The Promise and Challenges of Intensive Repeated Measures for Cognitive Neuroscience Models of Adolescent Substance Use

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Abstract

Developmental cognitive neuroscience models attribute the increasing engagement in substance use during adolescence to within-person changes in the functional balance between the neural systems underlying incentive processing and cognitive control. In reviewing existing evidence for these models, we find that the evidence is suggestive, with adolescents high in sensation-seeking and low in impulse control, for example, being at increased risk for substance use. However, the experimental designs and analytic techniques used to date do not lend themselves to explicit tests of how *within-person change* and *within-person variability* in incentive processing and cognitive control place *individual* adolescents at risk for substance use. For a more complete articulation of these models, we highlight the promise and challenges of using intensive repeated measures data (encompassing 5 or more within-person measurement occasions) and associated analytic techniques. Use of intensive repeated measures will lend researchers the tools required to make within-person inferences in individual adolescents that will ultimately align cognitive neuroscience models of adolescent substance use with the methodological frameworks used to test them.

Keywords: dual-system models, risk-taking, substance use, intensive repeated measures

1. Introduction

Adolescence is a period of increasing engagement in drug use (Johnston et al., 2009; Moss et al., 2014). Substance use during adolescence sets the stage for future use and abuse, with the majority of daily smokers, for example, initiating smoking during adolescence (USDHSS, 2012). Understanding the causes of substance use during this gateway to adulthood will be a crucial step in reducing the global burden of substance use disorders (Raphael, 2013). While adolescent drug use is a multi-determined behavior, developmental cognitive neuroscience models of risk-taking have increasingly been employed to provide insight into adolescent substance use (e.g., Casey & Jones, 2010; Geier, 2013; Lydon et al., 2015).

From the perspective of cognitive neuroscience models, adolescents are particularly vulnerable to drug use due to normative increases in activity in limbic and paralimbic regions involved in incentive processing (Ernst et al., 2005; Galvan et al., 2006) alongside continued immaturities in the functioning of prefrontal regions involved in cognitive control (Hwang et al., 2010; Ordaz et al., 2013). This configuration results in an imbalance of limbic relative to prefrontal control that renders adolescents more sensitive to rewarding stimuli and less likely to inhibit impulses to approach rewards relative to both children and adults (Somerville et al., 2011). Adolescents with the greatest imbalance between limbic relative to prefrontal control are thought to be particularly vulnerable to substance use during this period of normatively heightened risk (Bjork & Pardini, 2015).

Empirical evidence supports roles for incentive processing and cognitive control in adolescent substance use (for reviews see Lydon et al., 2014; van Duijvenvoorde et al.,

2016). However, by providing an overview of cognitive neuroscience models of adolescent substance use and presenting a review of the empirical evidence, we highlight a discrepancy between the within-person processes outlined by these models and the between-person methodologies used to test them. This discrepancy between models and methods is associated with a lack of empirical evidence for how within-person changes in incentive processing and cognitive control in individual adolescents are associated with changes in substance use behaviors. After outlining this discrepancy, the promise and challenges of intensive repeated measures designs and analysis techniques for testing highlighted mechanisms and, thus, aligning models and methods, is discussed.

2. Cognitive Neuroscience Models of Adolescent Risk-Taking: A Brief Overview

Increases in risk-taking during adolescence have been observed in behaviors such as drug use (Chen & Kandel, 1995; Holford et al., 2014) and reckless driving (Rhodes & Pivik, 2011; Tucker et al., 2015), and in performance on laboratory tasks designed to assess risky decision-making (Burnett et al., 2010; although see Defoe et al., 2015). The increase in risk-taking during adolescence is also conserved across species (Laviola et al., 2003; Spear, 2000). In line with these cross-species observations, cognitive neuroscience models highlight an adolescent-specific organization of brain circuitry as an evolutionary feature in attempts to provide insight into risk-taking during this period (Casey et al., 2008; Steinberg, 2008). These models have their historical roots in dual-process models of self-control (Baumeister & Heatherton, 1996; Bechara, 2005; Metcalfe & Mischel, 1999). Self-control successes and failures, from these perspectives, are dependent on the nature of the interaction between bottom-up processes – typically associated with

temptations and impulses to approach reward – and relatively slower acting top-down processes involved in the inhibition of impulses and the deliberative evaluation of potentially rewarding stimuli. Self-control failure results from excessive activation of bottom-up processes, insufficient activation of top-down process, or a combination of both (Heatherton & Wagner, 2011). Mesocorticolimbic regions and pathways (particularly the ventral striatum and the midbrain dopamine system) have been highlighted as key to bottom-up, temptation processes while top-down processes have been consistently mapped onto prefrontal regions (Knoch et al., 2006; Kuhnén & Knutson, 2005; McClure et al., 2004).

Models of adolescent risk-taking (Casey et al., 2008; Steinberg, 2008) highlight the differing timescales of the development of a bottom-up, socio-emotional system and a top-down, cognitive control system. The maturation of the socio-emotional system occurs early in adolescence and is related to the onset of puberty (Nelson et al., 2005; de Macks et al., 2011). In contrast, the cognitive control system develops gradually, is not conceived of as being tied to pubertal onset (Luna, 2009; Orr et al., 1988), and does not demonstrate adult competencies until the mid-twenties. Due to more functionally mature limbic regions as well as immature functional connectivity between subcortical and prefrontal regions, there is a combination of heightened responsiveness to rewards and limitations in behavioral control – resulting in adolescents being susceptible to seeking immediate rather than long-term rewards.

Recent iterations and alternative formulations of cognitive neuroscience models have broadened the scope of dual-system models to consider pathways to risk-taking and drug use beyond failures of self-control (e.g., Geier, 2013; Lydon et al., 2014; Romer et

al., 2017). For example, under some conditions, the decision to engage in behaviors deemed risky, especially in the case of drug use, is based on deliberation rather than on impulse and involves the recruitment of cognitive control to meet one's desired goal (Kopetz & Orehek, 2015; Rawn & Vohs, 2011). As such, engagement in drug use behaviors may not result from an inability to inhibit urges to engage in smoking or alcohol but, instead, may result from the exertion of self-control to engage in a behavior perceived as noxious in order to achieve an alternative goal (e.g., peer approval; Trucco et al., 2011).

A common evaluation across these more recent formulations is that it is overly simplistic to assume that an independent, bottom-up subcortical system biases individuals towards risk-taking, and an independent cognitive prefrontal system biases individuals away from risk-taking. Subcortical and cortical systems interact and are interdependent. Regions within the prefrontal cortex depend on subcortical regions (such as the amygdala) for input (Bechara, 2001; Floresco & Ghods-Sharifi, 2007). Inputs from subcortical regions may be suppressed or modulated under some circumstances, especially if bottom-up inputs are not aligned with current goals (Cooper et al., 2013; Siep et al., 2012). However, affective input may be elaborated on by prefrontal systems, thus reflecting interactive rather than inhibitory processes across subcortical and prefrontal systems (Frank et al., 2009). In line with this idea, one iteration of Casey and colleagues' (2008) model, has moved away from simple dichotomies for bottom-up and top-down brain systems and towards a greater consideration of interconnections within and across neural circuits that might regulate or intensify emotions, desires, and actions (Casey, 2015; Casey et al., 2016). While cognitive neuroscience models of adolescent

risk-taking have become more nuanced over time, their core maintains a key role for functions associated with the socio-emotional and cognitive control systems, as well as their interactions, in explaining adolescent risk-taking and substance use.

3. Cognitive Neuroscience Models of Adolescent Drug Use: The Empirical Evidence

Empirical evidence supporting cognitive neuroscience models of adolescent risk-taking has been the subject of numerous reviews (Bjork & Pardini, 2015; Richards, et al., 2013; Smith et al., 2013). Many of these studies have specifically argued for the value of cognitive neuroscience models for understanding substance use as a specific risk-behavior (for reviews see Geier, 2013; Gladwin et al., 2011; Lydon et al., 2014; van Duijvenvoorde et al., 2016; see also Silveri et al., 2016). Here we review findings specific to adolescent substance use.

Between-person differences in sensation-seeking and impulse control are viewed as psychological manifestations of core components of dual-system models (Shulman et al., 2016; but see Harden et al., 2017 for discussion of levels of analysis). Both sensation-seeking and impulse control are associated with cigarette smoking. Participants higher in sensation-seeking (Hwang & Park, 2015; Malmberg et al., 2010) and lower in impulse control (Lydon-Staley & Geier, 2017; Martínez-Loredo et al., 2015) are more likely to currently use drugs and to use drugs at follow-up assessments (Heinrich et al., 2016). Slower declines in sensation-seeking and impulsivity, as well as related constructs (e.g., reward sensitivity), through adolescence are associated with increased drug use during this period (Urošević et al., 2015; Quinn & Harden, 2013). These data provide evidence

for the importance of between-person differences in changes in constructs highlighted by dual-system models for understanding adolescent drug use.

Findings from functional magnetic resonance imaging (fMRI) studies also suggest a role for the relevance of processes highlighted by dual-system models in understanding adolescent drug use. Broadly, this body of work utilizes a wide variety of tasks and diverse indices of socio-emotional and cognitive control system structure and function to test the relevance of dual-system models in adolescent drug use (see van den Bos & Eppinger, 2016 for discussion). One particularly notable finding is a positive association between nucleus accumbens volume and frequency of alcohol use in a sample of juvenile justice-involved adolescents (Thayer et al., 2012). Moreover, nucleus accumbens activation in response to feedback related to winning *versus* losing monetary reward was positively associated with current, but not future, rates of alcohol consumption in a sample of adolescents and young adults (Braams et al., 2016). Both findings are consistent with a role for the socio-emotional system in adolescent drug use.

As well as being relevant for understanding concurrent substance use, neuroimaging studies have observed that between-person differences in the socio-emotional and cognitive control systems are associated with future substance use behaviors. The self-reported likelihood of engaging in risky behaviors, including drug use, in the future was associated with greater nucleus accumbens activation during anticipation of monetary reward in adolescents (Galvan et al., 2007). Smaller volumes of the left dorsal and rostral paralimbic anterior cingulate cortex, which are regions involved in a range of executive functions including impulse control, at age 12 years predicted alcohol-related problems at age 16 years (Cheetham et al., 2014; see also Squeglia et al.,

2014). Less positive connectivity between the amygdala and the orbitofrontal cortex at rest was associated with alcohol use two years later in a sample ranging in age from 8 to 25 years (Peters et al., 2017). Alcohol misuse, defined as a minimum of three lifetime binge drinking episodes, at age 16 years was associated with increased activity in the superior frontal gyrus when receiving a reward as well as greater activity in premotor cortex during inhibition failures at age 14 years relative to participants who did not go on to misuse alcohol (Whelan et al., 2014; see also Wetherill et al., 2013). Adolescents showing declines over the course of approximately 1.5 years in self-reported risk-taking, including drug use, showed greater declines in reactivity of the ventrolateral prefrontal cortex and ventral striatum during risk-taking (Qu et al., 2015).

In sum, drug use during adolescence is associated with between-person differences in traits, behaviors, and neurobiological features associated with the functioning of the socio-emotional and cognitive control systems. Between-person differences in changes in these features are associated with changes in drug use through adolescence. Thus, cognitive neuroscience models provide a useful framework for understanding adolescent drug use. However, a number of issues remain open that will benefit from the use of intensive repeated measures designs and analysis techniques.

4. A Mismatch Between Models and Methods: Intraindividual Change and Intraindividual Variability in Individual Adolescents

The designs and analytic techniques utilized to date are limited in the extent to which they can appropriately test the importance of the mechanisms proposed by dual-systems models in promoting adolescent drug use. Dual-systems research often aims to

examine *intraindividual change* and *intraindividual variability* in socio-emotional and cognitive control system functioning to understand increases and decreases in the vulnerability for risk-taking, including drug use. Intraindividual change refers to within-person change resulting from long-term processes, such as gradual brain maturation over the course of years. Intraindividual variability, in contrast, refers to within-person fluctuations occurring on relatively shorter timescales (Nesselroade, 1991; Ram & Gerstorf, 2009; see Figure 1).

[FIGURE 1 ABOUT HERE]

Describing *change* within *individuals* facilitates explicit testing of dual-system models and supports efforts to use related findings to explain and prevent adolescent risk-taking behaviors. Notice, for example, the focus on the individual in this excerpt summarizing cognitive neuroscience research on adolescence in order to inform the workings of the juvenile justice system (Steinberg, 2009, pp. 466, italics added for emphasis):

“There is...compelling neurobiological evidence for *changes* in brain structure and function during adolescence and early adulthood that facilitate improvements in self-regulation that *permit individuals to modulate their inclinations* to seek rewards...”.

It is the capacity to make inferences linking within-person change in brain structure and function to improvements in self-regulation in individuals that makes the most compelling argument for a focus on the neurobiological level of analysis.

It is also clear that describing intraindividual variability in adolescent functioning will be required to fully articulate dual-systems models of adolescent drug use. While dual-systems research has focused on the extent to which adolescents take more risks relative to children and adults, the notion of variability in risk-taking is particularly salient during adolescence. For example, adolescent risk-taking, including drug use, shows marked day-to-day variability in real-world contexts (Arbel et al., 2016). Further, laboratory tasks indicate that the proposed adolescent-specific increase in risk-taking is context-dependent. The adolescent peak in risk-taking is especially likely to be observed in the presence of peers and in emotionally-salient contexts that arouse the socio-emotional system (Chein et al., 2011; Figner et al., 2009; Gardner & Steinberg, 2005).

While much less work has examined the variability of risk-taking within rather than across particular contexts, intriguing results emerged from a study of children and adolescents between the ages of 8 and 18 years on the Balloon Analogue Risk Task (BART; McCormick & Telzer, 2017). In the BART (see Lejuez et al., 2002), participants inflate a computer-generated balloon to earn money. With each pump, money is earned and stored in a temporary bank account until participants stop pumping. At this point, the money is transferred to a permanent bank account. However, the balloon can explode at predetermined points that are unknown to participants, resulting in a loss of money that has not been transferred to the permanent bank if participants continue to pump the balloon beyond these points. Risk behavior, operationalized as the average number of pumps on non-exploded trials, was positively associated with age. Insight into risk behavior variability was obtained by computing a learning rate that indexed participants' likelihood of changing the number of times they pumped a balloon on a trial based on

whether or not the previous trial was an explosion trial. Interestingly, there was a positive association between age and learning rate indicating that adolescents were more likely than children to change their risk behavior on a trial-by-trial basis in response to previous trial feedback. Additional evidence for relatively rapid changes in behavior in adolescents relative to other developmental groups in the context of changes in reward contingencies has emerged from non-human animal studies (Johnson & Wilbrecht, 2011).

The context-specific nature of risk-taking is in line with even the earliest iterations of dual-system models. Since the early days of dual-system models (e.g., Casey et al., 2008), it has been emphasized that a decision-making style that would promote risk-taking is not a stable characteristic of adolescents. Instead, greater risk-taking was proposed to occur in situations that arouse the socio-emotional system. Relatedly, frameworks highlighting adolescence as a period of increased flexibility in behavior (Crone & Dahl, 2012; see also Li, 2017) have been drawn upon to understand the within-task variability in adolescent risk-taking (e.g., McCormick & Telzer, 2017). From these perspectives, flexibility in the engagement of cognitive control systems is a hallmark of adolescence due to a tendency to quickly shift priorities resulting from heightened responses to incentives.

The adolescent propensity to take risks in emotionally salient contexts, such as those in which substance use occurs (Delorme et al., 2003; Friedman et al., 1985), as well as the tendency to quickly shift priorities based on the social and motivational salience of a goal, are both thought to place adolescents at risk for substance use. Thus, while cognitive neuroscience models of risk-taking implicitly emphasize intraindividual variability in risk-taking and processes associated with the socio-emotional and cognitive

control systems, the extent to which that intraindividual variability is relevant for our understanding of adolescent drug use remains unclear.

5. Aligning Models and Method Using Intensive Repeated Measures

There is, then, a gulf between the inferences that the majority of studies on dual-systems models of adolescent drug use can make and the inferences investigators would often like to make in order to fully test the role of dual-systems mechanisms in drug use. These limitations have not gone unnoticed in previous work. Indeed, the limitation sections of many manuscripts call for longitudinal designs in order to allow within-person inferences. Notably, large-scale, longitudinal studies hold the promise of doing just that (e.g., the ABCD study; Bjork et al., 2017). Longitudinal designs will allow us to overcome a number of difficulties but it is suggested here that the longitudinal designs must be coupled with appropriate analytic techniques and, further, that *intensive* longitudinal designs will be necessary to provide a complete picture of the role for mechanisms posited by dual-systems models in impacting adolescent drug use.

Intensive longitudinal methods is an umbrella term that subsumes a variety of names used to describe methods that employ repeated assessment of individuals (using five or greater measurement occasions), sometimes *in situ*, using a wide array of technologies, including daily diaries and smartphones (Bolger & Laurenceau, 2013). Intensive longitudinal designs can span multiple time frames and are appropriate, indeed necessary, for the analysis of phenomena that unfold over the course of seconds (e.g., changes in the configuration of functional brain systems during cognitive control performance; Braun et al., 2015), days (e.g., day to day changes in adolescent mood and

family functioning; Fosco & Lydon-Staley, in press), weeks (e.g., improvements in cognitive abilities through training; Schmiedek et al., 2010), and years (e.g., the pubertal process; Marceau et al., 2011). Coupled with appropriate analysis techniques, intensive longitudinal designs also allow examinations of the interplay between processes across these multiple timescales (Ram et al., 2014). Below, we highlight the potential applications of intensive longitudinal designs to understand adolescent drug use by capturing both *intraindividual change* and *intraindividual variability* in adolescents while also highlighting the challenges associated with these designs and analysis techniques.

5.1. Matching Models and Method: Capturing Intraindividual Change. There are few longitudinal investigations of intraindividual change in the core components of dual-systems models and how they relate to change in adolescent drug use. The vast majority of studies have been cross-sectional, limiting what we can say about the effect of development on drug use. Further, they do not allow a test of at least two different developmental trajectories to drug use during adolescence that involve the socio-emotional and cognitive control systems (Romer, 2010). One potential trajectory involves the increased opportunities for drug use available during adolescence relative to childhood that may allow pre-existing rank-order differences in sensation-seeking, for example, to express themselves in the form of engagement in substance use. Indeed, levels of sensation-seeking during pre-adolescence predict adolescent substance use at age 15 years (Charles et al., 2017; see also Romer et al., 2009). The second, and not mutually exclusive, trajectory involves the risk conferred from a normative increase in sensation-seeking as participants enter adolescence (Harden & Tucker-Drob, 2011;

Romer et al., 2010; Steinberg et al., 2008), which raises individuals who are not particularly high in sensation-seeking to high levels of sensation-seeking relative to their typical levels.

Longitudinal data capturing pre-existing rank-order differences as well as normative growth in socio-emotional and cognitive control system functioning will be necessary to disentangle these trajectories. However, longitudinal data by itself will not be sufficient to describe the intraindividual change posited by the second trajectory unless appropriate analytic techniques are employed. Paulsen and colleagues (2015), for example, examined developmental changes in incentive-motivational circuitry longitudinally using an anti-saccade task. Youth aged 10 to 22 years were sampled two to three times over approximately 15-month intervals in an accelerated longitudinal design. Accelerated longitudinal designs greatly reduce the measurement collection time and result in the collection of data spanning age ranges required to test theories of adolescent development. However, the parameters of interest, in this case the linear and quadratic trends in incentive processing with age, represent population average rates of change (Galbraith et al., 2014). They may not describe the developmental trajectory of any single individual in the sample and with two or three time points per person, intraindividual change through adolescence is not being described.

Collection of intensive repeated measures will allow the modeling of intraindividual change and an enhanced ability to describe differences in developmental trajectories. The teasing apart of intraindividual change also requires appropriate analytic techniques. Imagine, for example, that we have collected data on both sensation-seeking and alcohol use across seven waves, and we want to know how within-person change in

sensation-seeking is associated with change in an individual's alcohol use. We might model the data using a multivariate latent growth curve (see Grimm et al., 2016) and examine the association between the slope for sensation-seeking and the slope for alcohol use. If the association between these two slopes is positive, then as sensation-seeking increases, so too does risk-taking. However, only a between-person inference is possible here. The slope parameters, despite being made up of repeated measures within individuals, are between-person descriptions of rates of change. Thus, our conclusion is that people with greater rates of change in sensation seeking have greater rates of change in risk-taking. This is not the inference we often set out to make.

To find an answer to the question of what happens to an individual's level of risk-taking when that individual's level of sensation seeking increases, we must disaggregate the between-person and within-person components of change over time as repeated measures data simultaneously contain information on between-person and within-person variation (Curran & Bauer, 2011; Raudenbush & Bryk, 2002). There are a number of ways to perform this disaggregation. Typically, time-dependent variables are calculated as deviations from person-level means (see Figure 2).

[FIGURE 2 ABOUT HERE]

Associated with this approach is the implicit assumption that these variables do not change systematically with time. However, as the time-varying variables of interest are hypothesized to exhibit meaningful change over time during adolescence – i.e., rising from childhood into adolescence before decreasing – intraindividual change in these

time-varying variables is expected and this should be addressed in our methodology. One particularly relevant approach is to deviate the time-varying variables with respect to an individual-specific regression line (Curran & Bauer, 2011). Once this disaggregation is complete, we may make inferences about intraindividual change.

5.2. Matching Models and Method: Capturing Intraindividual Variability.

Although dual-system models, through their focus on context-dependent change in risk-taking and notions of behavioral flexibility, highlight intraindividual variability as a core feature of adolescent behavior (see also Montez et al., 2017; Tamnes et al., 2012), little work has been conducted on how within-person variability in the processes highlighted by dual-system models may relate to drug use. Emerging evidence, however, suggests that variability may be important. Goldenberg and colleagues (2016), for example, observed that adolescents exhibiting greater response variability on a risk-taking task also had lower perceptions of real-world risks (including drug use).

There are a number of ways an intensive longitudinal perspective may be employed to further examine intraindividual variability in components of dual-systems models across development. The field has captured intraindividual change in core components of dual-system models over the course of years and also variability in cognitive control and socio-emotional processing on the order of seconds, minutes, and the length of task blocks (e.g., Chein et al., 2011; Medaglia et al., in press; Tamnes et al., 2012). Little is known about the extent to which processes related to the dual-systems model vary within-person across relatively short stretches of time (e.g., days).

Appreciating variability across multiple timescales is important for many reasons. By

assessing the functioning of the socio-emotional and cognitive control systems at one time point, we risk imposing a static framework onto what may be a dynamic processes. This is true even when task context is manipulated or approaches to examine dynamics during a session are employed. Only through intensive repeated measures may we assess the degree to which an individual may be thought of as a dynamic, labile, and fluctuating entity, thereby adequately capturing a component of individual functioning long-held to be essential for a thorough characterization of the developing individual (Nesselrode, 1991; see Figure 3).

[FIGURE 3 ABOUT HERE]

Fully appreciating the role of intraindividual variability in socio-emotional and cognitive control functioning as a risk for adolescent substance use will require examination of intraindividual variability at the daily and other intermediate timescales that have not yet been thoroughly investigated. Capturing many timescales will be important because different biopsychosocial antecedents may be implicated in variability observed at differing timescales. For example, in a study in which adults underwent 101 daily assessments of cognitive performance, trial-to-trial and day-to-day performance variability were unrelated to regional brain volume, while smaller prefrontal white matter volumes were associated with higher block-to-block variability (Lövdén et al., 2013). In contrast, variability at shorter timescales (e.g., day-to-day performance variability) may be related to fluctuations in stress and motivation (Brose et al., 2010; Sliwinski et al., 2006;), highlighting the heterogeneous underpinnings of intraindividual variability across

multiple timescales. Notably, in the context of adolescent substance use, processes unfolding at daily timescales that may impact the functioning of cognitive control and socio-emotional systems (e.g., sleep disturbances, family and peer relationships; Telzer et al., 2015; Telzer et al., 2014a; Telzer et al., 2013b) may be more amenable to intervention (e.g., Fosco et al., 2013; Paavonen et al., 2016) than those processes unfolding over the course of years (e.g., development of white matter tracts; Asato et al., 2010). This fact underscores the importance of increased empirical research at this timescale.

Combined with ecological momentary assessments that take place *in situ* to capture life "as it is lived" (Bolger et al., 2003; Shiffman et al., 2008), intensive repeated measures approaches can capture naturalistic changes in core functions associated with the socio-emotional and cognitive control systems. Foundational work indicating the promise of this approach for cognitive neuroscience models of adolescent drug use comes from Galván and McGlennan (2012), who employed an ecological momentary assessment approach to test the association between stress and risk-taking in adolescents. Participants' daily stress was monitored via self-report three times a day for two weeks. Participants were brought into the lab on a high stress day and a low stress day: that is, days on which self-reported stress fell above or below a specified threshold (a 1-point change on a 7-point scale) relative to a baseline level of stress, specific to each participant established during a 3-day baseline. All participants completed a laboratory task designed to assess risky decision-making. Adolescents made significantly more risky decisions under high *versus* low naturalistic stress conditions, suggesting that associations between stress and risk-taking previously observed in the laboratory following stress induction are observed in the context of naturalistic levels of stress as well. Using a similar protocol

and examining response inhibition, Rahdar & Galván (2014) observed less accurate performance in adolescents relative to adults in the high stress but not the low stress state, once more indicating greater variability in cognitive control in adolescents relative to adults but this time in the context of ecologically valid fluctuations in stress.

Another important feature relating to the capture of intraindividual variability is that it will allow important tests of within-person associations, moving from questions such as "Do people who are high in sensation-seeking engage in more drug use?" to "On days when people have greater sensation-seeking tendencies than usual, do they engage in more drug use than usual?" Critically, such an approach would allow us to align our methods to the within-person inferences that we often wish to make.

Despite interest in making within-person inferences, use of interindividual variation dominates cognitive neuroscience work on adolescent substance use. An implicit assumption of these studies is that examinations of interindividual variation can provide insight into intraindividual variation. For example, studies demonstrating that adolescents high in sensation-seeking have increased levels of drug use relative to those low in sensation-seeking suggest that manipulating levels of sensation-seeking within-person will impact drug use within-person. This assumption is invalid (see Molenaar, 2004 for mathematical treatment), with empirical studies observing different associations at interindividual and intraindividual levels of analysis (e.g., Newman et al., 2017). A classic example is that individuals who exercise more tend to drink less alcohol (interindividual association) while on days when individuals exercise more, they tend to drink more (intraindividual association; Conroy et al., 2015). Key to making within-person inferences and providing the empirical evidence motivating efforts to impact

processes highlighted by dual-systems models in efforts to prevent or reduce substance use is the capture of intraindividual variability through intensive repeated measures. Once a time series has been generated, within-person inferences can be made via the same disaggregation of between-person and within-person components of change over time discussed in the context of intraindividual change (Figure 2). This fact serves as a reminder that many of the methods involved in capturing within-person associations lend themselves to application across multiple timescales.

The use of intensive repeated measures to capture intraindividual variability, then, holds great promise for cognitive neuroscience models of adolescent substance use. A number of challenges may be anticipated. The feasibility of intensive repeated measures designs will rest on the availability of reliable measures of sensation-seeking, impulse control, and related constructs of interest for use in daily life. Tasks that have been used extensively in the laboratory (i.e., the BART task) to assess adolescent risk-taking have recently been extended to assess risk-taking *in situ* (MacLean et al., 2017). Tasks assessing functions associated with cognitive control system functioning have also been developed (Schuster et al., 2015) and have been used to assess fluctuations in performance in participants as young as 8 years of age (Dirk & Schmiedek, 2016). Furthermore, although sensation-seeking is typically measured as a trait, state scales designed to measure a person's sensation-seeking at a given point in time have dated as far back as Neary (1975; see also Zuckerman, 1979). An important first step is to establish that these measures can reliably capture within-person variability in adolescents. Methods to evaluate the sensitivity of measures to within-person variability have

emerged within the context of generalizability theory (Bolger & Laurenceau, 2013; Cranford et al., 2006).

A second challenge is the low-intensity of substance use in most adolescents. The use of *in situ*, intensive repeated measures designs to measure the occurrence of substance use at the day-to-day level in adolescents at low-risk for engaging in substance use may be excessive (but entirely appropriate for adolescents at high-risk for engagement in risk behaviors; see for example Russell et al., 2016). This intuition should be empirically verified by evaluating the speed with which substance use engagement rises and falls over different time frames in order to establish a baseline of engagement frequency (Shiyko & Ram, 2011). It may also be desirable to supplement measures of substance use with measures of risk-taking propensity (e.g., Meertens & Lion, 2008).

Even in the context of low levels of daily substance use, however, examining between-person differences in the extent of variability in socio-emotional and cognitive control system functioning during daily life as predictors of substance use behaviors over longer timescales (e.g., weeks, months, and years) will be interesting. A number of analytic options are available to quantify between-person differences in the extent of intraindividual variability. One of the most popular approaches to quantify within-person variability is to calculate the standard deviation of a distribution of scores obtained across repeated measurements within the same individual. This index is referred to as the intraindividual standard deviation, and measures the extent to which an individual's scores vary around their mean: a high score indicates a wide range of experiences and a low score indicates a narrow range of experiences. Many other options exist (see Ram & Gerstorf, 2009, p. 785 for a taxonomy of indices) and the approach taken should reflect

one's conceptual model of the process under study. This approach will provide insight into how intraindividual variability in dual-system processes act as risk-factors for adolescent substance use above and beyond trait measures of system function to determine the added value of capturing intraindividual variability (see e.g., Fosco & Lydon-Staley, in press).

With the intensive measurement protocols that come with intensive repeated measures designs, attrition is often a concern. However, intensive repeated measure designs have a long history of use in adolescent samples (Csikszentmihalyi et al., 1977) and compliance with *in situ* measurement is generally high in adolescents, even in adolescent samples for which low compliance may be expected (e.g., adolescent smokers undergoing smoking cessation; Gwaltney et al., 2008). Moreover, the emergence of passive data collection approaches (e.g., sensors integrated into watches, phones, bracelets, and other clothing; Nusser et al., 2006) will greatly reduce participant burden.

5.3. Matching Models and Method: Describing the Individual. Data from the group will only describe the functioning of any particular individual under very strict conditions (i.e., if participants comes from a homogeneous sample). The implications of this point are clear when we examine a typical study. When comparing BOLD activity in the ventral striatum across developmental groups, for example, data are generally aggregated across individuals in each group (e.g., Galvan et al., 2006). This group solution may not describe any single individual in the sample as it is a conglomerate of all the heterogeneity in each group.

The extent of heterogeneity in the functioning of cognitive control and socio-emotional systems during adolescence is beginning to be appreciated. At the behavioral level, the extent of individual differences in adolescents' sensitivity to expected risk and return during risky choice tasks are greater than those observed in adults (van Duijvenvoorde et al., 2015). Further, while increases in drug use occur during adolescence (e.g., Moss et al., 2014; USDHHS, 2012), *most* adolescents *do not* engage in drug use (Hooshmand et al., 2012; Johnston et al., 2009). At the level of psychological traits, tremendous heterogeneity in the magnitude of change in sensation-seeking and impulsivity across adolescence has been observed (Harden & Tucker-Drob, 2011). In regards to brain structure, Mills and colleagues (2014) observed the hypothesized earlier maturation of the nucleus accumbens relative to the prefrontal cortex in only 17 out of 33 participants with at least three scans in childhood through early adulthood, indicating substantial heterogeneity in the development of these structures. In terms of brain function, age typically accounts for a modest portion of the variance in ventral striatal response to rewards (Bjork et al., 2010) due to vast interindividual differences within age groups (Somerville et al., 2010).

These findings have led to the emergence of a perspective in which normative developmental changes in brain structure and function are unlikely to fully account for the changes in risky behaviors observed during adolescence (Bjork & Pardini, 2015). Instead, it is suggested that the majority of adolescents exhibit a modest imbalance between socio-emotional and cognitive control functioning and that it is a subset of individuals who exhibit an imbalance between these two systems that is sufficiently extreme to meaningfully affect risk-taking behaviors. Such findings and perspectives call

for greater consideration of between-person differences during this period of heightened engagement in risky behaviors in order to identify who may be most vulnerable to drug use and abuse during adolescence.

In order to better tailor our methods towards the inferences we would like to make and to suitably capture the heterogeneity that is a particularly salient feature of adolescence, there is a great need for an influx of person-centered research (Molenaar, 2004; Molenaar & Campbell, 2009). Intensive repeated measures lend themselves to an idiographic approach that aims to make predictions about the individual through the analysis of within-person variation over time. Recent methodological developments have leveraged the intensive repeated measures data available with fMRI to take a more person-specific approach that will allow us to have greater confidence that we are capturing individual functioning. In the domain of effective connectivity, for example, Group Iterative Multiple Model Estimation (GIMME; Gates & Molenaar, 2012) has emerged as an analysis technique capable of capturing heterogeneity in effective connectivity while still allowing broader descriptions of group structure. GIMME uses a unified structural equation modeling approach to estimate contemporaneous connectivity among regions of interest as well as sequential connectivity (Gates et al., 2010; Kim et al., 2007). GIMME leverages the automatic search procedure within LISREL to identify a group model of connectivity, one that is shared by most individuals in the sample – if one exists, by selecting paths in a data-driven manner. Once the group model has been established, deviations from the group model at the individual level are then pursued.

While GIMME allows for individual deviations from group maps to capture individual functioning, it relies on a group map due to the relatively low signal-to-noise

ratio of fMRI data (Welvaert & Rosseel, 2013). Recent innovations in intensive repeated measures data collection, whereby individuals are repeatedly assessed over timescales much longer than typical scans (e.g., 5 hours of resting state data collection), are providing opportunities to reliably characterize individuals without relying on group level data (Filevich et al., 2017; Gordon et al., 2017; Laumann et al., 2015). Collecting multiple scans within an individual is also providing the capacity to analyze intraindividual variability in brain function and its relation to fluctuations across a range of psychosocial processes (e.g., affect; Betzel et al., 2017).

Notably, while the intensive repeated measures associated with fMRI data lend themselves to person-specific models, time series approaches capable of capturing heterogeneity across persons may also be applied to behavioral data. This is routinely done (e.g., Lydon et al., 2016; Russell et al., 2016) within the context of multilevel models that accommodate the nested nature (with measurement occasions nested within participants) of repeated measures data (Snijders & Bosker, 2012). In this approach, random effects may be specified for an independent variable. Specifying a variable as random allows it to vary across participants (Snijders, 2005). This allows some degree of heterogeneity across participants to be captured. We note, however, that individual heterogeneity from this perspective is modeled as deviations or errors from the association observed in the prototypical individual in the sample. Further, the individual deviations are often assumed to follow a normal distribution, placing limits on the extent to which individual differences can be modeled (see Figure 4). An alternative approach, when sufficiently long time series are available, is to model each individual's data in a separate model and to then attempt integration at a higher level (e.g., Gatzke-Kopp et al.,

2017). While this approach allows one to emphasize heterogeneity across individuals, comparing individuals and summarizing groups based on these individual-specific models is not without difficulty. For example, when parameter estimates are taken from these individual specific models to the group level, the standard errors associated with these estimates are typically not brought with the estimates and are assumed to be zero.

[FIGURE 4 ABOUT HERE]

While multilevel modeling approaches are popular in behavioral research, unified structural equation modeling approaches utilized in fMRI studies have also been applied to behavioral data (Beltz et al., 2016; Wright et al., 2015). Notably, similar approaches have been applied at the individual level without the construction of a group model as an intermediate step, with indications that such a person-specific approach provides a good fit to the data (Fisher et al., 2017). A key challenge accompanying the use of multivariate time series approaches includes the collection of sufficient time points per individual, with multilevel models recommended when fewer than 20 time points are available per person (Beltz et al., 2016).

In sum, the extensive heterogeneity during adolescence forcefully argues for an influx of person-centered methodologies capable of capturing the functioning of individual adolescents. Major challenges associated with this approach include the collection of sufficiently dense measurement for each adolescent. However, the availability of existing analytic approaches as well as the increasingly feasible collection of dense measurements within individuals suggests great promise for the ability to

describe the functioning of socio-emotional and cognitive control systems in individual adolescents in future work.

6. Conclusions

Cognitive neuroscience models of adolescent risk-taking have the potential to provide insight into the processes underlying substance use and abuse. Use of intensive repeated measures, including ecological momentary assessment, will allow an assessment of intraindividual change and intraindividual variability in individual adolescents, bringing the field closer to understanding how changes in functions associated with the socio-emotional and cognitive control systems place adolescents at risk for engaging in substance use.

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Figure Captions

Figure 1. Intraindividual change and intraindividual variability (figure after Ram & Gerstorf, 2009). Intraindividual change (blue line) describes within-person change resulting from long-term processes over the course of years. Intraindividual variability refers to changes occurring on relatively shorter timescales that are conceived as fluctuations resulting from short-term processes. Differences between the two circles highlight that the extent of intraindividual variability may change with age. The adolescent period is highlighted by a gray background and is indicated by a peak in the magnitude of the dynamic characteristic under consideration. This peak was chosen to reflect findings of increased risk-taking and sensation-seeking during this adolescence relative to childhood and adulthood (e.g., Burnett et al., 2010). Further, greater intraindividual variation is portrayed during adolescence relative to adulthood. This reflects findings of greater variability in risk-taking in adolescents relative to children (McCormick & Telzer, 2017) as well as findings for increased behavioral flexibility during adolescence (Johnson & Wilbrecht, 2011).

Figure 2. Intensive repeated measures data for two participants (one participant in red, one participant in blue). The data simultaneously contain information on between-person (mean level across the time series of each participant illustrated using dotted lines) and within-person (person-specific deviations from their mean levels) that must be disaggregated before within-person inferences may be made based on the time series data (Curran & Bauer, 2011).

Figure 3. A sampling of the multiple timescales of cognitive control. Three timescales encompassing slow (bottom) and fast (top) timescales are presented. The individual is depicted as being characterized by changes in cognitive control accuracy across years (e.g., Ordaz et al., 2013) but also by fluctuations in cognitive control over the course of days (e.g., Rahdar & Galvan, 2014) and across trials on a task (e.g., Tamnes et al., 2012). A thorough characterization of the developing individual necessitates an assessment of function across these nested timescales.

Figure 4. An illustration of the use of random effects in multilevel models to capture heterogeneity across participants. The association between scores on a dependent variable across values of an independent variable is shown for multiple participants (each line represents a participant). The association for the prototypical participant is shown in blue. Individual differences in the association are captured but are assumed to be normally distributed, hence the fanning pattern of the gray lines on either side of the prototypical individual.

Figure 1.

Figure 2.

Figure 3.

Figure 4.