Linking Striatal Dopamine and Decision-Making to Adolescent Risk-Taking

by

Brenden Tervo-Clemmens

Bachelor of Arts, Duquesne University, 2010

Master of Science, Villanova University, 2016

Submitted to the Graduate Faculty of the

Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2021

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

This dissertation was presented

by

Brenden Tervo-Clemmens

It was defended on

March 3, 2021

and approved by

Jamie L. Hanson, Ph.D., Assistant Professor, Psychology

Brooke S.G. Molina, Ph.D., Professor, Psychiatry

Michael M.A. Sayette, Ph.D., Professor, Psychology

Aidan G.C. Wright, Ph.D., Associate Professor, Psychology

Dissertation Director: Beatriz Luna, Ph.D., Professor, Psychiatry

Linking Striatal Dopamine and Decision-Making to Adolescent Risk-Taking

Brenden Tervo-Clemmens, PhD

University of Pittsburgh, 2021

Adolescence is characterized by a peak in risk-taking behaviors that increases the likelihood of problematic substance use, sexually transmitted diseases, and fatal accidents. Prominent neurodevelopmental theories suggest these behaviors are driven by the maturation of the striatal dopamine (DA) system and its modulation of prefrontal-striatal circuitry. To date, research in this area has been limited, both by limitations in assessing DA systems *in vivo* in human adolescents and an incomplete understanding of the intermediate cognitive and affective processes linking striatal DA and risk-taking. This dissertation built upon a first-of-its kind longitudinal neuroimaging dataset (N=144) using direct (positron emission tomography [PET]) and indirect (brain tissue iron) measures of striatal DA, resting-state functional connectivity data, field-standard risk-taking measures, and a validated developmentally-sensitive decision-making task. To increase statistical power, an additional sample (N=187) with key overlapping measures was also examined. Across three aims, mixed support was found for the hypothesized integrative psychobiological model. Consistent with prior work, significant developmental differences were found in risk-taking propensity measures (both adolescent peaks and age-related decreases), in brain iron-based, indirect measures of striatal DA (age-related increases), and in model-based learning during the decision-making task (age-related increases). However, associations between risk-taking propensity measures and striatal DA measures were small in magnitude and not statistically significant. Evidence was found for an association between indirect striatal DA measures and an exploratory analysis of performance on the decision-making task, where those

with higher striatal iron for their age displayed more habitual responding during early adolescence. There was also evidence that striatal tissue iron measures were associated with frontostriatal connectivity. Nevertheless, broader circuit-level hypotheses of developmental changes in dopamine processing supporting changes in frontostriatal connectivity and subsequently risk-taking propensity were limited in this sample. Results suggest risk-taking may be related to striatal DA indirectly via decreased frontostriatal connectivity, although these associations were not developmentally sensitive in the current sample. These initial results establish testable hypotheses for larger developmental samples with more detailed phenotyping and expanded imaging metrics. Ultimately, this work can inform diverse neurodevelopmental pathways of adolescent risk-taking and contribute to biologically informed interventions for at-risk youth.

Table of Contents

List of Tables

List of Figures

Preface

I would like to express my deepest gratitude to everyone who has supported my academic journey. To my loving, supportive, and understanding wife who has never let me lose track of what is important in life. To my parents and sister, who have always possessed a patient understanding for my interest in life's complex questions, while also helping me realize the most important ones are those that end up helping other people.

To my wonderful academic advisor Beatriz Luna, PhD, a fearless and ground-breaking scientist, who has supported and inspired me through every turn. To all the collaborators and friends who have made me a better scientist and person.

1.0 Introduction

Adolescence is unique period of the lifespan, initiated by puberty and characterized by ongoing maturation of cognitive and affective brain systems (Luna et al., 2015). Behaviorally, studies from rodents, non-human primates, and across human cultures provide converging evidence that compared to adulthood, adolescence is marked by more risk-prone and impulsive behaviors (Spear, 2000). While historical perspectives viewed these behaviors as a sign of immaturity, contemporary neurodevelopmental (Luna & Wright, 2016)(Steinberg, 2010)(Casey et al., 2008) and psychosocial (Wills et al., 1994) theories suggest adolescent risky behavior reflects a tendency towards sensation-seeking and a normative drive towards environmental exploration, which may be essential for the late development of specialized cognitive and affective brain systems (Larsen & Luna, 2018). Yet, for some adolescents, risk- taking may lead to negative health outcomes, including problematic substance use, sexually transmitted diseases, and fatal accidents (Resnick et al., 1997).

Despite well-established developmental patterns of adolescent risk-taking and its potential negative health outcomes, the underlying psychobiological mechanisms governing adolescent risk-taking largely remain unknown. For example, multiple 'dual-system' perspectives (see Shulman et al., 2016 for review) suggest adolescent risk-taking is driven by a predominance of striatal-reward systems, mediated by functional changes in the dopamine (DA) neurotransmitter system, over prefrontal cortex, mediated by cortical cognitive control systems. However, owing to the contraindications of assessing striatal DA *in vivo* in human pediatric populations (via Positron Emission Tomography [PET]), there is limited evidence of unique adolescent DA processing in humans. Moreover, beyond the methodological challenges of imaging DA *in vivo*, a mechanistic

and integrative understanding of how striatal DA gives rise to adolescent risk-taking has remained elusive, in part due to the multiple behavioral functions ascribed to striatal DA. Finally, despite the implication of both the striatum and prefrontal cortex underlying adolescent risk-taking, limited work has examined how age-related change in prefrontal-striatal (frontostriatal) functional connectivity predicts adolescent risk-taking, particularly in the context of individual differences in striatal DA. This dissertation sought to address these gaps in knowledge, examining multiple levels of analysis within an integrative psychobiological model of adolescent risk-taking.

1.1 Adolescent Risk-Taking

The notion of adolescence as a period of heightened impulses and risks can be traced back for centuries. For example, writings from the mid 19th century noted the potential for "moral problems" following "internal revolutions" [puberty] in youth, which would subside following maturation (see (Demos & Demos, 1969) for review). While these early writings viewed adolescent behavior through a perspective of immaturity and morality that are now outdated (see below), they aptly reflect the transitional nature of adolescent risky behavior. Supporting this, considerable prior research has identified the adolescence, typically defined as the second decade of life in humans (10-20-years-old)(Sawyer et al., 2018), as a unique and sensitive period for various risky behaviors that are observed across species and cultures.

1.1.1 Defining Adolescent Risk-Taking

Most frequently, adolescent risk-taking is defined in epidemiological terms, where it has been demonstrated that across cultures, adolescence is a period when behaviors that increase mortality are more common, including reckless driving, risky sexual behavior, and problematic substance use (Duell et al., 2018)(Resnick et al., 1997). Nevertheless, it is well documented that the engagement of many of these behaviors is, in part, mitigated by access and opportunity (see (Duell et al., 2018) for discussion). To this end, adolescent risk-taking is also frequently defined in terms of propensity to engage in risky-behaviors, either through self-report measures of behavioral correlates of risk-taking (e.g., sensation-seeking, impulsivity, novelty-seeking, see below) or laboratory-based risk-taking behavioral tasks (e.g., Balloon Analogue Risk Task, (Lejuez et al., 2002)). The current project takes an inclusive perspective on the construct of "risk-taking", acknowledging observed correlations amongst these measures (Lejuez et al., 2002)(Lauriola et al., 2014)(Horvath & Zuckerman, 1993) that may support a common underlying construct. Nevertheless, its noted that various assessments of "risk-taking" and related constructs are not well correlated (Creswell et al., 2018)(Stamates & Lau-Barraco, 2017*)* or psychometrically validated (Hedge et al., 2018) and/or have no immediate analogue in animal models. This suggests a potential specificity among various definitions and measurements of "risk-taking". To this end, methodological variation is discussed and quantitatively explored throughout the project.

1.1.2 Adolescent Risk-Taking Across Cultures and Species

Converging evidence suggests that adolescence is a period of heightened risk-taking (Resnick et al., 1997; Shulman et al., 2016). Although early work demonstrating these

developmental patterns was performed primarily in the United States and Western Europe, recent work has demonstrated that across cultures, both epidemiological definitions of risk-taking (e.g., substance use, unprotected sex) and risk-taking behavioral analogues, display a developmental peak during adolescence or early adulthood (Duell et al., 2018). Of note a majority of this research has been performed within samples excluding for psychiatric and neurological disorders or large cohorts more closely approximating population variability, suggesting such an adolescent peak in risk-taking behavior represents a normative developmental trajectory.

Supporting a normative development of risk-taking behavior and a potential evolutionary precedent, animal models show marked differences during and after puberty in behaviors analogous to human risk-taking. For example, in maze paradigms, peripubertal mice and rats display increased "risk-taking" (time spent in physically unprotected areas) and "novelty-seeking" (time spent in novel unexplored areas) compared to adults (see (Laviola et al., 2003)(Spear, 2000)for a review). Similar observations have been made in peripubertal/adolescent non-human primates, who are more likely than adults to voluntarily leave their primary troop, a behavior associated with increased mortality (risk-taking), as well as explore novel food sources (novelty-seeking) (Spear 2000). Taken together, cross-cultural and cross-species research identifies increased risk-taking as a conserved and normative adolescent behavior.

1.2 Adolescent Neurocognitive Development and Models of Risk-Taking

Multiple models have been developed to account for adolescent increases in risk-taking. As mentioned above, the earliest of these perspectives viewed adolescent risk-taking as a sign of immaturity or "moral failings". Over time, these perspectives shifted and adolescent-risk taking

was considered to be the result of "cognitive deficiencies" and problems in "youth culture" (Steinberg, 2010)(Baumrind, 1987). Taken together, early perspectives considered adolescent risk-taking to be the result of *limitations* reflecting *non-functional* and *maladaptive* behaviors. In contrast, contemporary models situate risk-taking in the context of normative brain development and the result of a predominance of striatal-reward systems over cortically-mediated cognitive control (Luna & Wright, 2016). Critically, contemporary perspectives suggest risk-taking behaviors reflect *adaptive* processes of environmental exploration (Luna et al., 2015), which may be essential for psychosocial maturation (Crone & Dahl, 2012a) and the late development of specialized brain systems (Larsen & Luna, 2018).

1.2.1 Normative Adolescent Neurocognitive Development

Converging evidence from human neuroimaging and molecular studies in rodents suggests dynamic changes in the striatal reward system during and following puberty. For example, neuroimaging has suggested adolescents have increased functional recruitment of the ventral striatum in anticipation of rewards (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010)(Padmanabhan et al., 2011). Supporting these findings, rodent studies suggest a peripubertal/adolescent peak in dopaminergic function in the striatum (Gelbard et al., 1989), which is widely associated with reward signaling (Schultz, 2002) and motivated behavior (Cools, 2008). Other human neuroimaging has shown functional development during adolescence in a series of paralimbic regions more broadly associated with salience processing, including the amygdala (Ernst & Paulus, 2005)(Guyer et al., 2008) and insula (van Leijenhorst et al., 2006). This work has led to the contextualization of adolescents' heightened reward function within a broader domain of affective engagement (Crone & Dahl, 2012b), which may be part of an evolutionarily adaptive

process that supports independence and increases the odds of reproductive success (L. P. Spear, 2000).

In addition to normative changes in the striatal reward system, adolescence also marks a period of ongoing cognitive development. For example, although adolescents can perform complex "cognitive control" tasks, the ability to consistently implement cognitive control continues to mature through adolescence and into adulthood. Supporting this, adolescents display prolonged behavioral development within subdomains of cognitive control, including working memory (Geier, Garver, Terwilliger, & Luna, 2009)(Luciana et al., 2005) inhibitory control(Bjorklund & Harnishfeger, 1995)(Luna et al., 2004), and performance monitoring (Ordaz et al., 2013). Parallel evidence from human neuroimaging and animal studies suggests a network of 'top-down' control regions, including lateral prefrontal and posterior parietal cortices, support these cognitive control behaviors (see (Luna et al., 2015) for review). Initial developmental neuroimaging studies, during both inhibition (Rubia et al., 2006) and working memory (Klingberg et al., 2002) tasks, have shown differences in how lateral prefrontal and posterior parietal regions are recruited in adolescents compared to adults. Supporting this, non-human primate studies demonstrate developmental changes in neuronal firing patterns in similar lateral prefrontal regions (Zhou et al., 2016)(Lewis, 1997). Yet, longitudinal neuroimaging studies, particularly those that only analyze data from correct trials, and thus control for performance differences, find an age-related decrease in the recruitment of lateral prefrontal and posterior parietal regions that reach adult levels by mid-adolescence (Simmonds et al., 2017)(Ordaz et al., 2013). This may suggest adolescents become less dependent on domain general top-down control regions in favor of more specialized activation patterns. This idea is supported by recent work demonstrating that large-

scale patterns of brain activation stabilize during adolescence (Montez et al., 2017) and ensembles of brain regions (putative brain networks) become increasingly integrated (Marek et al., 2015).

1.2.2 Dual-Systems Models of Adolescence and Risk-Taking

Results demonstrating immaturities in prefrontal executive and striatal reward systems have led to 'dual systems' models, which suggest adolescence may be characterized by a relative predominance of reward systems over cognitive control systems (Shulman et al., 2016). Early versions of these models proposed that striatal systems matured earlier than a slow maturing prefrontal system (Casey et al., 2008). However, increasing evidence suggests striatal systems also have a protracted maturation through adolescence, with DAergic systems having greater function during the pubertal period (Wahlstrom et al., 2010)(Padmanabhan et al., 2011) and continued structural changes through adolescence (Raznahan et al., 2014). To this end, a second model proposed that, during an adolescent peak in striatal DAergic function, prefrontal systems were still maturing, resulting in a relative imbalance between reward and cognitive control systems (Steinberg, 2010). More recently, based on accumulating evidence that prefrontal systems can be engaged at adult levels by mid adolescence during executive function tasks (Ordaz et al., 2013)(Simmonds et al., 2017), the 'driven dual systems model' (Luna & Wright, 2016) suggests that adolescents' new access to cognitive control systems facilitates complex behaviors that are "driven" by a developmental peak in affective/reward system function that supports complex reward driven risk-taking.

Across all of these models, the relative imbalance between these "dual-systems" (reward vs. cognitive control) is thought to bias adolescence towards sensation-seeking and novelty-seeking in order to facilitate environmental exploration, which may be an *adaptation* to increase

independence and the odds of reproductive success (Spear 2000). Within this context, risk-taking behaviors (e.g., substance use, risky sexual behaviors, reckless driving) are viewed as the result of a combination of normative increases in sensation-seeking and increased autonomy from caregivers.

1.2.2.1 Neuroimaging Evidence Supporting Dual-Systems Models of Adolescent Risk-Taking

Existing functional neuroimaging (e.g., fMRI) studies provide mixed support for dual-systems models of adolescent risk-taking. Whereas growing evidence implicates the striatum in risk-taking like behaviors, less direct evidence has been found to support a role of cortical regions in adolescent risk-taking. For example, functional neuroimaging indicates that increased BOLD activation in the striatal-reward system is associated with both risk-taking behaviors and risk-taking propensity measures during adolescence (Galvan et al., 2007)(see (van Duijvenvoorde et al., 2016) for review). Moreover, a recent meta-analysis from our group demonstrates that adolescents at increased risk for substance use disorders (SUD), who are more likely to engage in risky-behavior, display increased striatal activation ((Tervo-Clemmens et al., 2020). In contrast, BOLD activation in the prefrontal cortex has been associated with risk-taking propensity measures, particularly the completion of laboratory-based analogues of risk-taking (Balloon analogue risk task) (Rao et al., 2008)(Schonberg et al., 2012)(Qu et al., 2015), but its association to more direct real-world adolescent risk-taking behaviors has been mixed (Tervo-Clemmens, Simmonds, Calabro, Day, et al., 2018)(Claus & Hutchison, 2012)(see (van Duijvenvoorde et al., 2016) for review). To this end, our recent meta-analysis did not find evidence for prefrontal associations with an increased risk for substance use among adolescents (Tervo-Clemmens et al., 2020). One possibility is that prefrontal activation differences only emerge in high-risk cohorts (Tervo-

Clemmens et al., 2017) or in the context of divergent developmental trajectories (Quach et al., 2020).

More recent research has examined functional connectivity between the prefrontal cortex and striatum while examining adolescent risk-taking. To this end, converging evidence suggests age-related increases in frontostriatal connectivity during adolescence is associated with reduced risk-taking propensity measures (Van Den Bos et al., 2015)(Christakou et al., 2011), where it has been suggested lower levels of risk-taking may result from prefrontal cortex exerting greater "top-down" control on the striatum into adulthood. To this end, disruption of this prefrontal cortex activity via Transcranial Magnetic Stimulation (TMS) leads to increases in risk-taking propensity measures (Knoch et al., 2006).

1.2.2.2 Summary and Remaining Questions

Overall, neuroimaging studies provide support for the basic tenets of dual-systems models predicting adolescent risk-taking, particularly a primary role for striatal-reward systems. A primary outstanding question for dual-systems models is the role of striatal dopamine in adolescent risk-taking behaviors. Dual-systems models build from rodent and primate studies, which have demonstrated that striatal DA is associated with behaviors analogous to human risk-taking (e.g., impulsive choice, see Striatal Dopamine and Risk-Taking) and undergoes functional changes during adolescence (see Normative Adolescent Neurocognitive Development). However, owing to the challenges of assessing striatal DA *in vivo* in human pediatric populations, there is limited evidence of unique adolescent DA processing in humans.

1.3 Striatal Dopamine and Risk-Taking

Converging evidence from animal models implicates striatal dopamine (DA) in behaviors analogous to human risk-taking, although the directionality of these associations is highly nuanced. From one perspective, a substantial body of work in rodents implicates lower levels of striatal DA, particularly in the ventral striatum/nucleus accumbens, as predictive of increased levels of "risk-taking like" behaviors, typically framed as "impulsive choice" (see (Jupp & Dalley, 2014) for relevant recent review). For example, in rats, reduced DA D2/D3 receptor expression (Mitchell et al., 2014) and over expression of dopamine transporter (DAT) (Adriani et al., 2009), both of which may index a reduced overall striatal DA tone, have been shown to decrease risky choices, in paradigms where rodents choose between larger uncertain [risky] rewards and smaller certain [less risky] rewards. This suggestion has some translation support, where human positron emission tomography (PET) studies have shown reduced striatal DA D2 binding in adults with substance use disorder (N. D. Volkow et al., 1997), who may be conceptualized as having higher levels of risk-taking. However, D2 agonists, which increase DA function, have been shown to increase drug seeking behavior (Self et al., 1996) and "impulsive choices" in the paradigm discussed above (Mitchell et al., 2014). Moreover, it remains unclear how a negative association between striatal DA and risk-taking fits with developmental observations, where it is thought that adolescents have higher striatal DA function and increased risk-taking. To this end, striatal DAergic effects may follow an inverted U pattern, with relatively low levels or relatively high levels leading to risky and impulsive behavior, analogous to the relatively well-characterized non-linear association between striatal DA and cognition (Cools & D'Esposito, 2011)(Williams & Goldman-Rakic, 1995). Importantly, the DA system is complex, and there remains the possibility that certain

behaviors, including risk-taking, may be more or less related to specific components (e.g., receptor subtypes, overall DA tone) of the DA system but not others.

Beyond directionality, the spatial specificity of associations between striatal DA and risk-taking behaviors is also nuanced. For example, opposing effects of DA on risk-taking have been observed in ventral and dorsal subdivisions of the striatum (Mitchell et al., 2014)(Palm et al., 2014). This may reflect the more general dorsal and ventral division of behavioral functions within the striatum, where the dorsal striatum, through direct connections with lateral prefrontal cortex, supports action selection and habit formation, while the ventral striatum, through direct connections with value-based circuits in the orbital frontal cortex, signals primary rewards (cf., (O'doherty et al., 2004). It is also possible the location of these effects may vary as a function of the severity of clinical status. For example, in the addiction literature, it has been suggested that early drug experimentation is driven by ventral-striatal reward function, while later problematic use is maintained by the dorsal-striatum's habit formation circuitry (Everitt & Robbins, 2005).

1.3.1 Summary and Remaining Questions

Taken together, animal models strongly implicate striatal DA in "risk-taking like" behaviors, although these effects are nuanced and appear sensitive to functional striatal subdivisions and potentially, clinical status. While studies using direct assessments of DA, via PET, have been performed in humans, these have primarily been done in psychiatric (e.g., addiction: see (Nora D. Volkow et al., 2007) for review) and neurological (e.g., Parkinson's disease: (Evans et al., 2009) for review) samples. Accordingly, normative associations between striatal DA and risk-taking behaviors during adolescence and adulthood remain largely unknown. Understanding the association between striatal DA and risk-taking across these developmental

periods is critical for understanding both the basic psychobiological mechanisms of risk-taking and through comparisons of indirect measures of striatal DA (see Methods), developmental patterns of risk-taking.

1.4 Decision-making Links Striatal DA and Adolescent Risk-Taking

Beyond methodological challenges in imaging striatal DA, difficulty remains in determining the exact mechanisms that transform individual differences in striatal DA to real-world behaviors. While striatal DA plays a major role in signaling reward (Schultz, 1998), it also underlies critical aspects of several cognitive and affective functions, including general motivational drive, the learning of environmental contingencies of rewards, and facilitation of complex executive functions (Friston et al., 2014). Nevertheless, it remains unclear how and under which conditions these more basic cognitive and affective processes link striatal DA to risk-taking. Understanding these intermediate, computational processes that link striatal DA and risk-taking is likely key to understanding variability in prior literature and the developmental mechanisms underlying the rise of these behaviors during adolescence.

Computational neuroscience provides a powerful approach to investigate associations between striatal DA and the prioritization of the cognitive and reward functions, hypothesized to be supported by striatal DA. For example, prior literature demonstrates that individual differences in striatal DA predict learning rates during reinforcement learning tasks, which have been shown to be altered in psychiatric disorders associated with risk-taking (e.g., ADHD: (Luman et al., 2010)). Developmentally, reinforcement learning rates have been shown to improve from adolescence to adulthood (Davidow et al., 2016). Beyond these basic reward learning tasks, recent work has utilized more complex decision-making tasks to examine both cognitive and reward

demands. To this end, emerging computational work (Deserno et al., 2015) indicates that striatal DA is associated with the balance of two decision-making strategies: 1) model-free learning, where recent reward history drives reactive choices vs. 2) model-based learning of rewards, where choices are deliberatively enacted based on a cognitive model of learned associations between actions and outcomes. As in simple reward tasks, these decision-making strategies have been shown to have developmental patterns. Adolescents have been found to utilize a combination of model-free and model-based learning strategies, while adults predominantly engage model-based strategies (Decker et al., 2016). Furthermore, supporting the relevance of these decision-making strategies to potential risk-taking behaviors, overreliance on model-free learning has been associated with adult substance use disorder (SUD) (Gillan et al., 2016).

1.4.1 Summary and Remaining Questions

Prior literature suggests striatal DA predicts reinforcement learning rates and the relative prioritization of rewards. Behaviorally, these intermediate reward and decision-making strategies have been shown to vary developmentally and are implicated in psychiatric disorders associated with risk-taking. Nevertheless, it remains unknown whether these intermediate decision-making processes link striatal DA and adolescent risk-taking. However, based on the reviewed developmental patterns in decision-making strategies, we hypothesized adolescence may mark a sensitive period where model-free and model-based decision-making strategies more readily interact, predicting normative increases in risk-taking. For example, the use of model-based learning may facilitate environmental exploration, leading to novel and in some cases, risk-prone contexts (parties with peers). At the same time, the continued use of model-free strategies may

lead to failures to consider long-term consequences (underage drinking citation), in favor of immediate and recent rewards (social bonding).

2.0 Specific Aims and Hypotheses

Across three aims, this project tested an integrative psychobiological model of adolescent risk-taking that built upon contemporary neurodevelopmental theory. First, we characterized associations between striatal DA and self-report and laboratory measures of risk-taking and how these relationships vary across development, testing the hypothesis that increased risk-taking in adolescence is driven by higher levels of striatal DA. Second, we sought to identify developmental changes in decision-making that may link striatal DA and adolescent risk-taking, formally testing a psychobiological model where reinforcement learning strategies mediate the association between striatal DA and risk-taking. Finally, we examined the effect of developmental changes in striatal DA on the strength of prefrontal-striatal connectivity and how these predict decision-making and risk-taking, seeking to determine the broader circuit dynamics underlying adolescent risky behavior.

3.0 Methods

3.1 Overview of Project Structure

The current project first proposed to use one existing longitudinal developmental neuroimaging dataset (Parent Project: Luna R01 MH080243: N=144, up to three visit per-participant, 319 total visits, *PET* sample). Based on subject attrition in this primary sample at the third visit, and in order to improve statistical power (particularly for those analyses using the decision-making task), a second dataset that included the Decker Two-Stage Sequential Learning Task (which measures model-free/model based approaches), risk-taking propensity measures, and neuroimaging data that could be used to assess striatal iron (an indirect measure of striatal dopamine) was also included (Parent Project: Luna R01 MH067924, N=187, *7T* sample). Both studies utilized accelerated longitudinal design, where subjects were initially recruited with a uniform age distribution, spanning early adolescence to adulthood (PET sample: ages 12-32, 7T sample: ages 10-30), and males and females were equally represented at each age. In the PET sample, following this initial baseline visit, subjects completed up to two follow up visits. In the final analysis sample from the PET study, 63 participants had three visits of data, 43 had two visits of data, and the remaining (38) had one visit of data. The average difference in time between both the first and second and second and third visits was approximately 20 months (1.71 and 1.66 years, respectively), with both of these follow-up visits including data from the adolescent period (second visit age range: 13.53-32.41 years; third visit age range: 15.06-33.34 years). The current project used all available data from the three visits and each analysis used the maximum sample size, in order to increase statistical power. We note that all included study measures were collected at all

three time points, except the Decker Two-Stage Sequential Learning Task (see below)**,** which was only collected in the third visit. The 7T sample has completed its first year of data collection, the data from which are presented in the current report.

The University of Pittsburgh's Institutional Review Board approved both studies. Adult participants provided informed consent. For minors, parents provided informed consent and youth (> 18-years-old) provided assent. Participants were compensated for completing research assessments.

3.2 Participants

General exclusion criteria for both samples were: self-reported (via online screen) history of a psychiatric disorder, either in the participant or a first-degree relative, T-scores above clinical cutoffs for any symptom scales on either the youth self-report (YSR) (subjects < 18-years-old) or adult self-report (ASR)(subjects > 18-years-old) psychopathology assessments (Achenbach, 2017), neurological disorders, MRI contraindications (e.g., non-removable metal in the body, past head injury with loss of consciousness, pregnancy), and IQ scores (Elliott, 2004) below 80.

3.3 Neuroimaging Measures

3.3.1 Direct Measures of Striatal DA

Using positron emission tomography (PET) (performed on a Siemens mMR dual modality PET/MR scanner) direct measures of striatal DA were collected in subjects 18- 32-years-old in the PET sample : [11C]Dihydrotetrabenazine (DTBZ) and [11C]Raclopride (RAC), reflecting presynaptic vesicular DA availability and D2/3 receptor concentration, respectively. RAC and DTBZ were collected with bolus+infusion paradigms and time activity curves were fit using the simplified reference tissue model (SRTM, with a cerebellar reference region) and Ichise's Multilinear Reference Tissue Model (MRTM, with a pericalcarine reference region) (Ichise et al., 1996) (Ichise et al., 2003), respectively to estimate binding potential (BP). We note PET image processing was completed with the PET center at the University of Pittsburgh, Department of Radiology.

3.3.2 Indirect Measures of Striatal DA

MR-based measures of tissue iron concentration were acquired for all subjects (12-32 years-of-age) in the PET sample, using a specialized tissue iron scan (R2'). Scans were performed with the same Siemens mMR dual modality PET/MR scanner as above. Tissue iron co-localizes with DA vesicles (Zucca et al., 2017), is necessary with DA synthesis (Ortega et al., 2007), has been found to change with development (Peterson et al., 2019)(Larsen & Luna, 2015), and in recent work from our group, has been shown to correlate with longitudinal changes in direct, DTBZ PET measures of DA availability (Larsen et al. 2020). To this end, we originally proposed

to use R2' as a putative indirect marker of striatal DA, with R2' estimated using validated procedures from recent work from our group (Larsen et al., 2020). However, given challenges in correcting R2' for head motion and other artifacts (see Larsen et al., 2020), the current project validated and further developed a method for assessing striatal tissue iron using standard functional neuroimaging data from a functional resting-state scan (see below). Specifically, building from an earlier protocol (Larsen & Luna, 2015), for each voxel (smallest unit of measurement in the neuroimaging data) we calculated the median value over all collected volumes (i.e., the full functional time course) and normalized these values across the brain, resulting in a single volume per visit (taT2*). In addition to the procedures developed in Larsen & Luna 2015, we also incorporated motion censoring procedure (threshold frame-wise displacement < .3 mm) to reduce the impact of head motion on these estimates. taT2* estimates were highly correlated with quantitative R2' tissue iron estimates (Figure 1) and consistent with our recent work (Larsen et al., 2020) were significantly associated with DTBZ direct measures of DA availability (see Appendix A). Therefore, taT2* was used as the indirect DA measure in the current project. taT2* images were computed for all available data in both the PET and 7T samples. ComBat, a batch-correction tool, originally developed for genomics data that has been widely used in neuroimaging (Fortin et al., 2018)(Fortin et al., 2018)(Radua et al., 2020) was used to harmonize the taT2* measures in PET and 7T samples. We note that because taT2* is negatively associated with tissue iron (see Figure 1), the direction of this measure was reversed in all subsequent figures to ease interpretation, such that higher values reflect higher levels of iron.

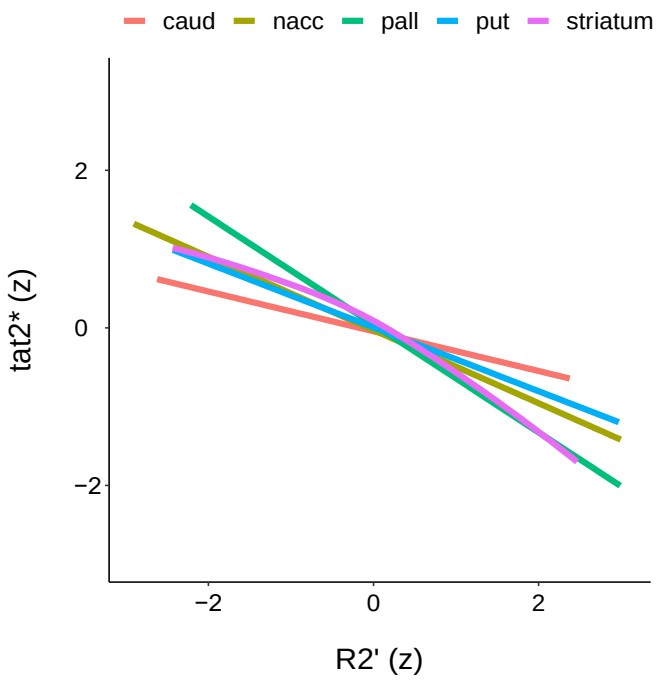


Figure 1 Tissue Iron-Specific Scan and Tissue Iron Estimated via Standard Functional Neuroimaging
The Association between R2' and taT2* was significant across all striatal regions (p's < .001): the caudate (caud), nucleus accumbens (NAcc), pallidum (pall), putamen (put), and whole striatum (striatum).

3.3.3 Resting-state Functional Neuroimaging

In the PET sample, two eight-minute scans (16 minutes total) of resting-state (eyes-open) were collected at each visit within the same session and using the same scanner as the PET data (Siemens mMR dual modality PET/MR scanner). Functional data were collected using an echo planar imaging (EPI) sequence with the following parameters: TR = 1.5s, TE = 30ms, Flip Angle = 80°, and 96 x 96 acquisition matrix with a field of view of 220 mm. Thirty-three slices were collected in the axial plane with an isotropic voxel size of 2.3 mm x 2.3 mm x 2.3 mm and a 2.3 mm gap between slices. In the 7T sample, an eight-minute resting-state scan (eyes-open) was performed with a 3D EPI acquisition, with an effective TR = 2.18s and 2.00 mm x 2.00 mm x 2.00m isotropic voxel size.

3.3.3.1 Preprocessing

Standard preprocessing techniques were used and relied on the same general pipeline as recent work from our (Tervo-Clemmens, Simmonds, Calabro, Montez, et al., 2018) that was designed to minimize confounding effects of head motion (Hallquist et al., 2013). Steps include: 4D slice-timing and head motion correction, wavelet despiking (Patel et al., 2014), brain extraction, non-linear registration of functional data to a standard anatomical brain (MNI-152c template) via subject structural image (MP-rage), spatial smoothing with a 5mm Gaussian kernel (Susan; (S. M. Smith & Brady, 1997)), intensity normalization, nuisance regression with six rigid body head motion parameters and their derivatives and non-gray matter signal (white matter and CSF and their derivatives), and bandpass filtering between 0.009 and 0.08 Hz. Volumes with significant head motion (frame-wise displacement > .3mm) were removed from analysis.

3.3.4 Striatal Regions-of-Interest

In order to increase the reliability of striatal DA estimates, while also permitting the exploration of striatal subdivisions, primary analyses examined direct striatal DA measures, mean binding potential estimates for D2/D3 receptor concentration (RAC) and vesicular DA (DTBZ), and the indirect DA measures R2' from anatomically-defined striatal regions of interests (ROIs): caudate, putamen, and nucleus accumbens, from the Harvard Oxford Atlas (Appendix B)**.** Following more detailed analyses of indirect measures of DA via iron, we also included estimates from the pallidum, another structure of the basal ganglia associated with reward and affective function, given this is among the most iron rich regions in the brain (see Appendix B), which has been corroborated by post-mortem research (Langkammer et al., 2012). In order to reduce the

number of statistical comparisons and reduce measurement error, estimates were averaged across hemispheres for each ROI.

3.4 Risk-Taking Assessments

Owing to the challenges of accurately assessing risk-taking behavior from a public health perspective (e.g., limitations of access and opportunity: see Defining Adolescent Risk-Taking), the current project utilized risk-taking propensity measures. In order to examine convergent validity, multiple risk-taking propensity measures were examined. With the exception of the Balloon Analog Risk Task (BART), which was only collected in the PET sample, all measures were available in both samples.

3.4.1 UPPS-P Impulsive Behavior Scale

The UPPS-P (Whiteside & Lynam, 2001) is a 59-item self-report assessment, designed to measure five facets of impulsivity (Negative and Positive Urgency, Lack of Premeditation, Lack of Perseverance, Sensation-Seeking), many of which have been associated with public-health defined risk-taking (e.g., substance use: (Whiteside & Lynam, 2003); risky sexual behavior: (Deckman & DeWall, 2011)). The UPPS-P has been psychometrically validated with respect to between-subject differences. In validation studies, UPPS-P factor structure has shown to be non-invariant across samples (Cyders, 2013) and subscales have been shown to have high internal consistency (Cronbach's alpha's > .85 (Carlson et al., 2013)) and test-retest reliability (r's > .8 (Weafer et al., 2013)). Given the high correlation between Negative and Positive Urgency (r=.69)

in the dataset and in order to reduce the overall number of statistical comparisons, the broader domain of Urgency was used, as in previous formulations of the measure (cf., (G. T. Smith & Cyders, 2016))

3.4.2 RT-18

The RT-18 is an 18-item self-report assessment, designed specifically to assess risk-taking propensity in youth (de Haan et al., 2011). Validation samples indicate the RT-18 has high internal consistency (Cronbach's alpha = .886), test-retest reliability (r = .94), and predicts risk-taking phenotypes (e.g., substance use) (de Haan et al., 2011).

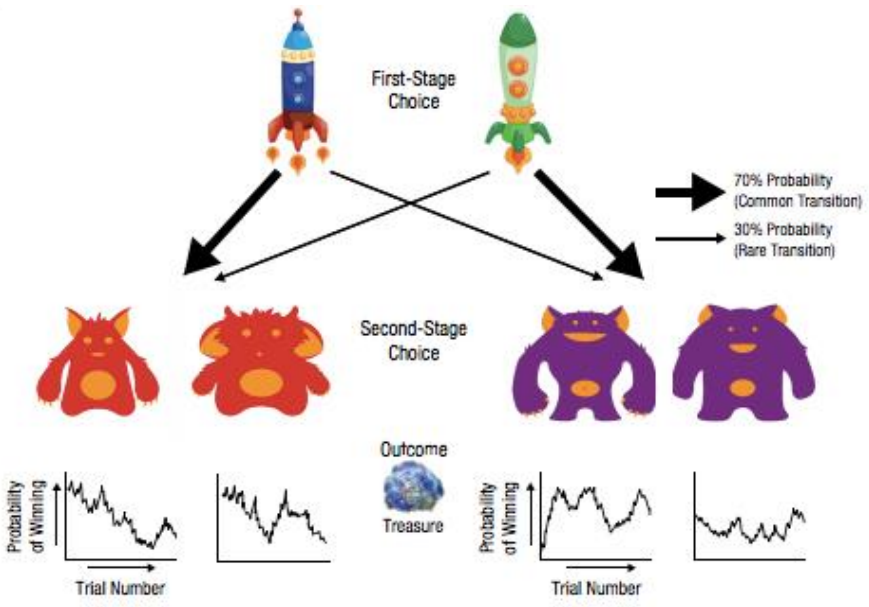
3.4.3 Balloon Analog Risk Task

The balloon analog risk task (BART) is a computer-based measure of risk-taking propensity (Carl W. Lejuez et al., 2002), which has been shown to predict public-health defined risk-taking (e.g., substance use & reckless behavior: Lejuez et al., 2002; (C. W. Lejuez et al., 2003) and show developmental changes during adolescence (Duell et al., 2018). In the task, a computer screen displays a small balloon and a display of "Total Money Earned". On each of the twenty trials, participants press a button on the keyboard to "pump the balloon" and earn 1¢ for each pump. Each balloon has a randomly selected popping point (signaled by a "pop" sound) where the participant loses all money from that trial. However, at any point in the trial, participants can stop pressing the pump button and can collect their earnings. The primary outcome measure is the number of pumps across balloons that didn't pop, which is conceptualized to reflect risk-taking in that more pumps indicates a greater risk of loss for a larger reward. In validation analysis, this

primary measure has been shown to have good within-session (r =.81, Lejuez et al., 2002) and acceptable daily (r =.71 (White et al., 2008)) test-retest reliability.

3.5 Decker Two-Stage Sequential Learning Task

Participants in both studies, completed a developmentally-validated task (Figure 2) that provides estimates of model-free and model-based decision-making (Decker et al., 2016). Within the task, participants must first choose between two rockets that have different probabilities (common: 70% vs. rare: 30%) of traveling to one of two planets. Once at the planets (the second stage choice), participants choose between one of two aliens and they are either rewarded (shown a stimulus of "space- treasure") or not-rewarded (shown an empty circle), according to a slowly drifting reward probability. A model-free decision strategy is conceptualized as a simple bias to recent rewards ("model-free learning"), where participants' choices of rockets are simply driven by whether or not they were rewarded on the previous trial. In contrast a model-based strategy is conceptualized as evidence of goal-directed behavior and meta-knowledge of the task ("model-based learning"), where for example participants choose the blue rocket if they had been previously rewarded on the red planet, as this maximizes the likelihood of returning to the red planet (Figure 2).



Decker et al. 2016

Figure 2 Developmental Two-Stage Sequential Learning Task

Building from this prior work, we developed another measure relevant to decision-strategy: repetitive choices, by modeling the frequency that each subject repeats the same choice of rocket on successive trials, across all trial conditions. This "repetitive-responses"/"first-stage stay" parameter captures participants' tendency to repeat the same choice of the rockets, irrespective of reward and probability structure. This measure become of interest during data analysis when strong evidence for this strategy was observed in all models and thus, was used in additional exploratory analyses. Recent research from collaborators of our group (Brown et al., 2020; Dombrovski lab, University of Pittsburgh, Department of Psychiatry) demonstrates acceptable test-retest reliability from outcome measures from this task across weeks (r's > .7) and good within-session (split-half) reliability (r's > .8). We note, unlike all other measures, this decision-making task was only collected in year 3 of the PET sample, in part, specifically for this dissertation project. This task was also collected in the 7T sample and served as the impetus to additionally include the 7T in the current project.

4.0 Analysis

See Figure 3 for an overview of proposed primary analyses. Panel models highlight primary study hypotheses and theoretical predictions. We also followed established guidelines (Muller et al., 2005) and general best practices in data analysis in order to ensure final statistical models are parsimonious and methodological ambiguity and limitations are clearly presented.

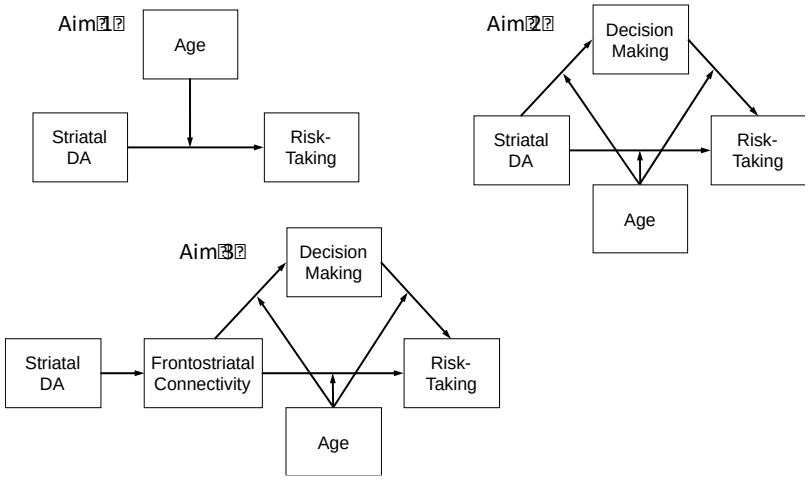


Figure 3 Analysis Overview

4.1 General Statistical Procedures

This project pre-defined a general set of a statistical procedures in order to reduce potential bias and improve transparency. In the rare cases where final analyses differed from this set of general procedures (included in the initial proposal), rationale for deviations accompanies analysis. 1) *Distributions of variables*: Distributions were examined for normality for all study variables. 2) *Outlier detection:* univariate outliers (operationalized as 3 standard deviations above the mean)

were examined for potential removal. When possible, these data points were also assessed with respect to regression leverage statistics (cooks distance, with a cut off determined as 3 standard deviations above the mean). Data points determined to be both univariate outliers and leverage points were removed from analysis. 3) *Inclusion of covariates*: head motion (frame-wise displacement following volume censoring: see Resting-State Functional Neuroimaging) was used as a covariate in all neuroimaging analyses. The initial analytic plan suggested inclusion of other covariates would include reporting significance of primary study variables with and without including these covariates. However, due to concern about the influence of non-developmental visit effects (e.g., practice, habituation to the scanning environment) biasing estimates (e.g., (Luna et al., 2020), visit number was likewise always included as a covariate. Sex was not shown to have a substantive main effect or interaction with age with respect to the primary outcome (risk-taking) and was therefore not used as a covariate (see Appendix C). *4) Multiple comparison correction*: multiple comparison correction was performed using the false discovery rate (FDR) with a threshold of $q < .05$. 5) *Sensitivity analysis*: a sensitivity analysis reviewing the above domains, as well as any addition analysis-specific domains, accompanies the reported results. 6) *Data reporting*: zero order correlations for primary risk-taking variables are reported (Appendix C). Intraclass correlation coefficients (ICCs) are reported for all primary longitudinal data (Appendix C). All significance values are reported to three decimal places. Wherever possible, standardized measures of the strength of the association between study variables are presented.

4.2 Modeling Overview

Based on the reviewed literature and hypothesized non-linear association between striatal DA and risk-taking, primary analyses used general additive models, with thin plate spline basis functions (MCGV in R: (Wood, 2012), allowing for a flexible and empirically-defined functional form. In cross-sectional analysis (see below), the employed GAM model had the following general structure:

$$Y = \beta + f_1(x_1) + f_2(x_2) + \cdots + e$$

where Y is the response variable, β, is the parametric model intercept, and f_1 and f_2 are smooth functions (thin plate splines: MCGV default) of the covariates $x_1$and x_2.

However, as discussed above, the PET sample was collected in an accelerated longitudinal design, with participants (N=144) starting the study at various ages (12- 32-years-old) and prospectively followed for up-to three visits. Accordingly, with the exception of the decision-making task (see above), all variables in the PET sample include longitudinal data. In order to provide the most precise estimates possible from the dataset, longitudinal data were always included when available.

Longitudinal data were handled within the GAM framework through the inclusion of random effects, where the GAM model utilizes the following general structure in the case of a random intercept:

$$Y_{ij} = \beta_{0i} + f_1(x_1) + f_2(x_2) + \cdots + \varepsilon_{ij}$$

where Y_{ij} is the response variable for an individual subject and the model intercept, β_{0i} is composed of fixed and random effects ($\beta_{0i} = \gamma_{00} + r_{0i}$, where γ_{00} is the grand mean of the response variable and r_{0i} is the random intercept term). All models were initially estimated with random intercepts and a random slope for the primary variable of interest. Following longitudinal modeling

guidelines, the random effects structure was simplified (random intercept only) in the rare cases when the model did not properly converge. In order to provide a simple measure of magnitude and direction in GAM/GAMM models, which given their non-linear and multilevel structure do not have a field-standard for standardized effect sizes, we provide Kendall's Tau as a descriptive measure. No inferential statistics are performed on Kendall's Tau parameters.

4.2.1 Aim 1: Characterize the Developmental Associations Between Striatal DA and Risk-Taking

This aim sought to test the hypothesis that increased risk-taking in adolescence is driven by higher levels of striatal DA. Primary analyses proceed in two steps. First, we examined the overall relationship between striatal DA and risk-taking, while covarying age. Associations between striatal DA measures were examined for each risk-taking propensity measure (UPPS-P subscales, RT-18, and BART, see above). Due to the potential non-linear associations between striatal DA and risk-taking measures (see above), primary analysis utilized generalized additive models (see *Modeling Overview***)**. Our second set of analyses examined whether the association between striatal DA and risk-taking measures varied as a function of age by including an interaction term between participant age and DA measures within the GAM framework. Given the focus on adolescent hypotheses, age-moderation was only examined in striatal tissue iron measures, which included the full age-range of participants (see above). In order to systematically examine potential age-varying associations, a time-varying effect modeling (TVEM)(Tan et al., 2012) approach was used within the GAM framework in R (Dziak et al., 2020). Across both sets of analyses (age constant and age varying), significance testing was carried out with each risk-

taking measure independently with multiple comparison correction (FDR) preformed across measures.

4.2.2 Aim 2: Identify Developmental Changes in Decision-Making That Link Striatal DA and Adolescent Risk-Taking

This aim sought to identify whether decision-making links striatal DA and risk-taking by examining associations between decision-making and striatal DA and risk-taking measures. We also sought to test the developmental hypothesis that age-related increases in model-based decision strategies during adolescence, driven by developmental changes in striatal DA, were associated with decreased risk-taking. We first examined age-invariant associations and then planned to determine the extent to which the mediating role of decision-making strategies on the relationship between striatal DA and risk-taking varies by age (Figure 3), where we hypothesized the largest indirect effect to be observed during adolescence.

Consistent with prior work using variants of the included decision-making task (Decker et al., 2016)(Gillan et al., 2016), primary analysis first estimated a single per-subject parameter characterizing the relative use of model-based strategy using a generalized linear mixed effects model. Within this framework, model-based strategies are defined by a reward (rewarded/non-rewarded) by transition type (common/rare) interaction term that is allowed to vary across subjects (i.e., random effect). Based on the observation during data analysis for subjects to repeat the same choice across trials, irrespective of task condition (see Methods section), we also performed secondary analysis examining this strategy, which was defined within the model framework as the per-subject random intercept (mean proportion of first-stage stays).

4.2.3 Aim 3: Determine How Developmental Changes in Striatal Dopamine Modulate Frontostriatal Circuitry to Predict Decision-Making and Adolescent Risk-Taking

Building on prior literature demonstrating 1) age-related increases in striatal dopamine 2) developmental decreases in risk-taking being associated with increased frontostriatal connectivity (Van Den Bos et al., 2015) and 3) emerging work demonstrating that increased striatal DA in humans predicts increased frontostriatal connectivity (Kelly et al., 2009), we hypothesized that frontostriatal connectivity was a mechanism by which striatal DA influences decision-making and risk-taking (Figure 3).

To first examine whether striatal DA predicts frontostriatal connectivity, we examined associations between individual differences in striatal DA measures (RAC, DTBZ, taT2*) and resting-state connectivity values, while covarying a smoothed (non-linear) functional form of age, within the GAM framework. We originally proposed to utilize a voxelwise frontostriatal connectivity approach, with mass univariate associations generated from striatal ROIs to the frontal cortex. However, based on concurrent work performed by our group (Marek & Tervo-Clemmens et al., 2020) demonstrating the low statistical power of many brain-phenotype association studies, a more targeted, hypothesis-driven approach was used. Specifically, based on the well-established literature on parallel frontostriatal connections (cf., (Haber, 2016)), we examined connectivity between our striatal ROIs and key cortical targets of dorsolateral prefrontal cortex, ventromedial prefrontal cortex, and pre-supplementary motor area (see Appendix D). Cortical ROIs were spheres (12mm radius) generated from peak coordinates from term-based meta-analyses from neurosynth.org. As in striatal ROIs, in order to reduce the number of statistical comparisons and reduce measurement error, estimates were averaged across hemispheres for bi-lateral ROIs (e.g., DLPFC; see Appendix D). Furthermore, in analyses examining associations

with striatal DA, in order to reduce the number of potential comparisons between DA measures in each striatal region (4 regions) and each frontostriatal connection (21 connections), mean DA measures across the striatum were used.

4.2.4 Power Considerations

This project's analyses were designed with consideration to "sensitivity" style power analyses, generated through Monte Carlo simulation and based on the original sample design. These results indicated the design was sufficiently powered (80%) to detect effect sizes, traditionally defined as small to moderate (.25-.3) (See Appendix E). In order to maximize power, this project additionally included a second sample (7T) with key overlapping measures in order to increase statistical power. In order to further maximize statistical power, which concurrent work from our group has raised concerns over in brain-behavioral phenotype studies in neuroimaging (Marek & Tervo-Clemmens et al., 2020), the largest available sample size is used for each analysis. Sample size details (number of unique subjects, total number of visits, which parent sample the participants came from) accompany all results.

5.0 Results

5.1 Aim 1: Characterize the Developmental Associations Between Striatal DA and Risk-Taking

5.1.1 General Developmental Patterns of Risk-Taking and Striatal DA

The examined risk-taking propensity measures (N=326 subjects, 528 total visits, PET + 7T samples) supported two distinct developmental trajectories (Figure 4; Table 1). The BART and UPPS Lack of Perseverance, Lack of Premeditation, and Urgency displayed significant linear age-related decreases, with younger participants having greater risk-taking than older participants. In contrast, UPPS Sensation-Seeking significantly, and RT18 as a trend, displayed an inverted u functional form of age, although expression of these measures appeared to peak in late adolescence/early adulthood (~20-years-old), rather than the mid-adolescent peak suggested in neurodevelopmental heuristic models.

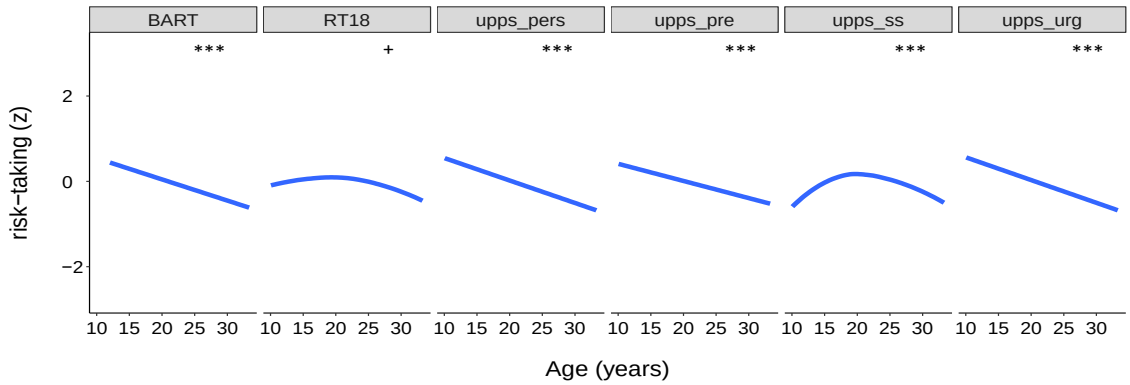


Figure 4 Age-related Changes in Risk-Taking Propensity Measures
Note, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency). * FDR q < .001, + FDR q < .10.**

Table 1 Model Results for Age-Related Changes in Risk-Taking Propensity Measures

	edf	Kendall Tau	FDR q
BART	1.000	-0.143	0.000
RT18	2.067	-0.051	0.070
upps_pers	1.000	-0.217	0.000
upps_pre	1.000	-0.180	0.000
upps_ss	3.244	0.020	0.001
upps_urg	1.000	-0.198	0.000

Note, edf: effective degrees of freedom; Kendall Tau: Aggregated (across all visits) Kendall Tau between Age and risk-taking measure. FDR q: corrected significance value

The distinction between the developmental trajectories of these measures was further supported by exploratory factor analysis demonstrating two factors that had patterns of loadings among the measures that mirrored the groupings of the measures' developmental effects (Appendix C)

Consistent with prior work (Larsen & Luna, 2015)(Larsen et al., 2020), indirect measures of striatal dopamine (N=212, 342 total visits, PET + 7T samples), as assessed via striatal tissue iron, displayed significant age-related increases (see Methods for sign interpretation) across all ROIs, except the caudate, which was not significant (Figure 5; Table 2). We note recent work from our group has investigated developmental patterns of direct measures of striatal DA as assessed by PET in adult participants, demonstrating for example, that D2/3 receptor density shows an age-related decrease from 18- to 30-years-old(Larsen et al., 2020).

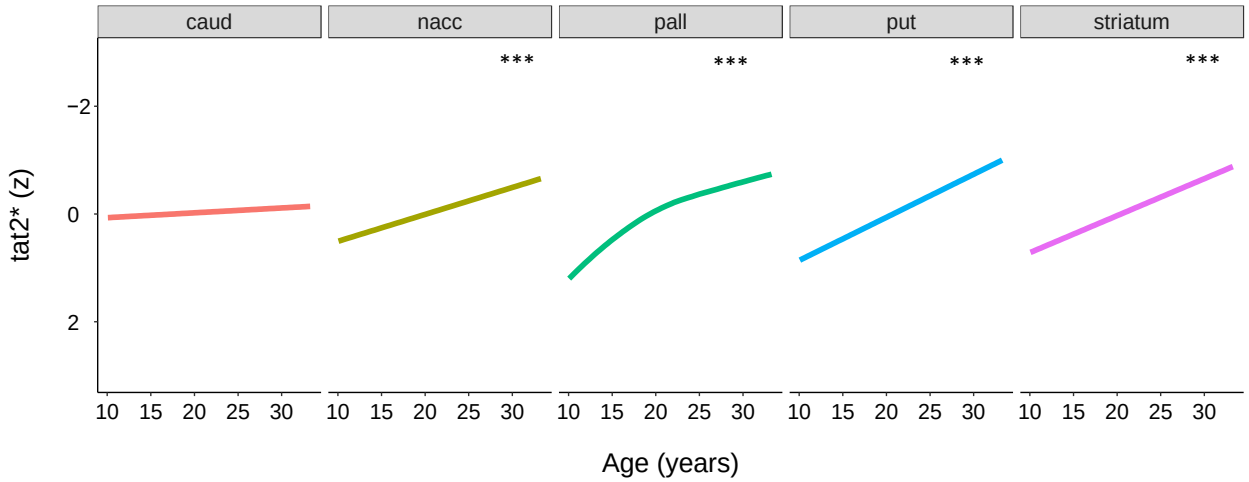


Figure 5 Age-related Changes in Striatal Tissue Iron

Age-related change in taT2* (reverse scored for interpretation; see Methods) in the caudate (caud), nucleus accumbens (NAcc), pallidum (pall), putamen (put), and whole striatum (striatum). Note, * FDR q < .001**

Table 2 Model Results for Age-related Changes in Striatal Tissue Iron

	edf	Kendall Tau	FDR q
caud	1.000	0.072	0.459
NAcc	1.000	0.175	0.000
pall	2.486	0.321	0.000
put	1.000	0.327	0.000
striatum	1.000	0.279	0.000

Note, edf: effective degrees of freedom; Kendall Tau: Aggregated (across all visits) Kendall Tau between Age and risk-taking measure (sign flipped from original scale to match plot; see Methods). FDR q: corrected significance value.

5.1.2 Links between Striatal DA and Risk-taking

Neither indirect (N=212, 342 total visits, PET + 7T samples) nor direct (N=78, 161 total visits, PET sample) PET DTBZ or RAC measures of striatal DA availability had corrected significant associations with risk-taking propensity measure in the age-invariant analyses

(covarying age) (FDR q's > .148) (Figures 6,7,8; Appendix F). Likewise, for the indirect striatal DA measure (which again had the full age-range or participants: 10-33-years-old), there were no corrected, significant age by DA interactions for any risk-taking propensity measure (FDR q's > .319)(Figures 9).

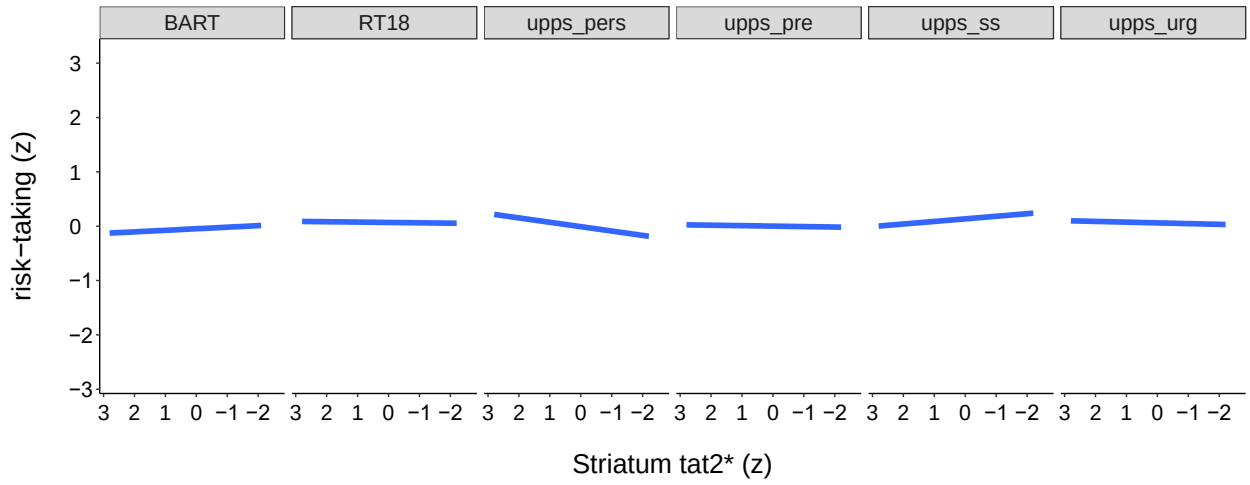


Figure 6 Association between Striatal Tissue Iron and Risk-Taking

Association between taT2* (reverse scored for interpretation; see Methods) in the whole striatum and risk-taking measures: BART, RT-18, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency). No associations were significant in the whole striatum (shown here) or any other striatal regions (see Appendix F)

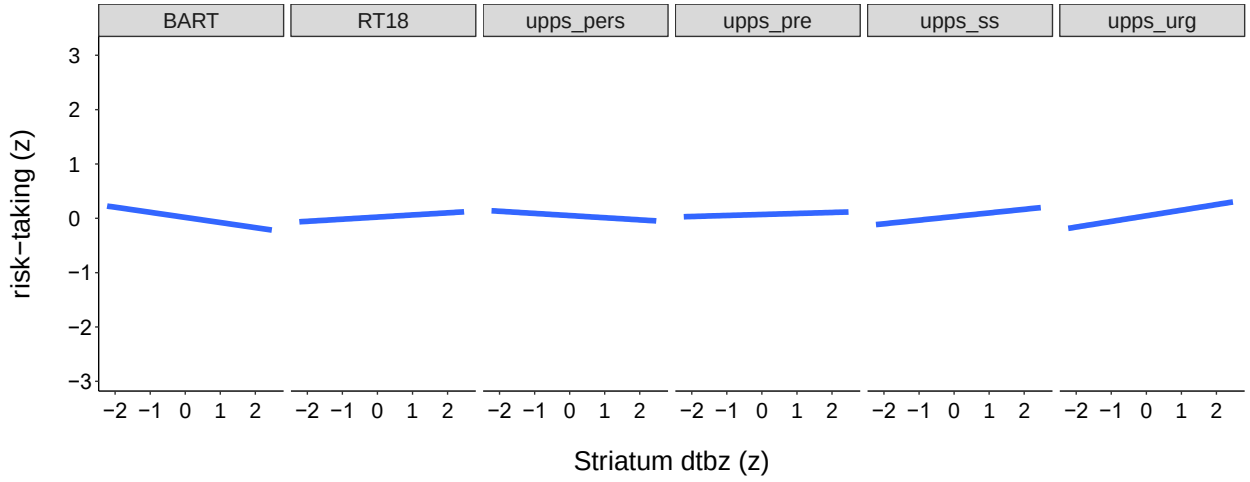


Figure 7 Association between Striatal PET Marker DTBZ and Risk-Taking

Association between DTBZ in the whole striatum and risk-taking measures: BART, RT-18, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency). No associations were significant in the whole striatum (shown here) or any other striatal regions (see Appendix F)

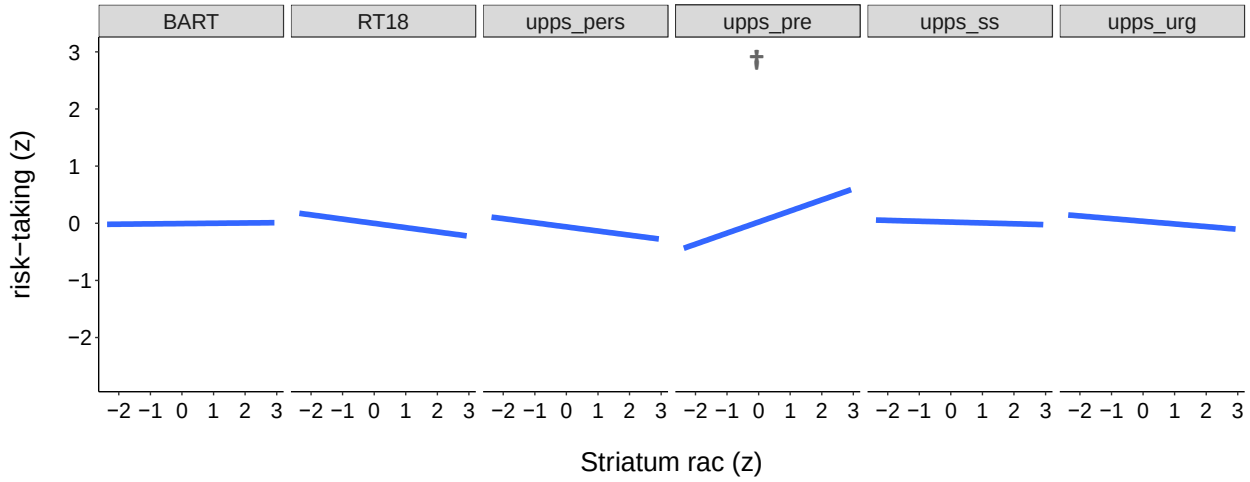


Figure 8 Association between Striatal PET Marker RAC and Risk-Taking

Association between RAC in the whole striatum and risk-taking measures: BART, RT-18, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency). No associations were significant after corrections for multiple comparisons in the whole striatum (shown here) or any other striatal regions (see Appendix F). †, p < .05 (uncorrected).

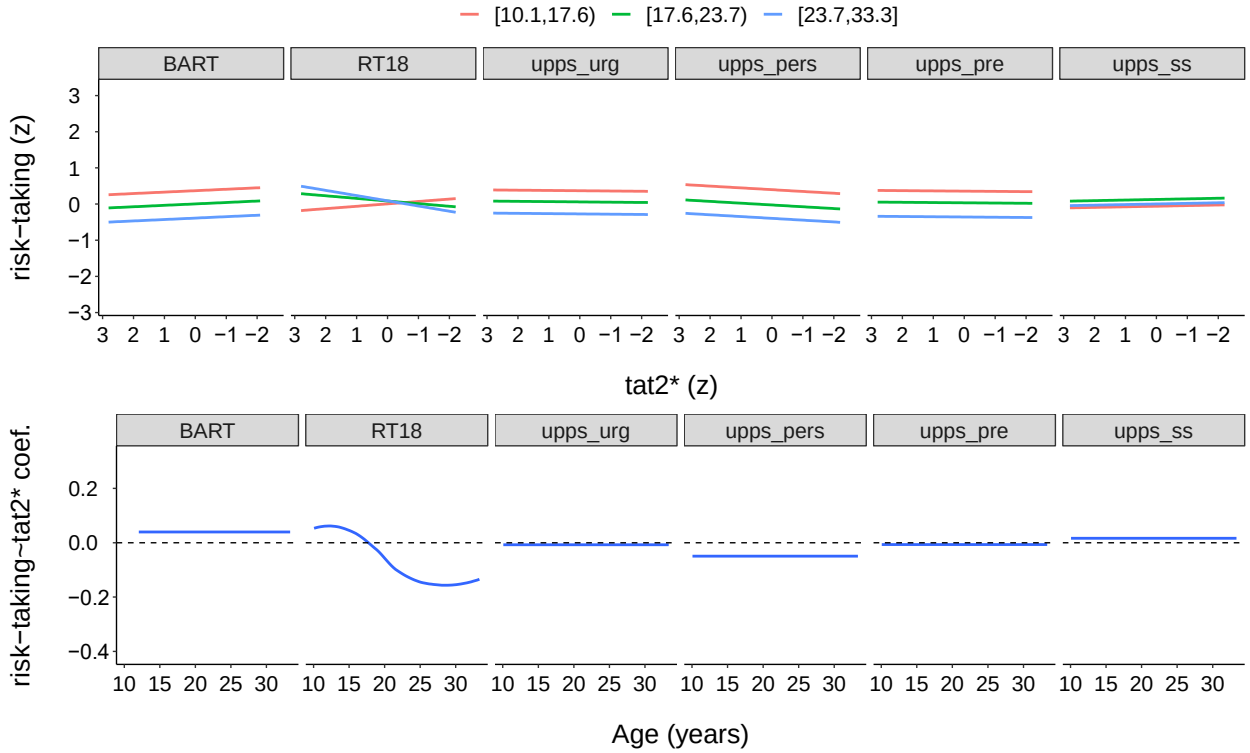


Figure 9 Age-varying Association between Striatal Tissue Iron and Risk-Taking

Top row displays association between whole striatum taT2* (reverse scored for interpretation; see Methods) and risk-taking measures: BART, RT-18, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency), for equally spaced age terciles (parsed from age by-taT2* interaction). Bottom row displays age-varying, risk-taking with taT2* coefficient (sign flipped

from original scale to match top plot: see Methods) estimated via TVEM. No corrected significant associations were significant in the whole striatum (shown here) or any other striatal regions.

5.2 Aim 2: Identify Developmental Changes in Decision-Making That Link Striatal DA and Adolescent Risk-Taking

5.2.1 General Developmental Patterns in Decision-Making Task

Consistent with prior work (Decker et al., 2016), a significant positive relationship (FDR $q < .001$) (N=213 subjects, 228 total visits, PET + 7T samples) was observed between participant age and model-based learning, where adults displayed more model-based learning than adolescents (Figure 10). As described above, during data analysis, we observed a substantial range of individual variability in the overall proportion of repetitive responses/first stage stays, which could not be simply attributed to model-based or model-free learning (Appendix G). This post-hoc parameter of proportion of repetitive responses was robustly positively associated with age (FDR $q < .001$)(Figure 10), where we suggest adults are more likely to display habitual/repetitive responding (higher first stage stays) than adolescents, who appear more exploratory and resistant to these behaviors. This suggestion is consistent with prior work in rodents (Serlin & Torregrossa, 2015)(Towner et al., 2020)(Rode et al., 2020)(see Discussion).

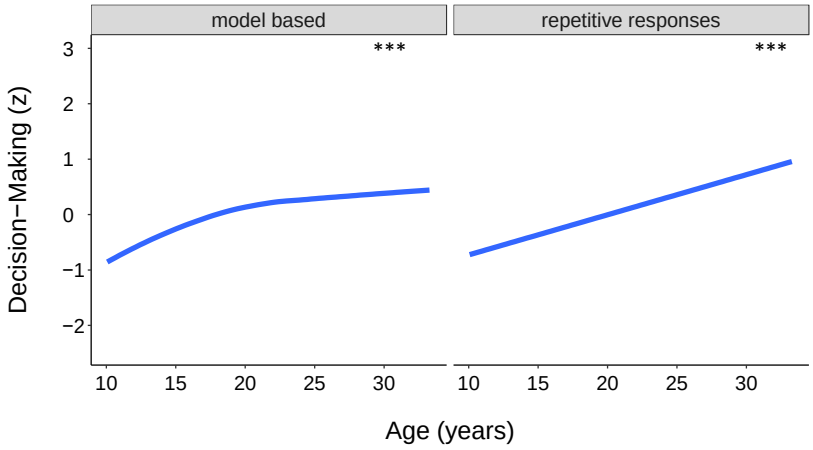


Figure 10 Age-related Change in Decision-Making Variables
Left, model-based learning; Right, repetitive responses. * FDR q < .001**

Table 3 Model Results for Age-related Changes in Striatal Tissue Iron

	edf	Kendall Tau	FDR q
Model-based	2.168	0.211	0.000
Repetitive Responses	1.000	0.296	0.000

Note, edf: effective degrees of freedom; Kendall Tau: Aggregated (across all visits) Kendall Tau between Age and decision-making measure. FDR q: corrected significance value.

5.2.2 Decision-making as a Mediator of the Relationships between Striatal DA and Risk-Taking

This aim was initially proposed to test whether decision-making mediates the relationship between striatal DA and risk-taking. Consistent with the original data analysis plan and proposed mediation model, we examined relationships between 1) striatal DA and decision-making and 2) decision-making and risk-taking metrics.

Neither indirect (FDR q's > .105) (N=124, cross-sectional sample, PET years + 7T) nor direct (FDR q's > .296)(N=31, PET sample) DA measures had corrected significant associations

with decision-making metrics in the age-invariant analyses (covarying age)(Figure 11; Appendix H).

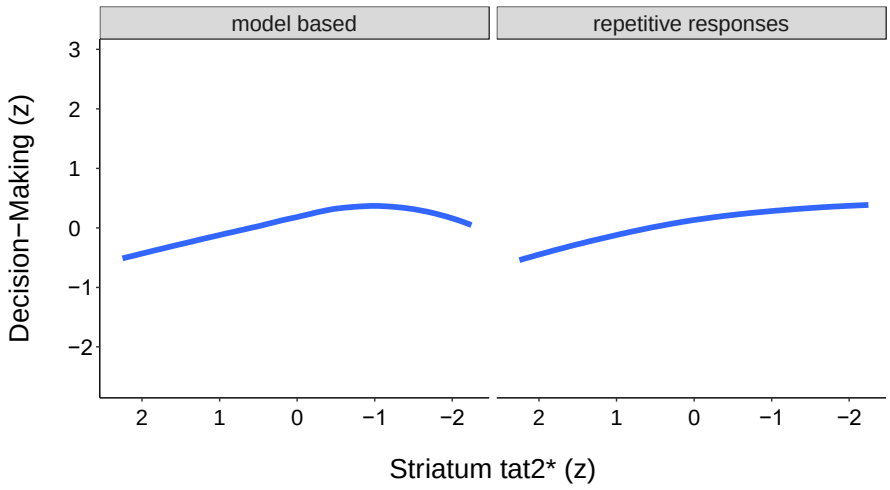


Figure 11 Striatal Tissue Iron with Decision-Making Variables

Association between whole striatum taT2* (reverse scored for interpretation; see Methods) and model-based (Left) and repetitive responses (Right) decision-making variables: No corrected significant associations were significant in the whole striatum (shown here) or any other striatal regions (see Appendix H).

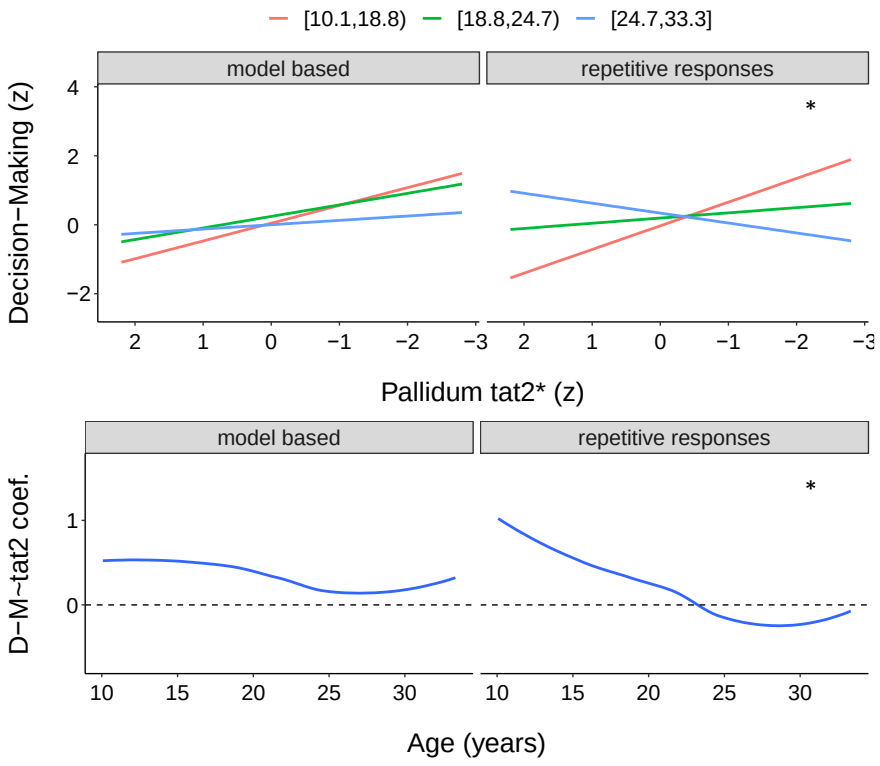


Figure 12 Age-Varying Association between Pallidum Tissue Iron and Decision-Making Variables

Top row displays association between pallidum taT2* (reverse scored for interpretation; see Methods) and model-based (Left) and repetitive responses (Right) decision-making variables for equally spaced age

terciles (parsed from age by-taT2* interaction). Bottom row displays age-varying, decision-making with taT2* coefficient (sign flipped from original scale to match top plot: see Methods) estimated via TVEM. See Appendix H for other regions. * FDR q < .05

In contrast, the indirect striatal DA measures, which we again note includes the full age-range of participants (10-33-years-old), displayed a corrected-significant age by iron interaction for the first stage stay/repetitive response parameter for iron in the pallidum (FDR q = .047)(Figure 12). Using TVEM to visualize this age by iron interaction in more detail demonstrated that there was a significant positive relationship between tissue iron and repetitive responses early in adolescence that subsequently decreased and was no longer significant by mid-to late-adolescence (Figure 12). Given the normative developmental trajectories of tissue iron (increasing with age) and repetitive responses (increasing with age), this may suggest that adolescents that are relatively "mature" for their age neurobiologically, are likewise more "mature" with respect to the behavioral phenotype, as would be observed in a parallel maturation of iron and repetitive responding. Nevertheless, this putative mechanism will need to be tested with expanded longitudinal data (see Discussion). We note due to the limited data and restricted age-range of the sample with both direct DA measures and the decision-making task, age moderation was not explored with these data.

To further examine the proposed model whereby decision-making mediates the relationship between striatal DA and risk-taking, we next examined the association between decision-making and risk-taking measures (N=213 subjects, 228 total visits, PET + 7T samples). The relationship between decision-making parameters (model-based learning and repetitive responses) and risk-taking measures was not significant in either the age-invariant analysis (controlling for age) (FDR q's > .556) (Figure 13), although effect sizes were near equivalent in magnitude to those from similar prior reports (Gillan et al., 2016)(see Discussion), or when examining an age by decision-making interaction predicting risk-taking (FDR q's > .678). Given

the general inconsistency of these results with the proposed mediational model (e.g., non-significant association between decision-making and risk-taking), whereby striatal DA leads to risk-taking indirectly, via decision-making, more complex models within this aim (e.g., moderated mediation) were not pursued.

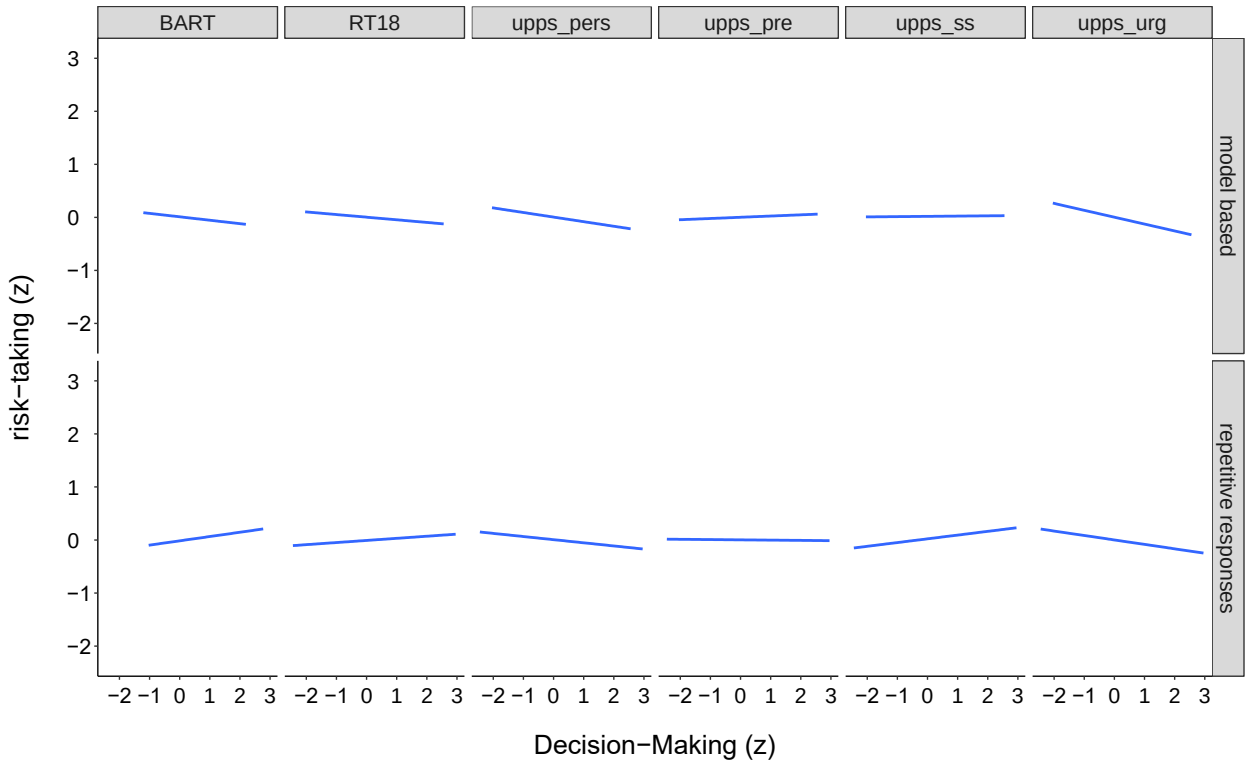


Figure 13 Association between Decision-Making and Risk-Taking Variables

Association between decision-making variables: model-based (top row), and repetitive responses (bottom row), and risk-taking: BART, RT-18, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency). No corrected significant associations were found.

5.3 Aim 3: Determine How Developmental Changes in Striatal Dopamine Modulate Frontostriatal Circuitry To Predict Decision-Making And Adolescent Risk-Taking

The third and final aim of this dissertation was proposed to test whether striatal DA may act indirectly through broader frontostriatal connectivity to influence decision-making and subsequently risk-taking. To investigate this perspective, while acknowledging some of the inconsistencies in the overarching psychobiological model (see Aims 1 and 2), we examined 1) the association between striatal DA measures and frontostriatal connectivity and 2) the association between frontostriatal connectivity and decision-making and risk-taking measures.

Consistent with recent work from our group using a different analytic approach within a portion of the PET sample (Parr et al., 2021), corrected significant associations (FDR q's < .05)(Appendix I)(N=212, 328 total visits, PET + 7T samples) were found between indirect measures striatal DA measures and frontostriatal connectivity. Furthermore, this effect was observed within the nucleus accumbens (NAcc) and ventromedial prefrontal cortex(vmpfc) (FDR q = .043)(Figure 14), a connection established in animal models as relevant for reward-related behavior (Haber, 2016). This was not observed with the direct PET DTBZ and RAC DA measures (FDR q's < .126). There was no evidence of an age by indirect striatal DA measure interaction predicting frontostriatal connectivity in any of the connections (FDR q's > .172), including the NAcc-vmpfc (Figure 15)(p =.467).

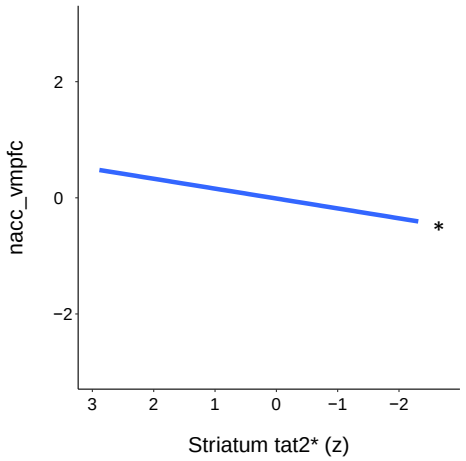


Figure 14 Association between Striatal Tissue Iron and NAcc-vmpfc Connectivity

Association between striatum taT2* (reverse scored for interpretation; see Methods) and NAcc-vmpfc connectivity. Higher iron scores are associated with lower connectivity. * FDR q < .05. See Appendix I for all connections.

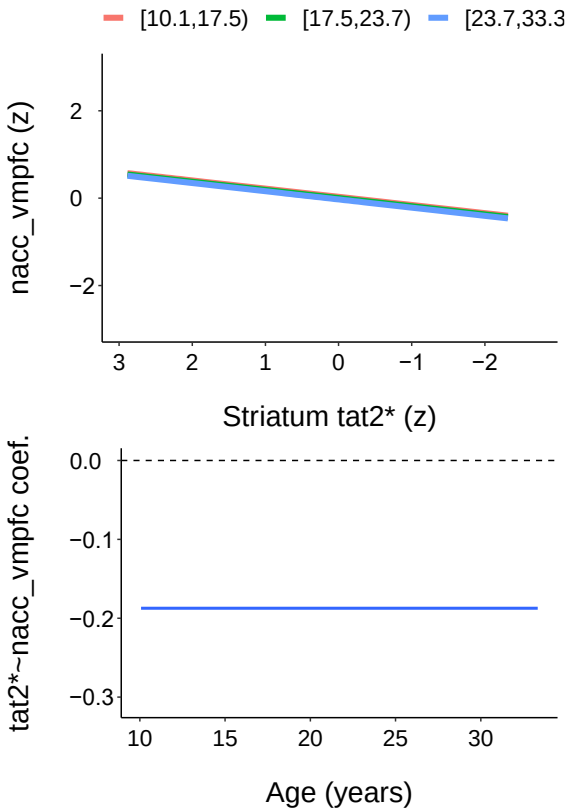


Figure 15 Association between Striatal Tissue Iron and NAcc-vmpfc Connectivity

Top row displays association between whole striatum taT2* (reverse scored for interpretation; see Methods) and NAcc-vmpfc connectivity for equally spaced age terciles (parsed from age by-taT2* interaction). Bottom row displays age-varying, taT2* with NAcc-vmpfc coefficient (sign flipped from original scale to match top plot: see Methods) estimated via TVEM.

Following up on the corrected, significant NAcc-vmpfc connection, we examined associations between NAcc-vmpfc connectivity and the risk-taking and decision-making measures. In a basic model (covaring age, visit, and head motion) there was an uncorrected significant associations linking connectivity to RT-18 (p = .039, FDR q = .207), with higher NAcc-vmpfc associated with lower risk-taking values (Figure 16). Nevertheless, this was reduced to an uncorrected trend when covaring for striatal iron (p=.073, FDR q= .357), limiting the implication of this result in the proposed psychobiological models of risk-taking. NAcc-vmpfc connectivity was not associated with the decision-making variables (FDR q's > .132).

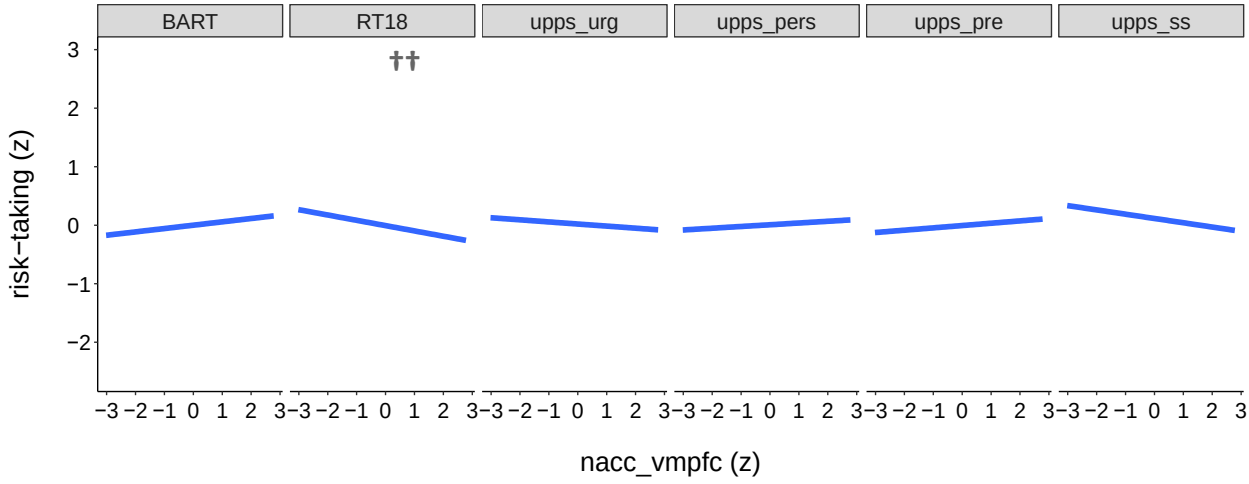


Figure 16 Association between NAcc-vmpfc Connectivity and Risk-Taking

Association between NAcc-vmpfc connectivity and risk-taking: BART, RT-18, upps_pers (Lack of Perseverance), upps_pre (Lack of Premeditation), upps_ss (Sensation Seeking), upps_urg (Urgency). ††, p < .05 (uncorrected) without covariates, p > .05 (uncorrected) with covariates (see Main text).

6.0 Discussion

Overall, mixed support was found for the proposed integrative psychobiological model of DA-related processes underlying adolescent risk-taking. Critical replications of emerging developmental work were observed, including age-related increases in tissue iron-based, indirect measures of striatal dopamine availability, age-related decreases and adolescent peaks in risk-taking propensity measures, and age-related increases in model-based learning in the decision-making task. Nevertheless, in the current analyses, striatal DA measures were not significantly associated with risk-taking measures. There was evidence that indirect striatal DA measures were associated with habitual responding in the decision-making task and frontostriatal connectivity. Nevertheless, broader circuit level-hypotheses of developmental changes in dopamine processing supporting changes in frontostriatal connectivity and subsequently decision-making and risk-taking propensity were not supported.

6.1 Developmental Patterns of Risk-Taking

We observed significant age-related change in almost all risk-taking propensity measures. Among the examined risk-taking measures, two general developmental trajectories were observed, with one group of measures (BART, UPPS Lack of Perseverance, Lack of Premeditation, Urgency) showing linear decreases, and two other measures (UPPS sensation seeking, and as a trend the RT-18) showing late adolescent peaks in expression. These results are highly consistent with prior work that has identified linear decreases in “impulsivity” (Harden & Tucker-Drob,

2011) but an adolescent peak, or inverted "u" functional form of age, in "sensation-seeking" (Duell et al., 2018)(Harden & Tucker-Drob, 2011)(Romer & Hennessy, 2007). Critically, the inverted "u" functional form of age in sensation seeking is consistent with predominant neurodevelopmental models (see (Shulman et al., 2016) for review), although this has not been universally supported, empirically (e.g.,(Littlefield et al., 2016)). While the current project adopted an inclusive view of risk-taking (see Introduction), the distinct developmental trajectories among the included measures, may suggest a possible substantive distinction between more "impulsivity" and "sensation-seeking" facets of risk-taking. This was supported by exploratory psychometric work in the current project (see Appendix C) that identified two factors with one having strong loadings for the UPPS Lack of Perseverance, Lack of Premeditation and one having strong loadings for the RT-18 and UPPS Sensation Seeking, even when residualizing the measures with respect to age.

The current work primarily focused on the developmental trajectories of risk-taking measures and their association with neurodevelopmental features. However, future work may examine associations among these risk-taking measures in more detail. In particular large-scale longitudinal data that can compare these putative broad-scale factors to more focused assessment-specific factor structures (e.g., UPPS (Whiteside & Lynam, 2001)), including within the context of parallel maturation and correlated within-person change (Collado et al., 2014)(Harden & Tucker-Drob, 2011). Broad between and within-person factor structures may also be useful to further examine associations with executive function development during adolescence (e.g., (Romer et al., 2011)(Lane et al., 2003)). Ultimately, this work can not only clarify the developmental trajectories of these key constructs, but also provide insight into how the normative

adolescent peaks in risk-taking may be related to psychopathology that emerges during this period (e.g., problematic substance use).

6.2 Age-related Change in Iron-Based Indirect Measures of Striatal Dopamine

Consistent with prior work, we observed significant, moderate effect sizes suggesting age-related increases in striatal tissue iron (Larsen & Luna, 2015) (Larsen et al., 2020) which were likewise associated with individual differences in PET measures of vesicular dopamine availability. These results thus support our group's initial work demonstrating a striatal iron-vesicular dopamine connection (Larsen et al., 2020) and the interpretation of adolescence as a period of change in the dopaminergic system (Larsen et al., 2020)(Luna et al., 2015)(Tarazi et al., 1998)(Andersen et al., 1997)(Teicher et al., 1995).

Methodologically, our group initially showed a significant association between iron-based measures from specialized scans (R2') and PET measures of vesicular striatal dopamine (Larsen et al., 2020). Supporting and expanding upon this, the current project demonstrated that a tissue iron-based measure calculated from standard functional neuroimaging data (taT2*) was likewise associated with PET measures of vesicular striatal dopamine. Therefore, this work further supports suggestions (Larsen et al., 2020)(Luna et al., 2020) to consider brain tissue iron as an indirect measure of striatal dopamine in neurodevelopmental studies.

A remaining substantive complexity in this area is that striatal iron has been shown to seemingly accumulate across the lifespan (Acosta-Cabronero et al., 2016), which differs from predominant neurodevelopmental theories of striatal dopamine that predict a developmental peak during the adolescent period (e.g.,(Luna et al., 2015)). Accordingly, while striatal tissue iron and

striatal dopamine may share common mechanisms, evidenced by their small to moderate correlation at the individual difference level, their maturation may also be driven by some divergent developmental mechanisms. Future work bridging cellular and molecular neuroscience and human neuroimaging metrics (e.g., opto-genetic based fMRI in rodents) is necessary to more precisely dissociate these common and specific developmental mechanisms. However, given its significant association with gold-standard PET dopamine measures and ease of calculation from existing functional neuroimaging data, additional work considering the functional associations of striatal tissue iron is clearly indicated.

6.3 Striatal DA and Risk-Taking Propensity Measures

In contrast to prior reports (Buckholtz et al., 2010)(Dalley et al., 2011)(see (Dalley & Roiser, 2012) for review), we did not find evidence for links between individual differences in striatal DA and risk-taking propensity measures. Nevertheless, its critical to contextualize this result within the current state of human individual difference research using positron emission tomography [PET] and neuroimaging more broadly. First, as part of the innovation of this project, few studies, all with relatively small samples (e.g., N=32 (Buckholtz et al., 2010)), compared to the current project's direct striatal DA measure sample: N=78, 161 total visits) have examined associations between individual differences measures of risk-taking and impulsivity and direct measures of dopamine. This number of studies is even smaller when excluding the larger proportion of studies that examine impulsivity within the context of psychiatric (e.g., (N. D. Volkow et al., 1997; Nora D. Volkow et al., 2007; Nora D. Volkow & Wise, 2005)) or neurological diagnoses (e.g.,(Stark & Claassen, 2017)). As a result, the current analyses were predicated in part

on the idea that understanding the true magnitude of (effect size) of the association between normative individual differences in dopamine and risk-taking would likely require a larger sample than these prior studies. That the current sample, which is twice as large as key prior works in this area (e.g., (Buckholtz et al., 2010)), demonstrated a non-significant association likely reflects the need for even larger studies to precisely estimate effect sizes in this area. To this end a small true, population effect size linking striatal DA to risk-taking measures and expected variability across small samples (sampling variability) could parsimoniously account for the discrepancy between the current work and prior reports. This suggestion is supported by concurrent work from our group on broader neuroimaging brain-behavior associations (Marek & Tervo-Clemmens et al., 2020).

Acknowledging statistical challenges in the still emerging field of human neuroimaging links between striatal dopamine and risk-taking, it is also noteworthy that prior work has used different PET dopamine assessments. For example, Buckholtz and colleagues (2010) notable prior work in this area also used a D2/3 radiotracer like the current project did for the adult sample. However, their work further used an amphetamine challenge, where endogenous dopaminergic binding was compared to amphetamine-induced binding, a procedure which can dissociate dopamine *release* from *D2/3 receptor concentration* (Nora D. Volkow et al., 1994). While the current work and the motivating neurodevelopmental literature (Luna et al., 2015), hypothesized general individual differences across the dopamine system, it is possible this more precise dissociation of dopamine *release* is particularly relevant for risk-taking related behaviors. Therefore, although the current work assessed two distinct aspects of the dopaminergic system (vesicular DA and D2/3 receptor concentration), further work comparing multiple radiotracers in the context of amphetamine-induced DA release may be necessary to test fully characterize the specificity of dopamine-risk-taking associations.

It is also relevant to consider the temporal structure of dopaminergic signaling and the current project's focus on aggregate, mean-level individual differences, or what might be considered more "trait" like dopamine assessments. To this end, while prior animals studies provide support for an association between aggregate mean-level/"tonic" dopamine and risk-taking type behaviors (Adriani et al., 2009)(Mitchell et al., 2014), more recent work has suggested these relationships may be more closely associated with time-varying "phasic" responses to for example, individual rewards (e.g.,(Stopper et al., 2014)(Freels et al., 2020)). Indeed, a prominent theory in the addiction literature suggests links between the DA system and risk-taking and impulsive behaviors evolve overtime, as phasic DA responses to rewards change in magnitude and timing (see (Berridge & Robinson, 2016). Nevertheless, such temporally varying associations between the dopamine system and risk-taking behaviors remain challenging to test with human neuroimaging that relies on aggerate per-session mean levels of DA. Parallel analyses with within-person fMRI analyses and striatal DA measures (Calabro et al., 2020) may thus be an important area of future work in examining the neurobiology of risk-taking.

Another potential explanation for the observation of non-significant dopamine-risk-taking associations is that the current sample excluded for current and prior psychopathology and neurological disorders. As alluded to above, a significant majority of prior work on associations between PET-based striatal DA and individual differences has been performed in participants meeting diagnostic criteria for psychiatric or neurological disorders. Accordingly, the true underlying association between DA and risk-taking related behaviors may be non-linear, with associations considerably magnifying at clinical levels of severity. Such an explanation may likewise account for low reproducibility in normative ranges, where a smaller effect size would require larger sample sizes to achieve adequate statistical power and high rates of reproducibility.

Future work may test these predictions by examining dopamine-risk-taking associations across a full range of severity, spanning normative variability to clinical presentations.

6.4 Age-related Changes in Decision-Making Task

Consistent with prior work (Decker et al., 2016), we observed age-related increases in model-based learning in a developmental version of the two-stage sequential reinforcement task. Non-linear modeling of this association (via general additive models) suggested rapid improvements during late childhood and early adolescence that stabilized to adult-levels by late adolescence. Given model-based learning has been described as requiring goal-directed behavior, this result may be consistent with the general observation of adolescence as a sensitive period in the development of goal-directed cognitive behaviors ("cognitive control": (Larsen & Luna, 2018; Luna et al., 2015)). Supporting this, prior work in adults has shown that individual differences in model-based learning are associated with putative subcomponents of cognitive control (e.g., working memory (Otto et al., 2013). Given the demonstrated replicability of adolescent changes in model-based learning and the growing interest in the construct, future, more detailed work may investigate common and specific developmental patterns of model-based learning and cognitive control.

In addition to replicating age-related changes in model-based learning, the current project also presented an exploratory, novel characterization of age-related differences in repetitive responses/first-stage stays in the decision-making task. Specifically, observing the strong main effect of age on this parameter, we sought to further understand this potential strategy. Within the context of the task, this "first-stage stay" parameter captures participants' tendency to repeat the

same choice of the rockets, irrespective of reward and probability structure, where high values are thought to correspond to habitual choices and low values corresponded to more exploratory choices. From this perspective, we observed adolescents as more exploratory and adults as more habitual in their responding. Consistent with this, considerable prior animal work has characterized adolescence as a period of heightened exploration (Linda P. Spear, 2000) and that adolescents are more resistant to behavioral habits than adults (Serlin & Torregrossa, 2015)(Towner et al., 2020)(Rode et al., 2020). Critically, it has also been suggested that this habitual behavior may be independent of goal directed cognitive control (Balleine & O'doherty, 2010). To this end, we observed significant age-related increases in "first-stage stays" across all trial types, suggesting this effect was independent of goal directed, model-based learning and may represent an alternative developmental shift in strategy. This result may reflect an adaptive nature of adolescent peaks in sensation-seeking and risk-taking that support environmental exploration (Linda P. Spear, 2000) necessary for specialization and establishment of adult trajectories (Larsen & Luna, 2018). Future work should further investigate the developmental overlap in this exploratory-habit-like behavior and model-based learning within the context of broader adolescent cognitive development. Of particular interest may be the distinction between experience-dependent (habitual responding, automaticity) and experience-independent (executive function) processes and how these reflect broader views of adolescent neurocognitive development (Romer et al., 2017).

6.5 Decision-Making Strategies and Risk-Taking Measures

In contrast to the hypothesized integrative model of risk-taking, we found small, non-significant associations, when covarying age, between decision-making strategies from the sequential learning task and risk-taking measures. It is worth noting however, that detailed review of some prior work using a variant of this task with risk-taking related phenotypes (Gillan et al., 2016), suggests that the observed effect sizes of the association between model-based learning and our risk-taking measures were broadly consistent with this prior report. We also found similar effect sizes for the association between the post-hoc first-stage stay parameter and risk-taking measures. Given the small magnitude of these results and some consistency with secondary analyses from prior work (Gillan et al., 2016), larger sample sizes are likely needed for consistent statistical inferences to be drawn on associations between these decision-making strategies and risk-taking measures. Alternatively, growing work has shown that behaviors that share features with risk-taking (e.g., impulsivity)(Tomko et al., 2014)(Stevens et al., 2020)(Pedersen et al., 2019) have substantive day-to-day variability that is predictive of real-world outcomes (e.g., alcohol use (Stevens et al., 2020)(Pedersen et al., 2019)). Therefore, future work may explore associations between decision-making strategies and daily variability in risk-taking related behaviors. In summary, based on the current project and related prior work, the magnitude of the effect linking these decision-making strategies to phenotypic risk-taking measures appears small and prompts more detailed investigations of underlying mechanisms, across varying timescales.

6.6 Striatal DA and Decision-Making Strategies

Preliminary evidence was found for the predicted association between striatal DA and decision-making strategies. Among the full sample (adolescents and adults), we observed significant associations between tissue iron-based indirect measures of striatal DA and the post-hoc repetitive responses/first-stage stay parameter during early adolescence (in the presence of an age by striatal iron interaction predicting repetitive responses). Specifically, during early adolescence a positive association was observed, with higher tissue iron being associated with more repetitive responses. These results therefore support predictions from foundational animal work suggesting adolescent changes in dopamine give rise to changes in reward related-behavior (cf., (Linda P. Spear, 2000)). Moreover, as alluded to above (see Results), the direction of this association and the normative trajectories of striatal tissue iron and repetitive responses parameter may suggest a parallel maturation of striatal DA and these habitual responses. Given this and the specificity of the striatal tissue iron-habitual response association to early and mid-adolescence, this result may speak to timing differences in adolescent development that subsequently normalize when most individuals reach adult-levels of maturity. Future work may test these predictions in prospective longitudinal data. Prospective longitudinal data can likewise be used to test whether deviations from normative development of the striatal tissue iron-repetitive responding pairing is associated with the emergence of habit-related adolescent psychopathology (e.g., substance use), as would be predicted by prominent neurodevelopmental frameworks (see (Shulman et al., 2016)). Such longitudinal work in humans would be particularly well served by parallel molecular studies in rodents that unpack the common/specific maturation of striatal tissue iron and striatal dopamine (see Age-related change in Iron-Based Indirect Measures of Striatal Dopamine), given challenges in PET imaging in adolescent humans.

More broadly, the significant association between striatal tissue iron and repetitive responses but the lack of any significant relationships between striatal dopamine measures and risk-taking assessments highlights a potential neurodevelopmental dissociation between decision-making and risk-taking. While the current project built upon predominant adolescent theory that typically emphasizes a broad range of potentially inter-related affective behaviors (e.g.,(Steinberg, 2004)), some contemporary work has emphasized potential key neurodevelopmental differences among decision-making and risk-taking processes (Hartley & Somerville, 2015). Acknowledging general differences among laboratory and self-report measures (see Towards Robust Links among Multi-method Data), this result may speak to risk-taking more as the end result of diverse neurodevelopmental and genetic inputs and decision-making as more directly linked to underlying striatal development. In support of this perspective, the hypothesis for the current project predicted decision-making would mediate the relationship between striatal dopamine and risk-taking, which ultimately situates risk-taking as a more distal target of striatal development (compared to risk-taking). Nevertheless, this mediation model was not supported. However, the current result of links between indirect striatal dopamine measures and decision-making may prompt future work to examine broader, multivariate associations across neurodevelopmental systems in predicting risk-taking. While the current model of striatal dopamine predicting risk-taking via decision-making was not directly supported, it may nevertheless be relevant within the context of a broader multi-system understanding of risk-taking.

6.7 Frontotriatal Connectivity, Dopamine, and Behavior

Within the context of a multi-system understanding of risk-taking, the current project hypothesized that striatal dopamine's association with decision-making and risk-taking would ultimately unfold through frontostriatal connectivity. Supporting this perspective, we found a significant association between striatal tissue iron and nucleus accumbens (NAcc)-ventro medial prefrontal cortex (vmpfc) resting-state connectivity, which was also found in recent work from our group that used a subsample of the data from the current work (Parr et al., 2021). This association is particularly relevant given the well-established anatomical basis of this circuit in primates (Haber, 2016), where vmpfc projects to the NAcc, and the considerable research implicating it in adolescent reward-related behaviors and decision-making (Galvan et al., 2006)(see (Luciana & Collins, 2012) for review).

Mechanistically, striatal tissue iron may modulate frontostriatal connectivity through multiple pathways. First, as established, iron is involved in the synthesis of dopamine (Ortega et al., 2007)(Zucca et al., 2017), co-localizes with dopamine vesicles (Ortega et al., 2007), and as shown in our groups prior work ((Larsen et al., 2020) and expanded upon here, is associated with individual differences in gold-standard measures of dopamine in humans. To this end, while acknowledging direct measures of dopamine were not associated with frontostriatal connectivity in the smaller subsample of adults who had those measures, the association between striatal tissue iron and NAcc-vmpfc functional connectivity may suggest a modulatory role of dopamine on this circuit. A potential mechanism of this modulation could be through established interactions between striatal dopamine and prefrontal glutamate (Kalivas, 2009)(McFarland et al., 2003). As an alternative or complementary explanation, tissue iron also supports myelination via modulation of oligodendrocytes (Todorich et al., 2009). To this end, this result may speak to a mediating role

of for example, intracortical myelin (Huntenburg et al., 2017) in the relationship between striatal tissue iron and frontostriatal resting-state functional connectivity. Nevertheless, recent work our group did not find evidence of this when explicitly modeling inter-individual differences in myelination (Parr et al., 2021). Ultimately, a mechanistic account of the link between striatal tissue iron and frontostriatal connectivity will rely on detailed animal work and parallel multimodal human neuroimaging.

Further consistent with the proposed model whereby fronstoriatal connectivity would mediate the relationship between striatal dopamine and decision-making and risk-taking, we found a nominally significant association between NAcc-vmpfc connectivity and risk-taking measure (RT-18). However, given this relationship was no longer significant in the current set of analyses following more stringent covariate control, some ambiguity remains in determining the behavioral relevance of the examined frontostriatal connections. Nevertheless, it's worth considering concurrent work from our group (Marek & Tervo-Clemmens et al., 2020) demonstrating that many of the effect sizes linking resting-state connectivity to individual differences among psychological variables (e.g., cognition, mental health) are considerably smaller than prior work suggests (e.g., top 1% r=~.06). Therefore, considerably larger sample sizes may be required to make reliable statistical inferences regarding associations with resting-state connectivity and individual difference measures. Alternatively, emerging work has shown that resting-state connectivity associations with individual differences in behavior may be best understood in the context of broad, multivariate patterns of connectivity spanning multiple brain systems (Marek & Tervo-Clemmens et al., 2020)(S. M. Smith et al., 2015). Future work from the author plans to investigate both of these ideas through multivariate predictive models developed in large-scale consortia neuroimaging data. Furthermore, as above, more detailed molecular based neuroimaging (e.g.,

intensive longitudinal pharmacology studies) and/or intensive longitudinal sampling can better examine these associations between frontostriatal connectivity, dopamine, and behavior from a within-subject perspective.

6.8 Towards Robust Links Among Multi-Method Data

The current project had mixed success in testing an integrative model of risk-taking using various different types of data (e.g., neuroimaging, laboratory-based cognitive performance, self-reported risk-taking). Challenges in linking this type of multi-method data have been widely discussed in the related literature on individual differences of impulsivity. Here, a number of studies have found self-report and laboratory-based cognitive measures to be at best, moderately associated (cf., (Gerbing et al., 1987).; see (Lane et al., 2003)(Stevens et al., 2020) for more recent discussion). From this work, it has been suggested that self-report and laboratory-based cognitive measures may assess distinct aspects of psychological constructs (e.g., impulsivity), each with some predictive utility on real-world outcomes (e.g., (Sharma et al., 2014)).

Based on the current projects' mixed success, and challenges in the broader neuroimaging field with individual difference associations between neuroimaging data and psychological variables (see (Marek & Tervo-Clemmens et al., 2020) (Poldrack et al., 2017)), it is worth considering optimal strategies for linking multi-method data moving forward. A possibility for future work, particularly in the context of the still emerging field of developmental cognitive neuroscience, is to find ways to incorporate standardized assessment batteries across studies and research groups to improve statistical power. Comprehensive assessments of both self-reported risk-taking measures and multiple laboratory-based measures in such standardized batteries would

also be essential. Such a strategy would facilitate methodological and theoretical development in construct definitions that have been designed with multi-method data in mind and go beyond heuristics and conceptual similarity.

6.9 Design Strengths and Limitations

This project was characterized by a number of strengths, including a first-of-its kind longitudinal PET design in normative subjects, the use of multiple field-standard risk-taking propensity measures, and the testing of integrative psychobiological mechanisms of risk-taking. However, it is worth noting a few key limitations. First, although a portion of this project utilized a fairly large accelerated longitudinal neuroimaging sample size and added a second sample to improve statistical power, some analyses relied on smaller subsamples and the effective statistical power of typical neuroimaging studies is an area of active debate (see Marek & Tervo-Clemmens et al., 2020). Despite the limited sample size, we highlight the strength of the current analyses given their theorized role linking striatal DA and risk-taking in the extant literature and that the included sample size is significantly larger or equivalent to prior high impact publications utilizing these measures (e.g., developmental changes in the decision-making task (N=80)(Decker et al., 2016); links between the decision-making task and striatal DA (Deserno et al., 2015)(N=29)). Moreover, we suggest even non-significant results from these analyses are essential to the literature, with reported effect sizes critically guiding future research in this area.

An additional potential limitation of the current analyses was that not all analyses contained longitudinal data and even those that did relied on an accelerated longitudinal design. Although this design has the advantage of incorporating both within- and between subject estimates of age-

related change in developmental studies, within-subject estimates are, in part, constrained by participants' starting ages. For example, those subjects who enter the study at 25-years-old, when the majority of normative brain development has occurred, likely have limited within-subject change that is driven by developmental processes. While the current analyses incorporated all available data (see Modeling Overview), we note further longitudinal research using cohort designs will be required to fully characterize within-subject processes (e.g., temporal precedence) among these constructs.

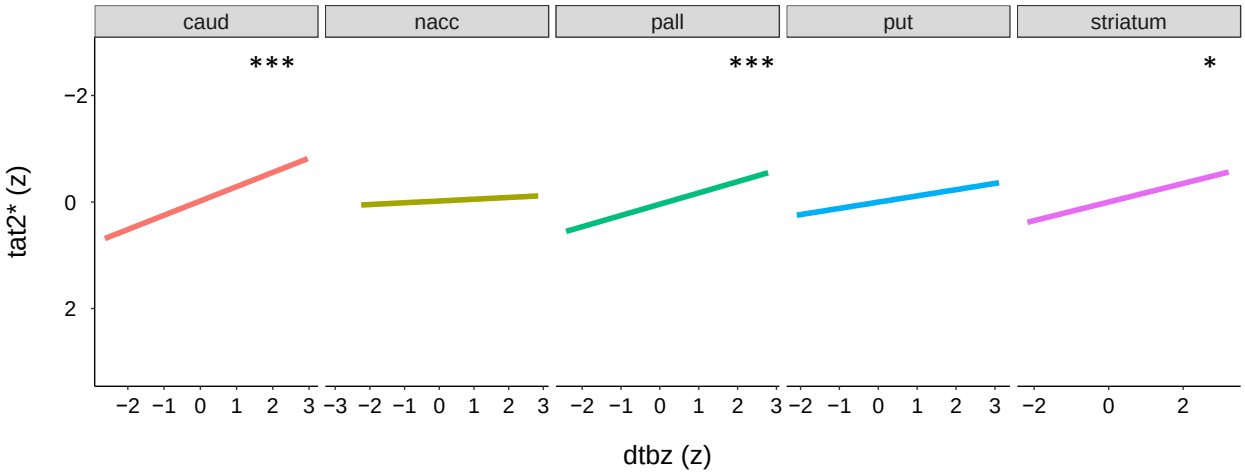
Finally, this project excluded subjects with a reported history of a psychiatric disorder, either in themselves, or in a first-degree relative. Given that risk-taking behaviors are exaggerated in certain forms of psychopathology (e.g., impulse control disorders), this exclusion criteria may have limited the ability of the reported results to characterize the highest end of the population distribution of risk-taking behaviors. However, we highlight that this approach provides an essential focus on *normative* adolescent processes, which are critical to understand from both a more basic developmental neuroscience perspective and for informing models of the *emergence* of psychopathology during this period.

7.0 Conclusion & Implications

Seeking to address the gap between prior neuroimaging studies and foundational neurodevelopmental models, we leveraged a first-of-its-kind longitudinal neuroimaging dataset that collected direct and indirect measures of striatal DA to test an integrative psychobiological model of adolescent risk-taking. Across three aims, we found mixed support for the integrative model linking neurobiological, computational, and circuit dynamics underlying adolescent risk-taking. Consistent with prior work, significant developmental changes were found in risk-taking propensity measures (age-related decreases), in iron-based, indirect measures of striatal DA (age-related increases), and in model-based learning during the decision-making task (age-related increases). We also provide an exploratory novel characterization of repetitive responding that is associated with tissue iron. However, associations between individual differences in self-report measures of risk-taking propensity and both direct (PET) and indirect, tissue iron based (taT2*) striatal DA measures and resting-state connectivity were small in magnitude and largely not statistically significant. Results from this study can inform future work seeking to test foundational neurodevelopmental theory in humans, which is essential to understanding and developing interventions for substance use disorders, sexually transmitted diseases, and fatal accidents that emerge during adolescence.

Appendix A Validation of Tissue Iron Measure

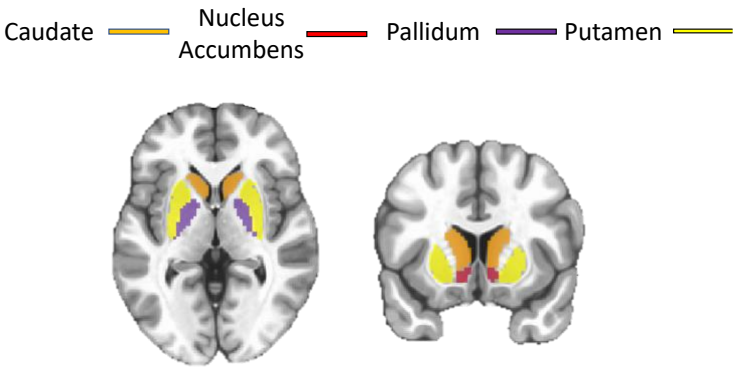
In order to validate the tissue iron measure used in the current project, which again we note was estimated from standard functional neuroimaging data as opposed to specialized iron scans (see Methods), we examined the association between this measure taT2* and the same PET-based striatal dopamine measure (DTBZ) our group recently showed (Larsen et al., 2020) was associated with tissue iron. Using the same analytic procedures as the remainder of the project (GAMM models; see Modeling Overview), we show that taT2* is significantly associated with DTBZ across multiple regions of the striatum, in whole striatum on average, and the pallidum (Appendix Figure 1).



Appendix Figure 1 taT2* with DTBZ

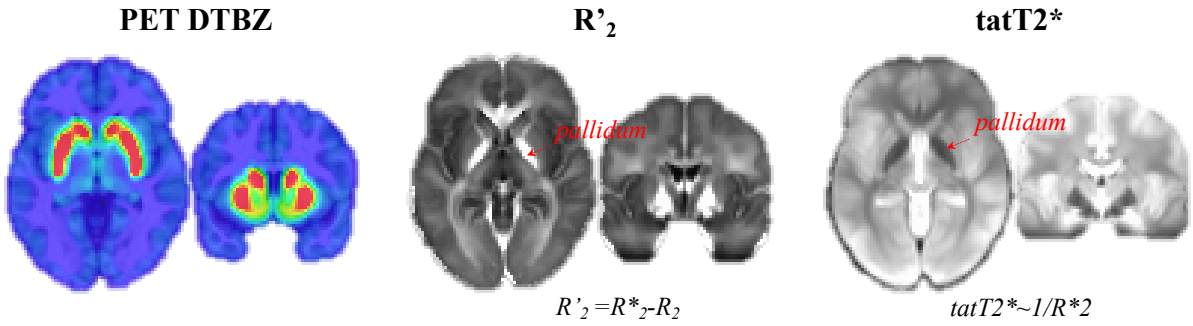
Associations between taT2* (reverse scored for interpretation; see Methods) and PET marker of vesicular dopamine, DTBZ, in the caudate (caud), nucleus accumbens (NAcc), pallidum (pall), putamen (put), and whole striatum (striatum). Note, *** p < .001, * p < .01

Appendix B Striatal and Pallidal Regions of Interest



Appendix Figure 2 Harvard Oxford Striatal and Pallidal Regions of Interest

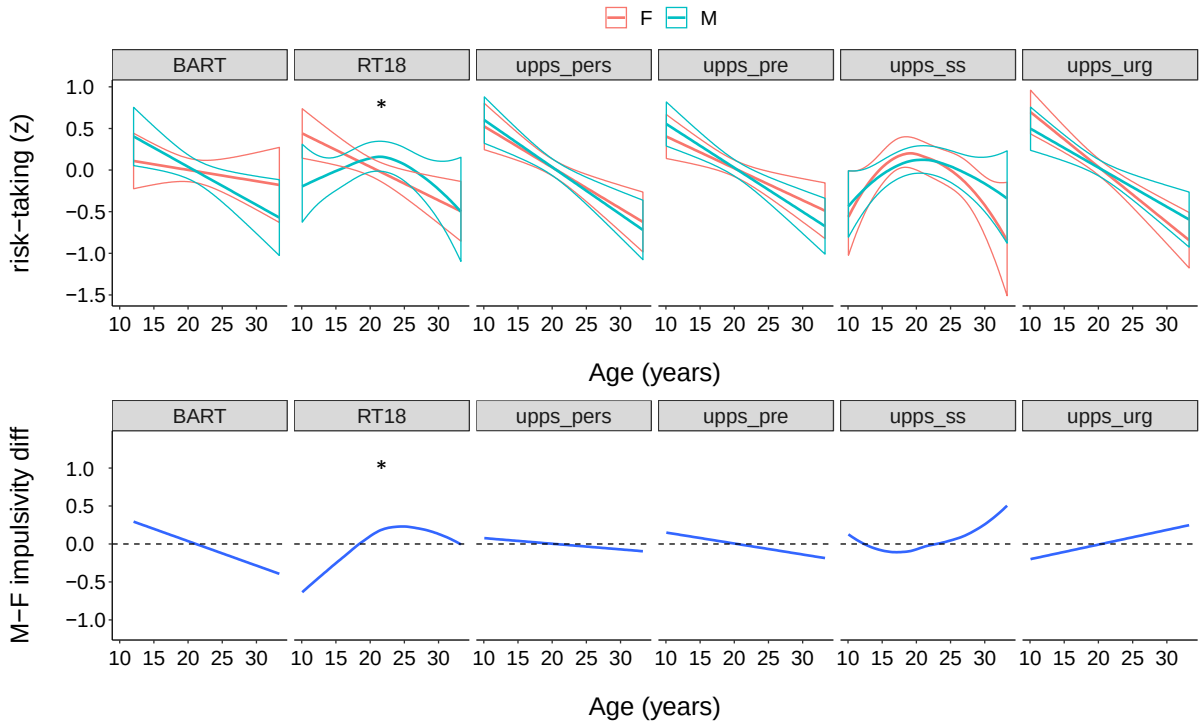
Striatal regions of interest were chosen based on a priori hypotheses concerning the striatum and the pallidum was included given it has the highest striatal tissue iron concentration in the brain (see Appendix Figure 3).



Appendix Figure 3 Grand Mean Values of DTBZ, R2', and taT2*

Appendix C Psychometric Analyses

Sex: Age by biological sex (self-reported Male or Female) interactions in risk-taking measures (N=323, 523 total visits, PET + 7T samples) were generally non-significant with the exception of the RT-18 (Appendix Figure 4, overlap of 95% CI [shaded area] and estimate [line] indicates non-significance, p > .05). Furthermore, visualization of age-trajectories revealed minimal evidence of main effects of sex. Given the minimal evidence of main or interactive effects with age, sex was not further examined as a covariate in the current analyses for the sake of parsimony.



Appendix Figure 4 Age by Sex Effects in Risk-Taking

Top row displays smoothed age trajectories (via GAMM; see methods) for male and female participants. Bottom row displays difference between male and female estimates (line) and its 95% confidence interval. * indicates a significant (p < .05) sex differences were found in the RT-18 by age, as indicated by ages where CI of difference estimate does not include zero

Longitudinal Stability of Primary Study Measures: Across striatal ROIs, both indirect (N=72 with two visits, PET + 7T samples) and DTBZ direct (N=62 with two visits, PET sample) striatal DA measures had moderate to good longitudinal stability between study visits (~18 months)(intraclass correlation coefficients, ICCs: indirect measures: .614-.894, DTBZ direct measures: .661-.864). RAC direct PET measures (N=57 with two visits, PET sample) had lower stability (ICC's: .298-.585). Risk-taking (N=119 with two visits, PET) metrics had moderate stability (ICCs: .570-.75), except for the BART which had poor stability (ICCs: .387). Consistent with prior work (see (Noble et al., 2019) for review), the stability of resting-state connectivity (N=66 with two visits, PET sample) was uniformly low (ICC's < .458).

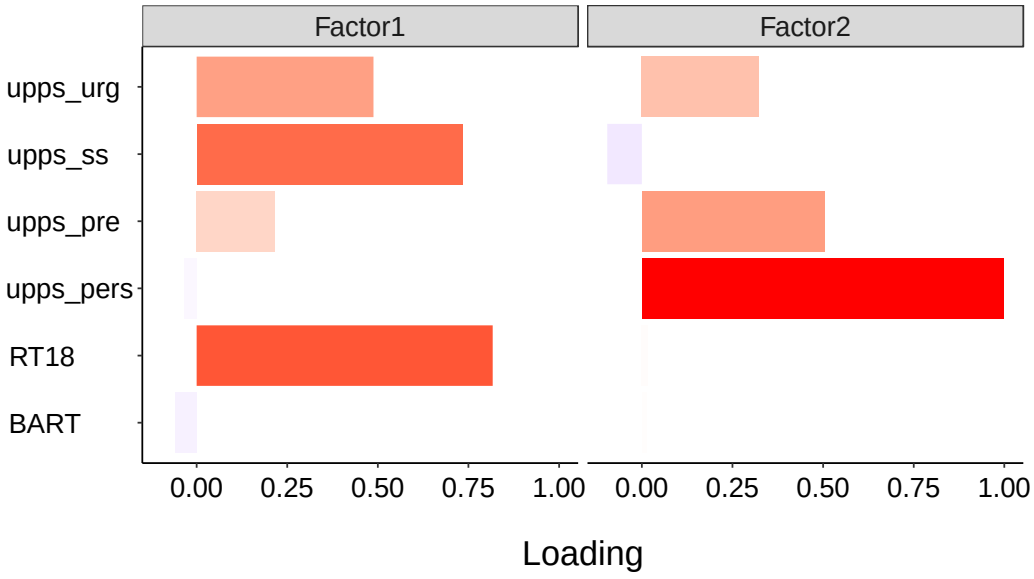
Correlation and Factor Structure of Risk-Taking Measures: Pearson correlations among risk-taking measures (full cross-sectional sample: N=326 subjects, PET + 7T samples) are presented below (Appendix Table 1).

Appendix Table 1 Pearson Correlations Among Risk-Taking Measures

	BART	RT18	upps_urg	upps_pers	upps_pre
RT18	-0.051				
upps_urg	-0.032	0.434			
upps_pers	0.012	0.015	0.321		
upps_pre	0.058	0.164	0.231	0.503	
upps_ss	-0.052	0.592	0.309	-0.097	0.200

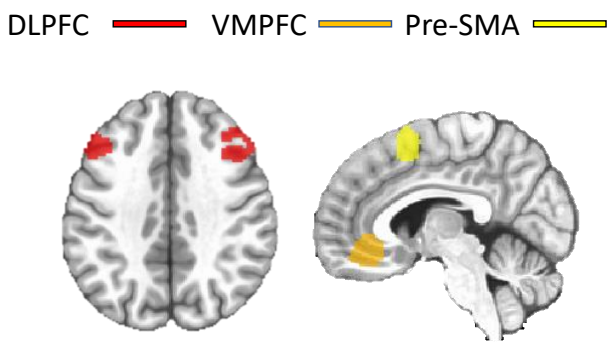
In order to examine potential structure among the correlations among these measures, an exploratory factor analysis (oblique rotation: goemin) was used with the full cross-sectional risk-taking sample (N=326 subjects, PET + 7T samples) and the number of factors extracted (two factors extracted) determined through a parallel analysis of simulated data of the same size. Factor

loadings (Appendix Figure 5) support a potential distinction between more affect-related risk-taking focused measures (RT-18 and UPPS Sensation Seeking) compared to more cognitive-based impulsivity-related measures (UPSS Lack of Perseverance and Lack of Premeditation). Interestingly, the BART did not have a large loading on either factor, which is likely explained by its low correlation with the other measures and poor reliability/longitudinal stability (see above). We note these results were unchanged (including the number of factors and general loading structure) when residualizing all variables with respect to age.



Appendix Figure 5 Factor Loadings of Risk-Taking Measures

Appendix D Cortical Regions of Interest



Appendix Figure 6 Cortical Regions of Interest from Neurosynth

Appendix E Power Analysis

This project reports "sensitivity" style power analyses, performed prior to the completion of data analysis, where we estimated the required effect size necessary to achieve a "statistically significant result" for a given α, Power, and sample size. Given the complexity of these style of sensitivity power analyses for the primary dataset (PET sample), which includes longitudinal data, we report the conceptual lower and upper bounds of statistical power. Furthermore, we recognize that protocols for *a priori* power analyses of interaction terms, which propagate error between two independent variables, are widely debated and it remains unclear how best to model the shared and specific error of each variable to best match an interaction term. To this end, here we report power analyses for bivariate relationships only.

Longitudinal and cross-sectional power analyses for the PET sample were conducted using Monte Carlo simulation via custom scripts in R. The advantage of this custom approach is that it allowed us to systematically vary key parameters influencing statistical power (e.g., underlying effect sizes, subject attrition, intraclass correlation coefficients (ICCs) of study variables) instead of relying on the built-in assumptions of many existing cross-sectional (e.g., G*power: (Faul et al., 2007)) and longitudinal power analysis protocols (e.g., SIMR: (Green & MacLeod, 2016)). Development versions of the functions used for this simulation are available through our groups' R package (Foran & Tervo-Clemmens, 2019: github.com/LabNeuroCogDevel/LNCDR/blob/master/R/multilevel_data_sim.R)

Within each iteration of the simulation (5,000 per parameter combination: see below), bivariate multilevel data was simulated by first generating a multivariate normal distribution (means zero, unit variances), corresponding to random intercepts and random slopes of two

theoretical variables with the same number of "subjects" as our dataset (N=144). Subsequently "data observations" (3 observations per subject, 432 observations total) were created for each of the two variables according to linear mixed effects model equations with the following structure:

$$Y_{ij} = \gamma_{00} + r_{0i} + \gamma_{01} + r_{1i} + \varepsilon_{ij}$$

where Y_{ij} is the observation of subject i at visit j, γ_{00} is the fixed effect intercept, r_{0i} is the subject's random intercept, $\gamma_{01}$is the fixed effect slope, r_{1i} is the subject's random slope, and ε_{ij} is level-1/measurement error. Attrition, which matched our expected attrition rate for the current study (15.27%), was simulated by randomly removing this proportion of observations in each iteration (missing completely at random, MCAR).

Across multiple runs of simulations, the magnitude of correlation between (e.g., intercept-intercept, intercept-slope, slope-slope) and within the simulated variables (slope-intercept) was iteratively manipulated via the correlation structure of the multivariate normal distribution generating random intercepts and slopes (see above). To simplify for simulation, univariate fixed effects were set to zero, such that each variable had a grand mean of zero (γ_{00}=0) and the variable did not change over visits on average ($\gamma_{01} = 0$). To provide a general estimate of power to detect bivariate relationships, correlations between variables (intercept-intercept, intercept-slope, slope-slope) were jointly adjusted, ranging from r's=.1 to r's=.6, in steps of .05. Realistic small to moderate within-variable slope-intercept correlations were tested (r's=0 to r's=.3, in steps of .1). The variance of level-1/measurement error was also iteratively adjusted such that in an intercept (fixed and random) only version of the data generation model (i.e., no fixed or random slopes: "unconditional model"), the simulated observations would have intraclass correlation coefficients (ICCs) ranging from .6 to .9, in steps of .1, according to the following ICC equation:

$$\frac{\sigma^2_{\alpha}}{\sigma^2_{\alpha} + \sigma^2_{\varepsilon}}$$

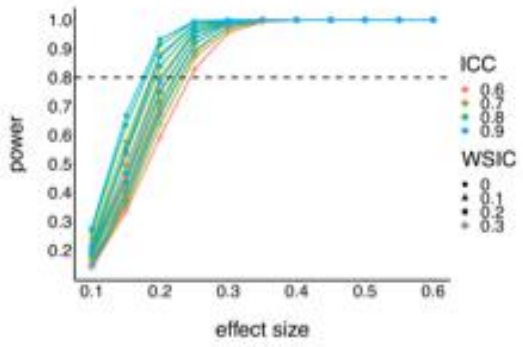
and solving for the error variance (σ^2_{ε}) gives

$$\sigma^2_{\varepsilon} = \sigma^2_{\alpha}(\frac{1}{ICC}\text{-}1)$$

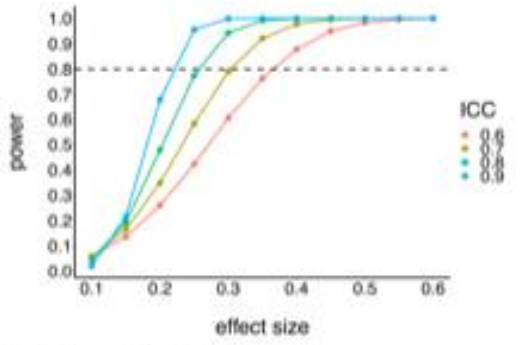
where σ^2_{α} is the variance of random intercepts, σ^2_{ε} is the level-1/measurement error variance, and ICC is the intraclass correlation. Error was added to each observation (see data generation model above) by drawing from a normal distribution with mean zero and variance equivalent to this computed error variance. Cross-sectional power analyses were performed by randomly selecting one visit from the multilevel data and running a simple correlation among the two variables.

Results from the simulation study suggest that under most conditions, bivariate analyses using the full sample with longitudinal data would be sufficiently powered (.80) to identify small effect sizes associations (between variable correlations < .25) at an alpha of .05 (Appendix Figure 7A). In the cross-sectional data, the simulation suggests that under most conditions, small to moderate effect size associations (correlations < .3) would be required to achieve an alpha of .05 (Appendix Figure 7B). However, as described in seminal early work (Spearman, 1904), we note that lower reliability (here, ICC values) attenuates observed correlations (see Appendix Figure 7C) and subsequently reduce statistical power. While prior validation studies have demonstrated high ICCs for the utilized risk-taking propensity measures (see above), the ICC values for the neuroimaging data are generally unknown. Per the *General Statistical Procedures* outlined in this project, we report all relevant ICC values in the results section.

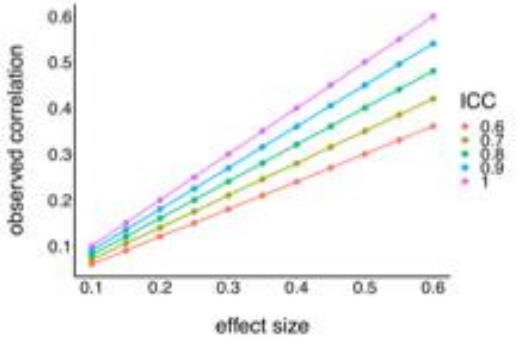
A. Full Sample Power Analysis



B. Cross Sectional Sample Power Analysis



C. Correlation Attenuation by ICC



Appendix Figure 7 Power Simulation Results

Appendix F Model Results for Links between Striatal DA and Risk-taking

Appendix Table 2 Model Results for taT2* and Risk-Taking

ROI	Risk-Taking	edf	Kendall Tau	FDR q
caud	BART	1.000	0.043	0.970
caud	RT18	1.000	-0.020	0.970
caud	upps_urg	1.000	-0.026	0.970
caud	upps_pers	1.000	-0.057	0.970
caud	upps_pre	1.000	-0.048	0.970
caud	upps_ss	1.000	0.028	0.970
nacc	BART	1.000	-0.069	0.970
nacc	RT18	1.000	-0.015	0.970
nacc	upps_urg	1.000	-0.023	0.970
nacc	upps_pers	1.000	-0.051	0.970
nacc	upps_pre	1.000	-0.080	0.970
nacc	upps_ss	1.000	-0.037	0.970
striatum	BART	1.000	-0.011	0.970
striatum	RT18	1.000	-0.055	0.970
striatum	upps_urg	1.000	-0.083	0.970
striatum	upps_pers	1.000	-0.118	0.970
striatum	upps_pre	1.000	-0.105	0.970
striatum	upps_ss	1.000	-0.003	0.970
pall	BART	1.000	-0.066	0.970
pall	RT18	1.000	-0.027	0.970
pall	upps_urg	1.000	-0.108	0.970
pall	upps_pers	1.000	-0.102	0.970
pall	upps_pre	1.000	-0.111	0.970
pall	upps_ss	1.000	0.020	0.970
put	BART	1.000	-0.023	0.970
put	RT18	1.000	-0.075	0.970
put	upps_urg	1.000	-0.107	0.970
put	upps_pers	1.000	-0.145	0.970
put	upps_pre	1.000	-0.122	0.970
put	upps_ss	1.000	-0.023	0.970

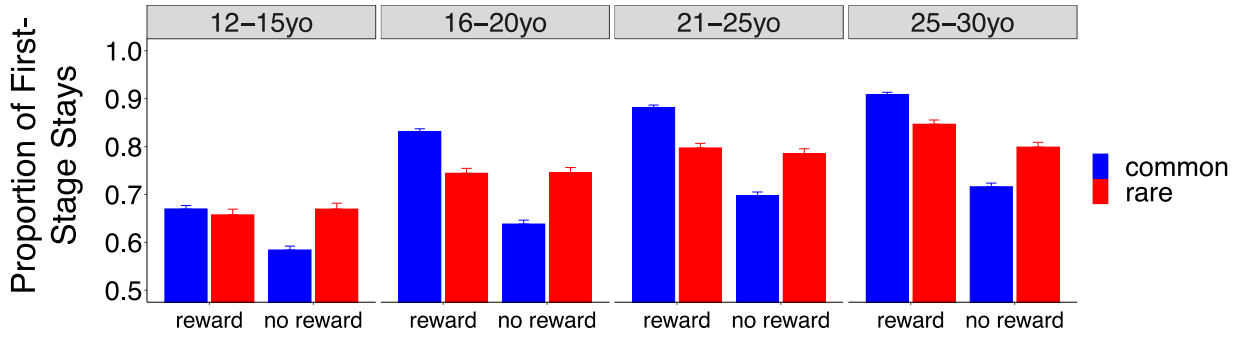
Appendix Table 3 Model Results for DTBZ and Risk-Taking

ROI	Risk-Taking	edf	Kendall Tau	FDR q
caud	BART	1.000	-0.016	0.997
caud	RT18	1.000	-0.040	0.997
caud	upps_urg	1.000	0.001	0.997
caud	upps_pers	1.000	-0.066	0.997
caud	upps_pre	1.000	-0.024	0.997
caud	upps_ss	1.000	-0.030	0.997
nacc	BART	1.000	-0.084	0.997
nacc	RT18	1.000	0.012	0.997
nacc	upps_urg	1.000	0.042	0.997
nacc	upps_pers	1.000	0.045	0.997
nacc	upps_pre	1.000	0.021	0.997
nacc	upps_ss	1.000	0.009	0.997
striatum	BART	1.000	-0.038	0.997
striatum	RT18	1.000	0.040	0.997
striatum	upps_urg	1.000	0.055	0.997
striatum	upps_pers	1.000	0.009	0.997
striatum	upps_pre	1.000	0.039	0.997
striatum	upps_ss	1.000	0.048	0.997
pall	BART	1.000	-0.033	0.997
pall	RT18	1.000	-0.040	0.997
pall	upps_urg	1.000	-0.014	0.997
pall	upps_pers	1.699	0.043	0.997
pall	upps_pre	1.000	0.010	0.997
pall	upps_ss	1.000	-0.021	0.997
put	BART	1.000	-0.030	0.997
put	RT18	1.000	0.071	0.997
put	upps_urg	1.000	0.087	0.997
put	upps_pers	1.000	0.062	0.997
put	upps_pre	1.000	0.069	0.997
put	upps_ss	1.000	0.078	0.997

Appendix Table 4 Model Results for RAC and Risk-Taking

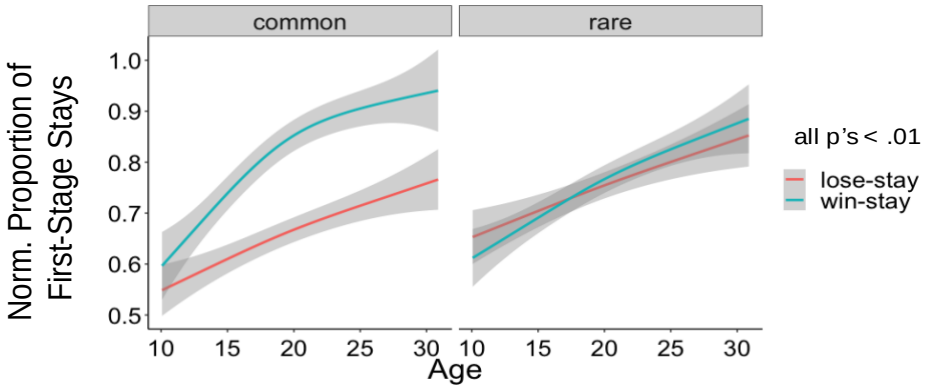
ROI	Risk-Taking	edf	Kendall Tau	FDR q
caud	BART	1.000	0.005	0.924
caud	RT18	1.000	0.062	0.924
caud	upps_urg	1.000	0.075	0.924
caud	upps_pers	1.000	-0.057	0.825
caud	upps_pre	1.000	0.161	0.615
caud	upps_ss	1.000	0.059	0.948
nacc	BART	1.000	0.008	0.924
nacc	RT18	1.000	0.015	0.924
nacc	upps_urg	1.000	0.124	0.825
nacc	upps_pers	2.084	0.064	0.615
nacc	upps_pre	1.000	0.248	0.148
nacc	upps_ss	1.000	0.052	0.930
striatum	BART	1.000	0.070	0.959
striatum	RT18	1.000	0.021	0.860
striatum	upps_urg	1.000	0.075	0.924
striatum	upps_pers	1.000	-0.043	0.825
striatum	upps_pre	1.000	0.235	0.259
striatum	upps_ss	1.000	0.040	0.924
pall	BART	1.000	0.035	0.924
pall	RT18	1.000	-0.083	0.924
pall	upps_urg	1.000	0.029	0.790
pall	upps_pers	1.000	0.012	0.924
pall	upps_pre	1.000	0.079	0.615
pall	upps_ss	1.000	-0.048	0.924
put	BART	1.000	0.075	0.924
put	RT18	1.000	0.003	0.615
put	upps_urg	1.000	0.074	0.924
put	upps_pers	1.000	-0.058	0.924
put	upps_pre	1.000	0.217	0.413
put	upps_ss	1.000	0.032	0.924

Appendix G Parsing Developmental Changes in Decision-Making Task



Appendix Figure 8 Decision-Making Task Results by Binned Age

Plotting the proportion of first-stage stays (repeating rocket ship choice: see Figure 2 Main text) as function of common and rare transitions and four age bins. The common by rare age interaction that defines age-related increases in model-based learning (see Figure 9 Main text) is evident by the relative heights among the bars. The main effect age in the proportion of first-stage stays or "repetitive responses" is evident by the average height of the bars.



Appendix Figure 9 Normed First-Stage Stays by Condition and Age

Plotting the normalized proportion of first-stage stays (normalized by the number of trials in each condition to equate across conditions), reveals that significant simple effects of age (p's < .01) are evident in all trial conditions. This is epitomized in trials common trials where adults are not rewarded and model-based learning would predict a switch, but they continue to have more first-stage stays than adolescents. We have interpreted these repetitive responses in the context of age-related changes in habitual responding (see Main text).

Appendix H Model Results for Links between Striatal DA and Decision-Making

Appendix Table 5 Model Results for taT2* and Decision-Making

ROI	Decision-Making	edf	Kendall Tau	FDR q
caud	model based	1.000	0.063	0.392
caud	repetitive responses	1.000	0.094	0.296
nacc	model based	6.756	0.114	0.105
nacc	repetitive responses	7.145	0.167	0.105
striatum	model based	2.602	0.174	0.194
striatum	repetitive responses	1.559	0.203	0.152
pall	model based	1.000	0.155	0.168
pall	repetitive responses	1.000	0.146	0.475
put	model based	4.609	0.175	0.194
put	repetitive responses	1.696	0.214	0.105

Appendix Table 6 Model Results for DTBZ and Decision-Making

ROI	Decision-Making	edf	Kendall Tau	FDR q
caud	model based	1.000	-0.147	0.854
caud	repetitive responses	1.000	-0.206	0.707
nacc	model based	1.000	-0.029	0.964
nacc	repetitive responses	1.000	0.206	0.531
striatum	model based	1.000	-0.074	0.707
striatum	repetitive responses	5.002	0.044	0.551
pall	model based	1.000	0.083	0.964
pall	repetitive responses	5.192	0.217	0.707
put	model based	1.000	-0.059	0.707
put	repetitive responses	3.628	0.147	0.531

Appendix Table 7 Model Results for RAC and Decision-Making

ROI	Decision-Making	edf	Kendall Tau	FDR q
caud	model based	2.241	-0.034	0.296
caud	repetitive responses	2.129	-0.048	0.521
nacc	model based	1.120	-0.202	0.296
nacc	repetitive responses	1.221	0.020	0.870
striatum	model based	3.016	-0.154	0.365
striatum	repetitive responses	1.000	-0.071	0.576
pall	model based	2.795	-0.007	0.576
pall	repetitive responses	4.316	0.255	0.296
put	model based	1.000	-0.099	0.576
put	repetitive responses	4.539	-0.071	0.576

Appendix I Model Results for Links between Striatal DA and Frontostriatal Connectivity

Appendix Table 8 Model Results for taT2* and Frontostriatal Connectivity

Connection	edf	Kendall Tau	FDR q
dlpfc_put	1.000	0.028	0.743
nacc_put	1.000	0.087	0.043
caud_put	1.000	0.027	0.352
pall_put	1.000	0.101	0.043
put_vmpfc	1.000	-0.009	0.743
put_sma	1.000	0.036	0.743
caud_dlpfc	1.000	0.022	0.743
caud_nacc	1.000	0.109	0.018
caud_pall	1.000	0.064	0.139
caud_vmpfc	1.000	-0.039	0.743
caud_sma	1.000	0.004	0.824
dlpfc_nacc	1.000	-0.021	0.764
nacc_pall	1.000	0.064	0.043
nacc_vmpfc	1.000	0.120	0.043
nacc_sma	1.000	0.016	0.352
dlpfc_pall	1.000	0.068	0.214
pall_vmpfc	1.000	-0.001	0.987
pall_sma	1.000	0.077	0.069
dlpfc_vmpfc	1.000	-0.006	0.743
dlpfc_sma	1.000	0.061	0.377
sma_vmpfc	1.000	0.024	0.428

Appendix Table 9 Model Results for DTBZ and Frontostriatal Connectivity

Connection	edf	Kendall Tau	FDR q
dlpfc_put	1.000	0.015	0.805
nacc_put	1.000	-0.030	0.805
caud_put	1.000	0.056	0.788
pall_put	1.000	0.028	0.788
put_vmpfc	1.000	0.022	0.805
put_sma	1.000	-0.006	0.805
caud_dlpfc	1.000	0.016	0.970
caud_nacc	1.000	-0.024	0.970
caud_pall	1.000	0.062	0.788
caud_vmpfc	1.000	0.027	0.805
caud_sma	1.000	-0.090	0.632
dlpfc_nacc	1.000	-0.036	0.788
nacc_pall	1.000	0.046	0.788
nacc_vmpfc	1.000	-0.157	0.404
nacc_sma	1.000	-0.001	0.805
dlpfc_pall	1.000	-0.042	0.805
pall_vmpfc	1.000	0.086	0.788
pall_sma	1.000	-0.020	0.788
dlpfc_vmpfc	1.000	0.163	0.128
dlpfc_sma	1.000	0.033	0.805
sma_vmpfc	1.000	0.070	0.788

Appendix Table 10 Model Results for RAC and Frontostriatal Connectivity

Connection	edf	Kendall Tau	FDR q
dlpfc_put	1.000	-0.074	0.484
nacc_put	1.000	-0.035	0.764
caud_put	1.000	-0.103	0.545
pall_put	1.000	0.041	0.931
put_vmpfc	1.000	-0.099	0.447
put_sma	1.000	-0.024	0.581
caud_dlpfc	1.000	-0.065	0.545
caud_nacc	1.000	-0.032	0.764
caud_pall	1.000	-0.009	0.931
caud_vmpfc	1.000	-0.083	0.447
caud_sma	1.000	0.022	0.764
dlpfc_nacc	1.000	0.004	0.764
nacc_pall	1.000	0.018	0.993
nacc_vmpfc	1.000	0.057	0.931
nacc_sma	1.000	-0.017	0.764
dlpfc_pall	1.000	-0.014	0.764
pall_vmpfc	1.000	-0.025	0.764
pall_sma	1.000	-0.053	0.447
dlpfc_vmpfc	1.000	0.054	0.598
dlpfc_sma	1.000	0.024	0.764
sma_vmpfc	1.000	0.077	0.675

Bibliography

Achenbach, T. M. (2017). Achenbach system of empirically based assessment (ASEBA). *Encyclopedia of Clinical Neuropsychology*, 1–7.

Acosta-Cabronero, J., Betts, M. J., Cardenas-Blanco, A., Yang, S., & Nestor, P. J. (2016). In vivo MRI mapping of brain iron deposition across the adult lifespan. *Journal of Neuroscience*, *36*(2), 364–374.

Adriani, W., Boyer, F., Gioiosa, L., Macri, S., Dreyer, J.-L., & Laviola, G. (2009). Increased impulsive behavior and risk proneness following lentivirus-mediated dopamine transporter over-expression in rats' nucleus accumbens. *Neuroscience*, *159*(1), 47–58.

Andersen, S. L., Rutstein, M., Benzo, J. M., Hostetter, J. C., & Teicher, M. H. (1997). Sex differences in dopamine receptor overproduction and elimination. *Neuroreport*, *8*(6), 1495–1497.

Balleine, B. W., & O'doherty, J. P. (2010). Human and rodent homologies in action control: Corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology*, *35*(1), 48–69.

Baumrind, D. (1987). A developmental perspective on adolescent risk taking in contemporary America. *New Directions for Child and Adolescent Development*, *1987*(37), 93–125.

Berridge, K. C., & Robinson, T. E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*, *71*(8), 670.

Bjorklund, D. F., & Harnishfeger, K. K. (1995). The evolution of inhibition mechanisms and their role in human cognition and behavior. In *Interference and inhibition in cognition* (pp. 141–173). Elsevier.

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., Baldwin, R. M., Schwartzman, A. N., Shelby, E. S., & Smith, C. E. (2010). Dopaminergic network differences in human impulsivity. *Science*, *329*(5991), 532–532.

Calabro, F. J., Montez, D., Larsen, B., Laymon, C., Foran, W., Hallquist, M., Price, J., & Luna, B. (2020). Striatal dopamine supports reward reactivity and learning: A simultaneous PET/fMRI study. *BioRxiv*.

Carlson, S. R., Pritchard, A. A., & Dominelli, R. M. (2013). Externalizing behavior, the UPPS-P impulsive behavior scale and reward and punishment sensitivity. *Personality and Individual Differences*, *54*(2), 202–207.

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*, *1124*(1), 111–126.

Christakou, A., Brammer, M., & Rubia, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *Neuroimage*, *54*(2), 1344–1354.

Claus, E. D., & Hutchison, K. E. (2012). Neural mechanisms of risk taking and relationships with hazardous drinking. *Alcoholism: Clinical and Experimental Research*, *36*(6), 932–940.

Collado, A., Felton, J. W., MacPherson, L., & Lejuez, C. W. (2014). Longitudinal trajectories of sensation seeking, risk taking propensity, and impulsivity across early to middle adolescence. *Addictive Behaviors*, *39*(11), 1580–1588.

Cools, R. (2008). Role of dopamine in the motivational and cognitive control of behavior. *Neuroscientist.*, *14*(4), 381–395.

Cools, Roshan, & D'Esposito, M. (2011). Inverted-U–shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, *69*(12), e113–e125.

Creswell, K. G., Wright, A. G., Flory, J. D., Skrzynski, C. J., & Manuck, S. B. (2018). Multidimensional assessment of impulsivity-related measures in relation to externalizing behaviors. *Psychological Medicine*, 1–13.

Crone, E. A., & Dahl, R. E. (2012a). Understanding adolescence as a period of social–affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*(9), 636.

Crone, E. A., & Dahl, R. E. (2012b). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*(9), 636–650. https://doi.org/10.1038/Nrn3313

Cyders, M. A. (2013). Impulsivity and the sexes: Measurement and structural invariance of the UPPS-P Impulsive Behavior Scale. *Assessment*, *20*(1), 86–97.

Dalley, J. W., Everitt, B. J., & Robbins, T. W. (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron*, *69*(4), 680–694.

Dalley, J. W., & Roiser, J. P. (2012). Dopamine, serotonin and impulsivity. *Neuroscience*, *215*, 42–58.

Davidow, J. Y., Foerde, K., Galván, A., & Shohamy, D. (2016). An upside to reward sensitivity: The hippocampus supports enhanced reinforcement learning in adolescence. *Neuron*, *92*(1), 93–99.

de Haan, L., Kuipers, E., Kuerten, Y., van Laar, M., Olivier, B., & Verster, J. C. (2011). The RT-18: A new screening tool to assess young adult risk-taking behavior. *International Journal of General Medicine*, *4*, 575.

Decker, J. H., Otto, A. R., Daw, N. D., & Hartley, C. A. (2016). From creatures of habit to goal-directed learners: Tracking the developmental emergence of model-based reinforcement learning. *Psychological Science*, *27*(6), 848–858.

Deckman, T., & DeWall, C. N. (2011). Negative urgency and risky sexual behaviors: A clarification of the relationship between impulsivity and risky sexual behavior. *Personality and Individual Differences*, *51*(5), 674–678.

Demos, J., & Demos, V. (1969). Adolescence in historical perspective. *Journal of Marriage and the Family*, 632–638.

Deserno, L., Huys, Q. J., Boehme, R., Buchert, R., Heinze, H.-J., Grace, A. A., Dolan, R. J., Heinz, A., & Schlagenhauf, F. (2015). Ventral striatal dopamine reflects behavioral and neural signatures of model-based control during sequential decision making. *Proceedings of the National Academy of Sciences*, *112*(5), 1595–1600.

Duell, N., Steinberg, L., Icenogle, G., Chein, J., Chaudhary, N., Di Giunta, L., Dodge, K. A., Fanti, K. A., Lansford, J. E., & Oburu, P. (2018). Age patterns in risk taking across the world. *Journal of Youth and Adolescence*, *47*(5), 1052–1072.

Elliott, R. W. (2004). *Reynolds Intellectual Assessment Scales.* Citeseer.

Ernst, M., & Paulus, M. P. (2005). Neurobiology of decision making: A selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*, *58*(8), 597–604.

Evans, A. H., Strafella, A. P., Weintraub, D., & Stacy, M. (2009). Impulsive and compulsive behaviors in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *24*(11), 1561–1570.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: From actions to habits to compulsion. *Nature Neuroscience*, *8*(11), 1481.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191.

Fortin, J.-P., Cullen, N., Sheline, Y. I., Taylor, W. D., Aselcioglu, I., Cook, P. A., Adams, P., Cooper, C., Fava, M., & McGrath, P. J. (2018). Harmonization of cortical thickness measurements across scanners and sites. *Neuroimage*, *167*, 104–120.

Freels, T. G., Gabriel, D. B., Lester, D. B., & Simon, N. W. (2020). Risky decision-making predicts dopamine release dynamics in nucleus accumbens shell. *Neuropsychopharmacology*, *45*(2), 266–275.

Friston, K., Schwartenbeck, P., FitzGerald, T., Moutoussis, M., Behrens, T., & Dolan, R. J. (2014). The anatomy of choice: Dopamine and decision-making. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1655), 20130481.

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*, *26*(25), 6885–6892.

Galvan, A., Hare, T., Voss, H., Glover, G., & Casey, B. J. (2007). Risk-taking and the adolescent brain: Who is at risk? *Developmental Science*, *10*(2), F8–F14.

Geier, C F, Terwilliger, R., Teslovich, T., Velanova, K., & Luna, B. (2010). Immaturities in Reward Processing and Its Influence on Inhibitory Control in Adolescence. *Cerebral Cortex*, *20*(7), 1613–1629.

Geier, Charles F., Garver, K., Terwilliger, R., & Luna, B. (2009). Development of Working Memory Maintenance. *Journal of Neurophysiology*, *101*(1), 84–99. https://doi.org/10.1152/jn.90562.2008

Gelbard, H. A., Teicher, M. H., Faedda, G., & Baldessarini, R. J. (1989). Postnatal development of dopamine D1 and D2 receptor sites in rat striatum. *Brain Research. Developmental Brain Research*, *49*(1), 123–130.

Gerbing, D. W., Ahadi, S. A., & Patton, J. H. (1987). Toward a conceptualization of impulsivity: Components across the behavioral and self-report domains. *Multivariate Behavioral Research*, *22*(3), 357–379.

Gillan, C. M., Kosinski, M., Whelan, R., Phelps, E. A., & Daw, N. D. (2016). Characterizing a psychiatric symptom dimension related to deficits in goal-directed control. *Elife*, *5*, e11305.

Green, P., & MacLeod, C. J. (2016). SIMR: An R package for power analysis of generalized linear mixed models by simulation. *Methods in Ecology and Evolution*, *7*(4), 493–498.

Guyer, A. E., Monk, C. S., McClure-Tone, E. B., Nelson, E. E., Roberson-Nay, R., Adler, A. D., Fromm, S. J., Leibenluft, E., Pine, D. S., & Ernst, M. (2008). A developmental examination of amygdala response to facial expressions. *Journal of Cognitive Neuroscience*, *20*(9), 1565–1582. https://doi.org/10.1162/jocn.2008.20114

Haber, S. N. (2016). Corticostriatal circuitry. *Dialogues in Clinical Neuroscience*, *18*(1), 7.

Hallquist, M. N., Hwang, K., & Luna, B. (2013). The nuisance of nuisance regression: Spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity. *Neuroimage*, *82*, 208–225.

Harden, K. P., & Tucker-Drob, E. M. (2011). Individual differences in the development of sensation seeking and impulsivity during adolescence: Further evidence for a dual systems model. *Developmental Psychology*, *47*(3), 739.

Hartley, C. A., & Somerville, L. H. (2015). The neuroscience of adolescent decision-making. *Current Opinion in Behavioral Sciences*, *5*, 108–115.

Hedge, C., Powell, G., & Sumner, P. (2018). The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behavior Research Methods*, *50*(3), 1166–1186.

Horvath, P., & Zuckerman, M. (1993). Sensation seeking, risk appraisal, and risky behavior. *Personality and Individual Differences*, *14*(1), 41–52.

Huntenburg, J. M., Bazin, P.-L., Goulas, A., Tardif, C. L., Villringer, A., & Margulies, D. S. (2017). A systematic relationship between functional connectivity and intracortical myelin in the human cerebral cortex. *Cerebral Cortex*, *27*(2), 981–997.

Ichise, M., Ballinger, J. R., Golan, H., Vines, D., Luong, A., Tsai, S., & Kung, H. F. (1996). Noninvasive quantification of dopamine D2 receptors with iodine-123-IBF SPECT. *Journal of Nuclear Medicine*, *37*(3), 513–520.

Ichise, M., Liow, J.-S., Lu, J.-Q., Takano, A., Model, K., Toyama, H., Suhara, T., Suzuki, K., Innis, R. B., & Carson, R. E. (2003). Linearized reference tissue parametric imaging methods: Application to [11C] DASB positron emission tomography studies of the serotonin transporter in human brain. *Journal of Cerebral Blood Flow & Metabolism*, *23*(9), 1096–1112.

Jupp, B., & Dalley, J. W. (2014). Convergent pharmacological mechanisms in impulsivity and addiction: Insights from rodent models. *British Journal of Pharmacology*, *171*(20), 4729–4766.

Kalivas, P. W. (2009). The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience*, *10*(8), 561–572.

Kelly, C., de Zubicaray, G., Di Martino, A., Copland, D. A., Reiss, P. T., Klein, D. F., Castellanos, F. X., Milham, M. P., & McMahon, K. (2009). L-dopa modulates functional connectivity in striatal cognitive and motor networks: A double-blind placebo-controlled study. *Journal of Neuroscience*, *29*(22), 7364–7378.

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood. *Journal of Cognitive Neuroscience*, *14*(1), 1–10. https://doi.org/10.1162/089892902317205276

Knoch, D., Gianotti, L. R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. *Journal of Neuroscience*, *26*(24), 6469–6472.

Lane, S. D., Cherek, D. R., Rhoades, H. M., Pietras, C. J., & Tcheremissine, O. V. (2003). Relationships among laboratory and psychometric measures of impulsivity: Implications in substance abuse and dependence. *Addictive Disorders & Their Treatment*, *2*(2), 33–40.

Langkammer, C., Schweser, F., Krebs, N., Deistung, A., Goessler, W., Scheurer, E., Sommer, K., Reishofer, G., Yen, K., & Fazekas, F. (2012). Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study. *Neuroimage*, *62*(3), 1593–1599.

Larsen, B., & Luna, B. (2015). In vivo evidence of neurophysiological maturation of the human adolescent striatum. *Developmental Cognitive Neuroscience*, *12*, 74–85.

Larsen, B., & Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neuroscience & Biobehavioral Reviews*.

Larsen, B., Olafsson, V., Calabro, F., Laymon, C., Tervo-Clemmens, B., Campbell, E., Minhas, D., Montez, D., Price, J., & Luna, B. (2020). Maturation of the human striatal dopamine system revealed by PET and quantitative MRI. *Nature Communications*, *11*(1), 1–10.

Lauriola, M., Panno, A., Levin, I. P., & Lejuez, C. W. (2014). Individual differences in risky decision making: A meta-analysis of sensation seeking and impulsivity with the balloon analogue risk task. *Journal of Behavioral Decision Making*, *27*(1), 20–36.

Laviola, G., Macrì, S., Morley-Fletcher, S., & Adriani, W. (2003). Risk-taking behavior in adolescent mice: Psychobiological determinants and early epigenetic influence. *Neuroscience & Biobehavioral Reviews*, *27*(1–2), 19–31.

Lejuez, C. W., Aklin, W. M., Jones, H. A., Richards, J. B., Strong, D. R., Kahler, C. W., & Read, J. P. (2003). The balloon analogue risk task (BART) differentiates smokers and nonsmokers. *Experimental and Clinical Psychopharmacology*, *11*(1), 26.

Lejuez, Carl W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., Strong, D. R., & Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied*, *8*(2), 75.

Lewis, D. A. (1997). Development of the Prefrontal Cortex during Adolescence: Insights into Vulnerable Neural Circuits in Schizophrenia. *Neuropsychopharmacology*, *16*(6), 385–398. https://doi.org/10.1016/S0893-133X(96)00277-1

Littlefield, A. K., Stevens, A. K., Ellingson, J. M., King, K. M., & Jackson, K. M. (2016). Changes in negative urgency, positive urgency, and sensation seeking across adolescence. *Personality and Individual Differences*, *90*, 332–337.

Luciana, M., & Collins, P. F. (2012). Incentive motivation, cognitive control, and the adolescent brain: Is it time for a paradigm shift? *Child Development Perspectives*, *6*(4), 392–399.

Luciana, M., Conklin, H. M., Hooper, C. J., & Yarger, R. S. (2005). The development of nonverbal working memory and executive control processes in adolescents. *Child Development*, *76*(3), 697–712. https://doi.org/10.1111/j.1467-8624.2005.00872.x

Luman, M., Tripp, G., & Scheres, A. (2010). Identifying the neurobiology of altered reinforcement sensitivity in ADHD: A review and research agenda. *Neuroscience & Biobehavioral Reviews*, *34*(5), 744–754.

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Development*, *75*(5), 1357–1372.

Luna, B., Marek, S., Larsen, B., Tervo-Clemmens, B., & Chahal, R. (2015). An integrative model of the maturation of cognitive control. *Annual Review of Neuroscience*, *38*(1), 151–170. https://doi.org/10.1146/annurev-neuro-071714-034054

Luna, B., Tervo-Clemmens, B., & Calabro, F. J. (2020). Considerations When Characterizing Adolescent Neurocognitive Development. *Biological Psychiatry*.

Luna, B., & Wright, C. (2016). *Adolescent brain development: Implications for the juvenile criminal justice system.*

Marek, S., Hwang, K., Foran, W., Hallquist, M. N., & Luna, B. (2015). The contribution of network organization and integration to the development of cognitive control. *PLoS Biology*, *13*(12), e1002328.

McFarland, K., Lapish, C. C., & Kalivas, P. W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *Journal of Neuroscience*, *23*(8), 3531–3537.

Mitchell, M. R., Weiss, V. G., Beas, B. S., Morgan, D., Bizon, J. L., & Setlow, B. (2014). Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. *Neuropsychopharmacology*, *39*(4), 955.

Montez, D. F., Calabro, F. J., & Luna, B. (2017). The expression of established cognitive brain states stabilizes with working memory development. *Elife*, *6*, e25606.

Noble, S., Scheinost, D., & Constable, R. T. (2019). A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *Neuroimage*, *203*, 116157.

O'doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, *304*(5669), 452–454.

Ordaz, S. J., Foran, W., Velanova, K., & Luna, B. (2013). Longitudinal growth curves of brain function underlying inhibitory control through adolescence. *The Journal of Neuroscience*, *33*(46), 18109–18124. https://doi.org/10.1523/JNEUROSCI.1741-13.2013

Ortega, R., Cloetens, P., Devès, G., Carmona, A., & Bohic, S. (2007). Iron storage within dopamine neurovesicles revealed by chemical nano-imaging. *PloS One*, *2*(9), e925.

Otto, A. R., Raio, C. M., Chiang, A., Phelps, E. A., & Daw, N. D. (2013). Working-memory capacity protects model-based learning from stress. *Proceedings of the National Academy of Sciences*, *110*(52), 20941–20946.

Padmanabhan, A., Geier, C. F., Ordaz, S. J., Teslovich, T., & Luna, B. (2011). Developmental changes in brain function underlying the influence of reward processing on inhibitory control. *Developmental Cognitive Neuroscience*, *1*(4), 517–529. https://doi.org/10.1016/j.dcn.2011.06.004

Palm, S., Momeni, S., Lundberg, S., Nylander, I., & Roman, E. (2014). Risk-assessment and risk-taking behavior predict potassium-and amphetamine-induced dopamine response in the dorsal striatum of rats. *Frontiers in Behavioral Neuroscience*, *8*, 236.

Patel, A. X., Kundu, P., Rubinov, M., Jones, P. S., Vértes, P. E., Ersche, K. D., Suckling, J., & Bullmore, E. T. (2014). A wavelet method for modeling and despiking motion artifacts from resting-state fMRI time series. *Neuroimage*, *95*, 287–304.

Pedersen, S. L., King, K. M., Louie, K. A., Fournier, J. C., & Molina, B. S. (2019). Momentary fluctuations in impulsivity domains: Associations with a history of childhood ADHD, heavy alcohol use, and alcohol problems. *Drug and Alcohol Dependence*, *205*, 107683.

Peterson, E. T., Kwon, D., Luna, B., Larsen, B., Prouty, D., De Bellis, M. D., Voyvodic, J., Liu, C., Li, W., & Pohl, K. M. (2019). Distribution of brain iron accrual in adolescence: Evidence from cross-sectional and longitudinal analysis. *Human Brain Mapping*, *40*(5), 1480–1495.

Poldrack, R. A., Baker, C. I., Durnez, J., Gorgolewski, K. J., Matthews, P. M., Munafò, M. R., Nichols, T. E., Poline, J.-B., Vul, E., & Yarkoni, T. (2017). Scanning the horizon: Towards transparent and reproducible neuroimaging research. *Nature Reviews Neuroscience*, *18*(2), 115.

Qu, Y., Galvan, A., Fuligni, A. J., Lieberman, M. D., & Telzer, E. H. (2015). Longitudinal changes in prefrontal cortex activation underlie declines in adolescent risk taking. *Journal of Neuroscience*, *35*(32), 11308–11314.

Quach, A., Tervo-Clemmens, B., Foran, W., Calabro, F. J., Chung, T., Clark, D. B., & Luna, B. (2020). Adolescent development of inhibitory control and substance use vulnerability: A longitudinal neuroimaging study. *Developmental Cognitive Neuroscience*, *42*, 100771.

Radua, J., Vieta, E., Shinohara, R., Kochunov, P., Quidé, Y., Green, M., Weickert, C., Weickert, T., Bruggemann, J., & Kircher, T. (2020). Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. *NeuroImage*, 116956.

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). *Neuroimage*, *42*(2), 902–910.

Raznahan, A., Shaw, P. W., Lerch, J. P., Clasen, L. S., Greenstein, D., Berman, R., Pipitone, J., Chakravarty, M. M., & Giedd, J. N. (2014). Longitudinal four-dimensional mapping of subcortical anatomy in human development. *Proceedings of the National Academy of Sciences*, *111*(4), 1592–1597.

Resnick, M. D., Bearman, P. S., Blum, R. W., Bauman, K. E., Harris, K. M., Jones, J., Tabor, J., Beuhring, T., Sieving, R. E., & Shew, M. (1997). Protecting adolescents from harm: Findings from the National Longitudinal Study on Adolescent Health. *Jama*, *278*(10), 823–832.

Rode, A. N., Moghaddam, B., & Morrison, S. E. (2020). Increased goal tracking in adolescent rats is goal-directed and not habit-like. *Frontiers in Behavioral Neuroscience, 13*, 291.

Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., Yang, W., & Hurt, H. (2011). Does adolescent risk taking imply weak executive function? A prospective study of relations between working memory performance, impulsivity, and risk taking in early adolescence. *Developmental Science*, *14*(5), 1119–1133.

Romer, D., & Hennessy, M. (2007). A biosocial-affect model of adolescent sensation seeking: The role of affect evaluation and peer-group influence in adolescent drug use. *Prevention Science, 8*(2), 89.

Romer, D., Reyna, V. F., & Satterthwaite, T. D. (2017). Beyond stereotypes of adolescent risk taking: Placing the adolescent brain in developmental context. *Developmental Cognitive Neuroscience, 27*, 19–34.

Rubia, K., Smith, A. B., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., & Brammer, M. (2006). Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Hum Brain Mapp*, *27*(12), 973–993.

Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., & Patton, G. C. (2018). The age of adolescence. *The Lancet Child & Adolescent Health*, *2*(3), 223–228.

Schonberg, T., Fox, C. R., Mumford, J. A., Congdon, E., Trepel, C., & Poldrack, R. A. (2012). Decreasing ventromedial prefrontal cortex activity during sequential risk-taking: An fMRI investigation of the balloon analog risk task. *Frontiers in Neuroscience, 6*, 80.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*(1), 1–27.

Schultz, W. (2002). Getting Formal with Dopamine and Reward. *Neuron*, *36*(2), 241–263. https://doi.org/10.1016/S0896-6273(02)00967-4

Self, D. W., Barnhart, W. J., Lehman, D. A., & Nestler, E. J. (1996). Opposite modulation of cocaine-seeking behavior by D1-and D2-like dopamine receptor agonists. *Science*, *271*(5255), 1586–1589.

Serlin, H., & Torregrossa, M. M. (2015). Adolescent rats are resistant to forming ethanol seeking habits. *Developmental Cognitive Neuroscience*, *16*, 183–190.

Sharma, L., Markon, K. E., & Clark, L. A. (2014). Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. *Psychological Bulletin*, *140*(2), 374.

Shulman, E. P., Smith, A. R., Silva, K., Icenogle, G., Duell, N., Chein, J., & Steinberg, L. (2016). The dual systems model: Review, reappraisal, and reaffirmation. *Developmental Cognitive Neuroscience*, *17*, 103–117.

Simmonds, D. J., Hallquist, M. N., & Luna, B. (2017). Protracted development of executive and mnemonic brain systems underlying working memory in adolescence: A longitudinal fMRI study. *Neuroimage*, *157*, 695–704.

Smith, G. T., & Cyders, M. A. (2016). Integrating affect and impulsivity: The role of positive and negative urgency in substance use risk. *Drug and Alcohol Dependence*, *163*, S3–S12.

Smith, S. M., & Brady, J. M. (1997). SUSAN—a new approach to low level image processing. *International Journal of Computer Vision*, *23*(1), 45–78.

Smith, S. M., Nichols, T. E., Vidaurre, D., Winkler, A. M., Behrens, T. E., Glasser, M. F., Ugurbil, K., Barch, D. M., Van Essen, D. C., & Miller, K. L. (2015). A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nature Neuroscience*, *18*(11), 1565–1567.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, *24*(4), 417–463.

Spear, Linda P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews*, *24*(4), 417–463.

Spearman, C. (1904). The proof and measurement of association between two things. *American Journal of Psychology*, *15*(1), 72–101.

Stamates, A. L., & Lau-Barraco, C. (2017). Impulsivity and risk-taking as predictors of alcohol use patterns and alcohol related-problems. *Addiction Research & Theory, 25*(5), 390–396.

Stark, A. J., & Claassen, D. O. (2017). Positron emission tomography in Parkinson's disease: Insights into impulsivity. *International Review of Psychiatry*, *29*(6), 618–627.

Steinberg, L. (2004). Risk taking in adolescence: What changes, and why? *Adolescent Brain Development: Vulnerabilities and Opportunities, Sep, 2003, New York, NY, US; This Paper Is the Result of the Aforementioned Conference Which Was Cosponsored by the New York Academy of Sciences and the University of Pittsburgh School of Medicine, Center for Continuing Education.*

Steinberg, L. (2010). A dual systems model of adolescent risk-taking. *Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology*, *52*(3), 216–224.

Stevens, A. K., Blanchard, B. E., Talley, A. E., Brown, J. L., Halvorson, M. A., Janssen, T., King, K. M., & Littlefield, A. K. (2020). State-level impulsivity, affect, and alcohol: A psychometric evaluation of the momentary impulsivity scale across two intensive longitudinal samples. *Journal of Research in Personality*, *85*, 103914.

Stopper, C. M., Maric, T. L., Montes, D. R., Wiedman, C. R., & Floresco, S. B. (2014). Overriding phasic dopamine signals redirects action selection during risk/reward decision making. *Neuron*, *84*(1), 177–189.

Tan, X., Shiyko, M. P., Li, R., Li, Y., & Dierker, L. (2012). A time-varying effect model for intensive longitudinal data. *Psychological Methods*, *17*(1), 61.

Tarazi, F. I., Tomasini, E. C., & Baldessarini, R. J. (1998). Postnatal development of dopamine D4-like receptors in rat forebrain regions: Comparison with D2-like receptors. *Developmental Brain Research*, *110*(2), 227–233.

Teicher, M. H., Andersen, S. L., & Hostetter Jr, J. C. (1995). Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. *Developmental Brain Research*, *89*(2), 167–172.

Tervo-Clemmens, B., Quach, A., Calabro, F. J., Foran, W., & Luna, B. (2020). Meta-analysis and review of functional neuroimaging differences underlying adolescent vulnerability to substance use. *NeuroImage*, *209*, 116476.

Tervo-Clemmens, B., Quach, A., Luna, B., Foran, W., Chung, T., De Bellis, M. D., & Clark, D. B. (2017). Neural correlates of rewarded response inhibition in youth at risk for problematic alcohol use. *Frontiers in Behavioral Neuroscience*, *11*, 205.

Tervo-Clemmens, B., Simmonds, D., Calabro, F. J., Day, N. L., Richardson, G. A., & Luna, B. (2018). Adolescent cannabis use and brain systems supporting adult working memory encoding, maintenance, and retrieval. *NeuroImage*, *169*, 496–509. https://doi.org/10.1016/j.neuroimage.2017.12.041

Tervo-Clemmens, B., Simmonds, D., Calabro, F. J., Montez, D. F., Lekht, J. A., Day, N. L., Richardson, G. A., & Luna, B. (2018). Early cannabis use and neurocognitive risk: A prospective functional neuroimaging study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(8), 713–725.

Todorich, B., Pasquini, J. M., Garcia, C. I., Paez, P. M., & Connor, J. R. (2009). Oligodendrocytes and myelination: The role of iron. *Glia*, *57*(5), 467–478.

Tomko, R. L., Solhan, M. B., Carpenter, R. W., Brown, W. C., Jahng, S., Wood, P. K., & Trull, T. J. (2014). Measuring impulsivity in daily life: The momentary impulsivity scale. *Psychological Assessment*, *26*(2), 339.

Towner, T. T., Fager, M., & Spear, L. P. (2020). Adolescent but not adult Sprague-Dawley rats display goal-directed responding after reward devaluation. *Developmental Psychobiology*, *62*(3), 368–379.

Van Den Bos, W., Rodriguez, C. A., Schweitzer, J. B., & McClure, S. M. (2015). Adolescent impatience decreases with increased frontostriatal connectivity. *Proceedings of the National Academy of Sciences*, *112*(29), E3765–E3774.

van Duijvenvoorde, A. C., Peters, S., Braams, B. R., & Crone, E. A. (2016). What motivates adolescents? Neural responses to rewards and their influence on adolescents' risk taking, learning, and cognitive control. *Neuroscience & Biobehavioral Reviews*, *70*, 135–147.

van Leijenhorst, L., Crone, E. A., & Bunge, S. A. (2006). Neural correlates of developmental differences in risk estimation and feedback processing. *Neuropsychologia*, *44*(11), 2158–2170.

Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Gatley, S. J., Hitzemann, R., Chen, A. D., Dewey, S. L., & Pappas, N. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature*, *386*(6627), 830.

Volkow, Nora D., Fowler, J. S., Wang, G.-J., Swanson, J. M., & Telang, F. (2007). Dopamine in drug abuse and addiction: Results of imaging studies and treatment implications. *Archives of Neurology*, *64*(11), 1575–1579.

Volkow, Nora D., Wang, G.-J., Fowler, J. S., Logan, J., Schlyer, D., Hitzemann, R., Lieberman, J., Angrist, B., Pappas, N., & MacGregor, R. (1994). Imaging endogenous dopamine competition with [11C] raclopride in the human brain. *Synapse*, *16*(4), 255–262.

Volkow, Nora D., & Wise, R. A. (2005). How can drug addiction help us understand obesity? *Nature Neuroscience*, *8*(5), 555–560.

Wahlstrom, D., White, T., & Luciana, M. (2010). Neurobehavioral evidence for changes in dopamine system activity during adolescence. *Neuroscience & Biobehavioral Reviews*, *34*(5), 631–648.

Weafer, J., Baggott, M. J., & de Wit, H. (2013). Test–retest reliability of behavioral measures of impulsive choice, impulsive action, and inattention. *Experimental and Clinical Psychopharmacology*, *21*(6), 475.

White, T. L., Lejuez, C. W., & de Wit, H. (2008). Test-retest characteristics of the Balloon Analogue Risk Task (BART). *Experimental and Clinical Psychopharmacology*, *16*(6), 565.

Whiteside, S. P., & Lynam, D. R. (2001). The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, *30*(4), 669–689.

Whiteside, S. P., & Lynam, D. R. (2003). Understanding the role of impulsivity and externalizing psychopathology in alcohol abuse: Application of the UPPS impulsive behavior scale. *Experimental and Clinical Psychopharmacology*, *11*(3), 210.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine Dl receptors in prefrontal cortex. *Nature*, *376*(6541), 572.

Wills, T. A., Vaccaro, D., & McNamara, G. (1994). Novelty seeking, risk taking, and related constructs as predictors of adolescent substance use: An application of Cloninger's theory. *Journal of Substance Abuse*, *6*(1), 1–20.

Wood, S. (2012). *mgcv: Mixed GAM Computation Vehicle with GCV/AIC/REML smoothness estimation*.

Zhou, X., Zhu, D., King, S. G., Lees, C. J., Bennett, A. J., Salinas, E., Stanford, T. R., & Constantinidis, C. (2016). Behavioral response inhibition and maturation of goal representation in prefrontal cortex after puberty. *Proceedings of the National Academy of Sciences*, *113*(12), 3353–3358.

Zucca, F. A., Segura-Aguilar, J., Ferrari, E., Muñoz, P., Paris, I., Sulzer, D., Sarna, T., Casella, L., & Zecca, L. (2017). Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Progress in Neurobiology*, *155*, 96–119.