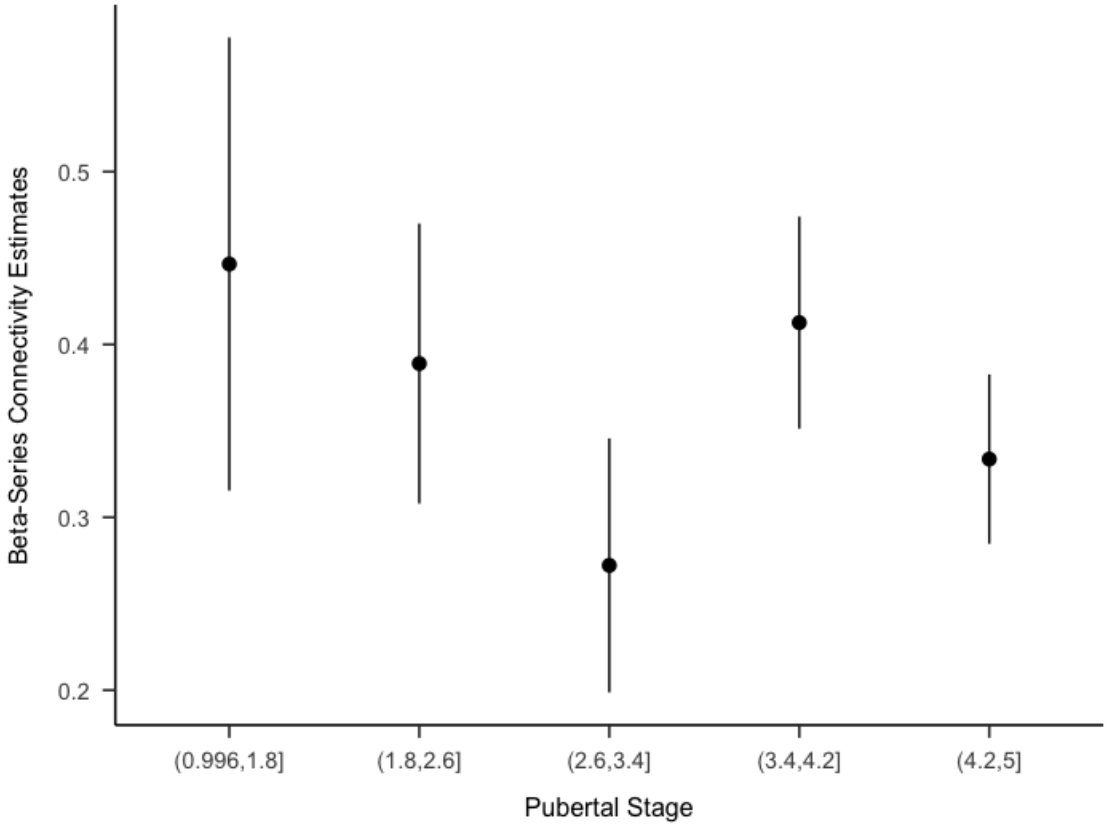
Models Predicting NAcc- Visual Cortex Resting-State Connectivity by Age and Pubertal Stage

	Model 1: Age			Model 2: Puberty			Model 3: Puberty + Age		
Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.09	-0.09 – 0.26	0.348	0.00	-0.02 – 0.03	0.792	0.05	-0.19 – 0.29	0.687
Age	-0.01	-0.02 – 0.01	0.292				-0.00	-0.02 – 0.02	0.707
Pubertal Stage (Linear)				-0.04	-0.10 – 0.03	0.256	-0.03	-0.11 – 0.05	0.468
Pubertal Stage (Quad)				0.00	-0.06 – 0.07	0.905	0.01	-0.06 – 0.07	0.853
Pubertal Stage (Cubic)				-0.02	-0.08 – 0.03	0.400	-0.02	-0.08 – 0.03	0.397
Pubertal Stage (Quartic)				0.01	-0.04 – 0.06	0.755	0.01	-0.04 – 0.06	0.733
Random Effects									
σ^2	0.03			0.03			0.03		
τ_{00}	0.00 $_{participant}$			0.00 $_{participant}$			0.00 $_{participant}$		
ICC	0.09			0.10			0.10		
N	159 $_{participant}$			158 $_{participant}$			158 $_{participant}$		
Observations	309			298			298		
Marginal R^2 / Conditional R^2	0.004 / 0.093			0.009 / 0.104			0.009 / 0.106		

Note. Only the best-fitting or simplest age model is shown. * *p<0.05* ** *p<0.01* ***p<0.001*

Figure A.1

Estimated beta-series connectivity values by pubertal stage



Note. Bars indicate 95% confidence intervals. Ranges of pubertal stage composite score ranges shown here were used to approximate pubertal stages 1-5.

APPENDIX B

Table B.1

Hierarchical Generalized Additive Models Examining Neural Predictor by Maturation Interactions for NAcc-Auditory Cortex Connectivity

	LTPM – Age			LTPM – Puberty			ALT – Age			ALT – Puberty		
Lagged Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	0.01	-0.02 – 0.04	0.607	0.01	-0.03 – 0.04	0.641	0.08 ***	0.04 – 0.11	<0.001	0.08 ***	0.04 – 0.11	<0.001
RSFC	0.11	-0.06 – 0.27	0.201	0.14	-0.03 – 0.30	0.104						
Beta							0.04	-0.13 – 0.21	0.643	0.05	-0.13 – 0.22	0.602
		F(2)	*p*		*F*(2)	*p*		*F*(2)	*p*		*F*(2)	*p*
Beta by age		0.771	0.464									
Beta by puberty					1.083	0.342						
RSFC by age								0.258	0.773			
RSFC by puberty											0.129	0.879
Observations	130			124			137			130		
R^2	0.023			0.032			0.005			0.004		

*Note. * p<0.05 ** p<0.01 *** p<0.001;* RSFC = resting-state functional connectivity; Beta = beta-series, task-based connectivity; LTPM = Long-Term Phasic Model; in LTPM models, the interaction between task-based beta-series connectivity and maturation predicted resting-state functional connectivity; ALT = Alternative model; in ATL models, the interaction between resting-state connectivity and maturation predicted task-based functional connectivity. All predictor variables were time-lagged by one time point. Omnibus tests evaluated the null hypothesis for the joined spline terms.

Table B.2

Hierarchical Generalized Additive Models Examining Neural Predictor by Maturation Interactions for NAcc-Visual Cortex Connectivity

	LTPM - Age			LTPM - Puberty			ALT - Age			ALT - Puberty		
Lagged Predictors	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*	Estimates	CI	*p*
(Intercept)	-0.04 *	-0.08 – -0.00	0.030	-0.05 *	-0.09 – -0.01	0.023	0.19 ***	0.12 – 0.25	<0.001	0.18 ***	0.11 – 0.24	<0.001
RSFC	0.12	-0.02 – 0.26	0.101	0.09	-0.06 – 0.23	0.252						
Beta							0.19 *	0.03 – 0.35	0.020	0.21 **	0.05 – 0.37	0.009
		F(2)	*p*		*F*(2)	*p*		*F*(2)	*p*		*F*(2)	*p*
Beta by age		1.416	0.246									
Beta by puberty					1.371	0.258						
RSFC by age								0.615	0.543			
RSFC by puberty											0.85	0.430
Observations	130			124			137			130		
R^2	0.043			0.033			0.044			0.061		

*Note. * p<0.05 ** p<0.01 *** p<0.001;* RSFC = resting-state functional connectivity; Beta = beta-series, task-based connectivity; LTPM = Long-Term Phasic Model; in LTPM models, the interaction between task-based beta-series connectivity and maturation predicted resting-state functional connectivity; ALT = Alternative model; in ATL models, the interaction between resting-state connectivity and maturation predicted task-based functional connectivity. All predictor variables were time-lagged by one time point. Omnibus tests evaluated the null hypothesis for the joined spline terms.

APPENDIX C

Table C.1

Effects of Behavioral Measures on Neural Measures Across Time Points

Connection	Effect	Standard Estimate & 95% CI
Beta-Series Connectivity		
NAcc-vmPFC	Friend Stability (B)	0.02 [-0.11, 0.15]
NAcc-vmPFC	PSE (W)	-0.04 [-0.14, 0.06]
NAcc-vmPFC	PSE (B)	0.01 [-0.11, 0.13]
NAcc-vmPFC	Friendship Quality (W)	-0.11 [-0.21, -0.01]
NAcc-vmPFC	Friendship Quality (B)	-0.04 [-0.16, 0.07]
NAcc-vmPFC	Perceived Support from Friends (W)	0.06 [-0.04, 0.16]
NAcc-vmPFC	Perceived Support from Friends (B)	0 [-0.11, 0.12]
NAcc-vmPFC	Co-Rumination (W)	0.07 [-0.03, 0.17]
NAcc-vmPFC	Co-Rumination (B)	0.04 [-0.08, 0.16]
NAcc-vmPFC	Depressive Symptoms (W)	0.05 [-0.05, 0.15]
NAcc-vmPFC	Depressive Symptoms (B)	-0.01 [-0.13, 0.11]
NAcc-vmPFC	Anxiety Symptoms (W)	-0.04 [-0.14, 0.06]
NAcc-vmPFC	Anxiety Symptoms (B)	-0.06 [-0.18, 0.06]
NAcc-vmPFC	Connectedness (B)	-0.03 [-0.2, 0.13]
NAcc-auditory	Friend Stability (B)	0.11 [-0.01, 0.22]
NAcc-auditory	PSE (W)	0.02 [-0.09, 0.12]
NAcc-auditory	PSE (B)	0.02 [-0.09, 0.14]
NAcc-auditory	Friendship Quality (W)	-0.08 [-0.18, 0.02]
NAcc-auditory	Friendship Quality (B)	-0.01 [-0.12, 0.1]
NAcc-auditory	Perceived Support from Friends (W)	0.02 [-0.08, 0.13]
NAcc-auditory	Perceived Support from Friends (B)	0.02 [-0.09, 0.13]
NAcc-auditory	Co-Rumination (W)	0.07 [-0.03, 0.18]
NAcc-auditory	Co-Rumination (B)	0.1 [-0.01, 0.22]
NAcc-auditory	Depressive Symptoms (W)	-0.09 [-0.2, 0.01]

NAcc-auditory	Depressive Symptoms (B)	-0.02 [-0.13, 0.1]
NAcc-auditory	Anxiety Symptoms (W)	-0.04 [-0.15, 0.06]
NAcc-auditory	Anxiety Symptoms (B)	-0.04 [-0.15, 0.07]
NAcc-auditory	Connectedness (B)	0 [-0.16, 0.16]
NAcc-visual	Friend Stability (B)	0.03 [-0.09, 0.16]
NAcc-visual	PSE (W)	-0.06 [-0.16, 0.05]
NAcc-visual	PSE (B)	0.04 [-0.07, 0.16]
NAcc-visual	Friendship Quality (W)	0.08 [-0.01, 0.18]
NAcc-visual	Friendship Quality (B)	-0.02 [-0.14, 0.09]
NAcc-visual	Perceived Support from Friends (W)	0.01 [-0.09, 0.11]
NAcc-visual	Perceived Support from Friends (B)	0.04 [-0.08, 0.15]
NAcc-visual	Co-Rumination (W)	-0.07 [-0.17, 0.03]
NAcc-visual	Co-Rumination (B)	0.06 [-0.06, 0.18]
NAcc-visual	Depressive Symptoms (W)	-0.07 [-0.16, 0.03]
NAcc-visual	Depressive Symptoms (B)	0.04 [-0.08, 0.15]
NAcc-visual	Anxiety Symptoms (W)	0 [-0.1, 0.1]
NAcc-visual	Anxiety Symptoms (B)	-0.1 [-0.22, 0.02]
NAcc-visual	Connectedness (B)	-0.01 [-0.17, 0.16]
Resting-State Functional Connectivity		
NAcc-vmPFC	Friend Stability (B)	0.03 [-0.07, 0.14]
NAcc-vmPFC	PSE (W)	-0.01 [-0.13, 0.1]
NAcc-vmPFC	PSE (B)	0 [-0.12, 0.11]
NAcc-vmPFC	Friendship Quality (W)	-0.02 [-0.13, 0.09]
NAcc-vmPFC	Friendship Quality (B)	-0.06 [-0.18, 0.05]
NAcc-vmPFC	Perceived Support from Friends (W)	-0.08 [-0.19, 0.03]
NAcc-vmPFC	Perceived Support from Friends (B)	0 [-0.11, 0.12]
NAcc-vmPFC	Co-Rumination (W)	-0.04 [-0.15, 0.07]
NAcc-vmPFC	Co-Rumination (B)	-0.02 [-0.13, 0.1]
NAcc-vmPFC	Depressive Symptoms (W)	0.05 [-0.07, 0.16]
NAcc-vmPFC	Depressive Symptoms (B)	-0.04 [-0.15, 0.07]

NAcc-vmPFC	Anxiety Symptoms (W)	-0.02 [-0.13, 0.1]
NAcc-vmPFC	Anxiety Symptoms (B)	0 [-0.12, 0.11]
NAcc-vmPFC	Connectedness (B)	0.11 [-0.05, 0.28]
NAcc-auditory	Friend Stability (B)	0.07 [-0.04, 0.18]
NAcc-auditory	PSE (W)	-0.05 [-0.15, 0.06]
NAcc-auditory	PSE (B)	-0.02 [-0.14, 0.11]
NAcc-auditory	Friendship Quality (W)	-0.1 [-0.21, 0]
NAcc-auditory	Friendship Quality (B)	0.08 [-0.04, 0.19]
NAcc-auditory	Perceived Support from Friends (W)	-0.12 [-0.22, -0.01]
NAcc-auditory	Perceived Support from Friends (B)	0.03 [-0.09, 0.15]
NAcc-auditory	Co-Rumination (W)	-0.05 [-0.15, 0.06]
NAcc-auditory	Co-Rumination (B)	-0.01 [-0.13, 0.11]
NAcc-auditory	Depressive Symptoms (W)	-0.05 [-0.16, 0.05]
NAcc-auditory	Depressive Symptoms (B)	0.04 [-0.08, 0.16]
NAcc-auditory	Anxiety Symptoms (W)	-0.13 [-0.23, -0.02]
NAcc-auditory	Anxiety Symptoms (B)	-0.01 [-0.13, 0.11]
NAcc-auditory	Connectedness (B)	-0.14 [-0.32, 0.03]
NAcc-visual	Friend Stability (B)	-0.02 [-0.13, 0.09]
NAcc-visual	PSE (W)	-0.07 [-0.18, 0.04]
NAcc-visual	PSE (B)	-0.07 [-0.19, 0.05]
NAcc-visual	Friendship Quality (W)	-0.04 [-0.15, 0.06]
NAcc-visual	Friendship Quality (B)	-0.08 [-0.2, 0.03]
NAcc-visual	Perceived Support from Friends (W)	-0.03 [-0.14, 0.08]
NAcc-visual	Perceived Support from Friends (B)	-0.04 [-0.16, 0.08]
NAcc-visual	Co-Rumination (W)	-0.14 [-0.25, -0.03]
NAcc-visual	Co-Rumination (B)	-0.09 [-0.2, 0.03]
NAcc-visual	Depressive Symptoms (W)	-0.08 [-0.19, 0.03]
NAcc-visual	Depressive Symptoms (B)	-0.09 [-0.21, 0.02]
NAcc-visual	Anxiety Symptoms (W)	-0.08 [-0.19, 0.03]
NAcc-visual	Anxiety Symptoms (B)	-0.02 [-0.13, 0.1]

NAcc-visual	Connectedness (B)	0.07 [-0.1, 0.25]

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Chapter 1

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Chapter 4

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Chapter 5

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