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Heterogeneity in development of aspects of working memory predicts longitudinal ADHD symptom change

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Abstract

The role of cognitive mechanisms in the clinical course of neurodevelopmental disorders is poorly understood. Attention Deficit Hyperactivity Disorder (ADHD) is emblematic in that numerous alterations in cognitive development are apparent, yet how they relate to changes in symptom expression with age is unclear. To resolve the role of cognitive mechanisms in ADHD, a developmental perspective that takes into account expected within-group heterogeneity is needed.

Method—The current study uses an accelerated longitudinal design and latent trajectory growth mixture models in a sample of children ages 7–13 years carefully characterized as with (n=437) and without (n=297) ADHD to: 1) identify heterogeneous developmental trajectories for response inhibition, visual spatial working memory maintenance, and delayed reward discounting and 2) to assess the relationships between these cognitive trajectories and ADHD symptom change.

Results—Best-fitting models indicated multiple trajectory classes in both the ADHD and typically-developing samples, as well as distinct relationships between each cognitive process and ADHD symptom change. Developmental change in response inhibition and delayed reward discounting were unrelated to ADHD symptom change, while individual differences in the rate of visual spatial working memory maintenance improvement predicted symptom remission in ADHD.

Conclusion—Characterizing heterogeneity in cognitive development will be crucial for clarifying mechanisms of symptom persistence and recovery. Results here suggest working memory maintenance may be uniquely related to ADHD symptom improvement.

Keywords

ADHD; executive function; working memory; delay discounting; longitudinal

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Cognitive impairments in neurodevelopmental disorders are important as potential endophenotypes— that is, relatively objectively measured characteristics that are part of disease liability or mechanisms of symptom change. These measures can potentially clarify how neurodevelopmental disorders progress and might be better prevented or treated. The importance of clarifying such mechanisms has been frequently emphasized by leading theorists in the field (Gottesman & Gould, 2003; Insel et al., 2010; Kendler & Neale, 2010; Sonuga-Barke & Halperin, 2010). Attention Deficit Hyperactivity Disorder (ADHD) is emblematic. Whereas some children with ADHD show a seemingly full remittance of symptoms by adolescence or early adulthood, many continue to experience clinically-impairing symptoms, even if sub-diagnostic threshold (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011; Sibley et al., 2012; Willoughby, 2003). Numerous alterations in cognitive development are also apparent in ADHD, yet how they relate to changes in symptom expression with age is unclear (Biederman, Mick, & Faraone, 2000; Lahey, Pelham, Loney, Lee, & Willcutt, 2005; Larsson, Dilshad, Lichtenstein, & Barker, 2011; Van Lier, Der Ende, Koot, & Verhulst, 2007).

The primary focus of the current investigation is on heterogeneity in neurocognition (a term that we use to encompass components of executive functioning and reward valuation that have specific theorized neural system linkages) and how this relates to ADHD symptom course. Both executive function and reward valuation are multi-componential constructs. We focus on three exemplar processes that have substantial theoretical and empirical basis in the ADHD literature, and select measures that are widely used in ADHD to enhance comparability of findings (Barkley, 1997; Castellanos & Tannock, 2002; Nigg, 2010; Sonuga-Barke, 2005). These targets are (1) response inhibition, which involves the ability to stop an ongoing response in order to do something else (Aron & Poldrack, 2005; Logan, 1994); (2) visual-spatial working memory maintenance (VWM), which involves the ability to actively maintain visual information in the focus of attention (Baddeley, 1996; De Luca et al., 2003; Engle, 2002; Kane, Conway, Hambrick, & Engle, 2007; Unsworth & Engle, 2007), and (3) delayed reward discounting, or the degree to which a reward loses its value the longer a person has to wait to receive it (Mitchell, 1999; Sagvolden, Aase, Zeiner, & Berger, 1998).

These cognitive processes are correlated, yet also quite separable (Karalunas, Bierman, & Huang-Pollock, 2016; Lee, Bull, & Ho, 2013; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Shing, Lindenberger, Diamond, Li, & Davidson, 2010). They rely on partially distinct neural circuitry (Arnsten, 2009; Arnsten & Rubia, 2012; Bunge & Wright, 2007; Dias et al., 2013) and may differ in their relationship to ADHD symptom domains and functional impairment (Solanto et al., 2001; Sonuga-Barke, Dalen, & Remington, 2003; Thorell, 2007). Our goal here was to examine their distinct relationships to changes in ADHD symptom severity, rather than to create phenotypic profiles across the combined measures. Understanding these distinct relationships is a critical step to determining what role these putative mechanisms may play in course of symptoms.

At least two competing characterizations of the relationships between neurocognition and ADHD symptoms have been proposed. On one hand, a *trait liability* hypothesis posits that neurocognitive impairments are directly related to etiology of the disorder (Barkley, 1997;

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Castellanos & Tannock, 2002) and persist over time independent of changes in symptoms. Liability models form the basis of research focusing on neurocognitive deficits as markers for ADHD regardless of disease status (e.g., Albrecht et al., 2008; Crosbie, Pérusse, Barr, & Schachar, 2008; Doyle et al., 2005; Gau & Shang, 2010; Uebel et al., 2010). Support comes from studies showing that siblings unaffected by ADHD nonetheless have neurocognitive weaknesses relative to children from unaffected families (Nikolas & Nigg, 2014). Under a liability model, changes in symptoms may be associated with psychosocial factors, such as family or parenting characteristics (Chronis-Tuscano et al., 2011; Musser, Karalunas, Dieckmann, Peris, & Nigg, 2016), or neurodevelopmental improvements in emotional regulation or social skills, without being reflected in measures of neurocognitive development.

Alternatively, a *cognitive maturation* hypothesis suggests that improvement in neurocognition (particularly in executive functioning) during middle childhood and adolescence contributes to ADHD symptom improvements observed during this same time period for some children (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010; El-Sayed, Larsson, Persson, Santosh, & Rydelius, 2003; Halperin & Schulz, 2006). Some perspectives suggest that executive function impairments are both the initial cause of symptoms and the mechanism of remittance. Others suggest that stable, subcortically-driven impairments initially cause symptoms (and are liability markers), and that improvements in prefrontally-mediated executive functions provide a compensatory mechanism contributing to symptom reduction (Halperin & Schulz, 2006). Both maturation perspectives suggest that heterogeneity in symptom recovery is explained by inter-individual differences in some aspect of neurocognitive development, and that the relevance of specific neurocognitive processes depends on age.

The literature on neurocognitive development in ADHD provides some support for both the liability and cognitive maturation hypotheses. Cross-sectional meta-analyses indicate that adults with ADHD have weaknesses on executive function tasks, but that these impairments are smaller in magnitude than those observed in children (Kasper, Alderson, & Hudec, 2012; Kofler et al., 2013; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005), suggesting some normalization by adulthood. The few available longitudinal studies are mixed with regard to the stability of executive functioning deficits in ADHD (Biederman et al., 2009; Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014) versus normalization by adulthood (Drechsler, Brandeis, Földényi, Imhof, & Steinhausen, 2005; Miller, Loya, & Hinshaw, 2013). Longitudinal neuroimaging studies examining the structural development of regions implicated in neurocognitive function have similarly mixed results. While some have reported early appearing, non-progressive volume reductions in both cortical and cerebellar regions in children with ADHD (Castellanos et al., 2002; Mackie et al., 2007), consistent with liability models, others have found delays in maturation of cortical thickness with eventual normalization, particularly in pre-frontal areas associated with executive functioning (Rubia, 2007; Shaw et al., 2007; Shaw et al., 2011) that are more consistent with a maturation hypothesis. Aside from sampling variation, the mixed results may reflect heterogeneity in which some individuals experience normalization of brain development and neurocognitive impairments by adulthood while others do not.

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Recent systematic review of the small number of longitudinal studies that directly address the relationship between neurocognition and ADHD symptom change concluded that executive function deficits are smaller for individuals whose ADHD diagnosis remitted as compared to those with persistent symptoms (Van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013), suggesting that cognitive maturation may play a role in symptom change. However, executive function was not fully normalized in remitted ADHD cases. Too few studies examined reward valuation measures across time to draw conclusions about their relationships to ADHD symptom change. Overall, conclusions from the review were limited by a lack of available studies that included longitudinal assessment of *both* ADHD *and* neurocognition, which is a key gap the present study aims to address.

Of the well-designed prospective studies that include multiple assessments of both symptoms and neurocognition, Biederman et al. (2009) found no difference between adults with persistent or remitted ADHD on a composite measure of neuropsychological functioning or on specific measures of verbal working memory or processing speed, suggesting stable, trait-like neurocognitive impairments. Assessments were widely spaced in time (at 4 years and 10 years after baseline) and comprehensive neuropsychological assessment was only available starting in mid-adolescence, leaving questions about how neurocognition relates to symptoms during the rapid developmental changes of middle childhood and early adolescence. In addition, use of diagnostic categories may be less sensitive than dimensional measures of symptom severity.

Two recent longitudinal studies have employed dimensional measures of symptoms. Vaughn et al. (2011) found that improvements on continuous performance test variables (omissions, commissions, reaction time measures) were not related to changes in dimensional measures of ADHD symptoms over one year in middle childhood, again consistent with liability model although covering a relatively brief developmental window of one year. Consistent with the Biederman et al. (2009) results, Miller et al. (2013) found no relationships between verbal working memory and symptom change in their longitudinal sample of girls with ADHD assessed at three time points spaced 5-years apart between childhood and young adulthood. However, in contrast to prior findings from both Biederman et al. (2009) and Vaughn et al. (2011), improvements in global executive functioning and commission errors on the CPT did predict improvement in ADHD symptoms over time, implicating cognitive maturation in symptom remission. Taken together, several of the largest prospective longitudinal studies of neurocognitive performance in ADHD have failed to find group level associations between verbal working memory or attention measures and ADHD symptom change, but results for response inhibition are contradictory. Other neurocognitive processes with large ADHD effects, such as spatial working memory and reward valuation (Willcutt et al., 2012) have not been considered. We address that gap here.

The primary novelty in the present study, however, is that prior studies of neurocognitive development and ADHD have not examined within-group heterogeneity from a developmental perspective— they have treated youth with ADHD as a single cognitive group. Yet the ADHD diagnostic group is likely to be cognitively heterogeneous in meaningful ways (Fair, Bathula, Nikolas, & Nigg, 2012; Karalunas & Huang-Pollock, 2011; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Solanto et al., 2001). Of particular interest

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here is how this type of neurocognitive variation within the ADHD population informs variations in symptom change in ADHD. It also remains unclear how neurocognitive heterogeneity in ADHD relates to normative variation in neurocognitive development because typically-developing children are treated as a homogenous comparison group. The current study uses an accelerated longitudinal design and latent trajectory growth mixture models in a large (n=734) sample of children spanning a developmental period from age 7–13 years to: 1) compare developmental trajectories of response inhibition, VWM, and delayed reward discounting in children with and without ADHD; 2) examine within-group heterogeneity; and 3) determine whether ADHD neurocognitive subgroups differ in symptom recovery.

Method

Participants

Children were recruited and screened from community volunteers who responded to public advertisements and mass mailings. The Institutional Review Board at Oregon Health & Science University approved the studies (protocols #4817 and #6258) and all procedures conformed to the Ethical Principles of Psychologists and Code of Conduct (American Psychological Association, 2002). Parents provided written informed consent for themselves and their children. All children also provided written informed assent.

The full sample included a total of 734 children (437 with ADHD) who were ages 7–12 at the time of entry into the study. See Table 1 for description of the sample. 585 children were enrolled with funding for planned longitudinal follow up that included three annual assessment visits (e.g., assessments at ages 7-, 8-, and 9-years-old or 10-, 11-, and 12-years-old, depending on age of enrollment). Of these, 469 (80%) completed all three annual assessments, 13% completed two annual assessments, 7% completed one annual assessment. An additional 146 children were enrolled under supplemental funding at baseline, but resources for follow up were not available, so their follow ups are missing by design. They are included to maximize power and reduce bias in parameter estimates (Allison, 2002; Graham, 2009; Schafer & Graham, 2002). Procedures for screening, diagnosis, and visits were identical for children enrolled with and without longitudinal funding available. Thus, it was not surprising that children missing by design did not differ from those with planned follow up with regard to sex ratio, rates of prescribed medication, IQ, or parent or teacher-rated ADHD symptom severity (all $p > .16$). Overall, 64% of the total sample (n=469) had data at three annual assessments, 10% (n=73) at 2 annual assessments, and 26% (n=190) one time-point of assessment. The mean age of the sample at years 1, 2, and 3 were 9.6, 10.4, and 11.4 years, respectively. The sample included 111 sibling pairs and one sibling trio. Clustering within families was accounted for statistically using the Cluster command in MPLUS.

Diagnostic Assessment

Clinical assessment—After an initial screening phone call, children were identified for the study via best-estimate confirmation procedure. A parent/guardian and teacher completed standardized rating scales, including Conners' Rating Scales-3rd edition (CRS-3,

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Conners, 2003), Strengths and Difficulties Questionnaire with impact supplement (SDQ, Goodman, 2001), and the ADHD Rating Scale (ADHD-RS, DuPaul, Power, Anastopoulos, & Reid, 1998). The parent/guardian also completed a semi-structured clinical interview administered by a Master's-degree level clinician who had achieved research reliability on the interview (Kiddie Schedule for Affective Disorders and Schizophrenia, Puig-Antich & Ryan, 1986). IQ was estimated based on a reliable and valid three-subtest short form of the WISC-IV (Vocabulary, Block Design, and Information, Sattler & Dumont, 2004; Wechsler, 2003). Academic achievement was assessed using the Word Reading and Numerical Operations subtests of the WIAT-II (Wechsler, 2002). Study data were (in part) collected and managed using REDCap electronic data capture tools hosted at OHSU. It provides a secure web-based and intuitive interface and export capabilities (Harris et al., 2009).

Final diagnosis—All materials were scored and presented to a clinical diagnostic team that included a board certified child psychiatrist with over 25 years of experience and a licensed child neuropsychologist with over 10 years of experience. Blind to one another's ratings and to the subsequent cognitive test scores, they formed a diagnostic opinion based on all available information. Their agreement rate was excellent (ADHD diagnosis kappa=. 88). Disagreements were conferenced and consensus reached. Cases where consensus was not readily achieved were excluded.

In determining their diagnostic impression, the clinicians used the following rules: If both parent and teacher ratings exceeded T-score >= 60 on at least one ADHD scale and both rated at least 3 symptoms as "often" or "very often" on the ADHD rating scale (teachers) and K-SADS (parents), then the "or" algorithm could be employed for counting symptoms towards the final diagnosis. Consistent with DSM criteria, to be in the ADHD group, the "or" algorithm needed to yield at least 6 symptoms of inattention, 6 symptoms of hyperactivity-impulsivity, or both. When informants disagreed (i.e., one of the informants did not have T-score >= 60 or did not report more than 3 symptoms), clinicians were asked to judge whether this was explained by successful medication treatment during the school day. If so, they used all available data to make a diagnostic determination. If the discrepancy was not easily explained by successful medication treatment during the day, then the case was rejected as failing to meet the DSM criteria of substantial symptoms present in more than one setting. In addition to symptom count criteria, children in the ADHD group were required to meet all other DSM criteria including (a) impairment (identified on the KSAD by the clinician as well as on the SDQ impact supplement section for parents and teachers), (b) onset prior to age 7 (current at the time we began enrollment), (c) sustained impairing symptoms > 1 year, and (d) symptoms of ADHD not better accounted for by comorbid conditions, trauma history, or other confounds. Non-ADHD comparison children, were required to have 4 or fewer symptoms of both inattention and hyperactivity-impulsivity using the "or" algorithm.

Exclusion Criteria—Baseline exclusion criteria included an estimated Full Scale IQ < 70, use of long-acting psychotropic medication (e.g., anti-depressants), diagnosis of current major depressive episode, lifetime mania or psychosis, pervasive developmental disorder (including autism), or major medical/neurological disorders or injuries for all children. In

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addition, children in the typically-developing control group were excluded if they met criteria for conduct disorder at baseline. Other psychiatric disorders were free to vary.

Medication and washout—Children prescribed stimulant medications (38% of children with ADHD at baseline, 45% at Year 2, and 50% at Year 3) were included in the study but were required to be off medication for 24 (for short-acting stimulant preparations) to 48 hour (for long-acting stimulant preparations) prior to testing. Other psychoactive medications were exclusionary at baseline. However, children who began taking a non-stimulant medication after the first year of participation were allowed to continue with annual assessments even though they did not washout of medications (< 1.3% of children). Medication status was included as a covariate in all analyses to be conservative but did not materially affect results.

Primary Measures

The three neurocognitive measures were administered as part of a longer battery. Tasks were administered in the same order for all participants

Response inhibition—Response inhibition was evaluated based on a tracking version of the stop task (Logan, 1994; Nigg, 1999). This task validly captures development of motor inhibition in children as young as 5-years-old through adulthood (Tillman, Thorell, Brocki, & Bohlin, 2008; Van De Laar, Van Den Wildenberg, van Boxtel, & van der Molen, 2011; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). ADHD effects on identical tasks have been found through adulthood (Nigg, Butler, Huang-Pollock, & Henderson, 2002). Our own data demonstrate good internal-consistency (.84–.87 across all waves of data collection). Acceptable test-retest reliability has been demonstrated for both children and adults (Soreni, Crosbie, Ickowicz, & Schachar, 2009; Weafer, Baggott, & de Wit, 2013)

For each trial, a central fixation point appeared for 500 ms. An “X” or an “O” then appeared for 1000 ms on 75% of trials (“go” trials), children were asked to indicate with a key press whether an “X” or an “O” appeared in the center of the screen. After 2000 ms. the next trial automatically commenced. On 25% of trials (“stop” trials), an auditory tone presented after the stimulus indicated that the child should not respond. The timing of the auditory stop signal varied adaptively based on participant performance. An initial mean reaction time (MRT) was determined based on the practice trials and the auditory stop tone was initially set to occur 250 ms before the MRT. The MRT was then dynamically recalculated after each correct go trial and the delay at which the stop tone was presented was adjusted dynamically in 50 ms increments to maintain an overall ~50 % accuracy rate. After 32 practice trials, children completed 8 blocks of 64 experimental trials. Prior to creating the total score across blocks, the following validity criteria (Nigg, 1999) were applied to each block: a) stop accuracy between 30–70%, b) “go” trial accuracy greater than 75%, and c) mean RT for the block between 100–1500ms (to avoid anticipations on current or next trial). Stop signal RT (SSRT), the primary measure of response inhibition, was calculated for each valid block by subtracting the average stop signal delay from the average RT (Logan, 1994).[1] Following convention, the practice trials and the first block of data were excluded from the final average to exclude warm-up effects. Valid block SSRT scores were averaged to create the

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final SSRT outcome variable. Average SSRTs less than 50ms were considered invalid. 2.2% of data were excluded at Year 1, 1.3% at Year 2, and 1.6% of cases at Year 3 because no blocks of data met the validity criteria; these were treated as missing data in analyses.

Visual-spatial working memory maintenance—VWM was assessed using a computerized spatial span backwards task identical to the Spatial Span subtest from the CANTAB test battery (De Luca et al., 2003). The task has been validated for use in children as young as 4-years-old, with documentation of good internal consistency, acceptable test-retest reliability, and ongoing developmental improvements into early adulthood (Henry & Bettenay, 2010; Luciana, 2003; Luciana, Conklin, Hooper, & Yarger, 2005).

Children viewed a screen containing 10 squares arranged in a fixed position. Individual squares changed color (from gray to yellow) in a fixed sequence. A tone sounded at the end of the sequence to indicate that it was finished. Children used the mouse to mark the squares in the *reverse* order in which they changed color. The number of squares in the sequence began at three and increased to nine, with two trials for each sequence length. The task discontinued when a child failed both trials at a specific sequence length. The primary outcome variable used was the number of items completed correctly. All children performed at better than chance levels (indicating they were not randomly guessing), so no children's data were excluded from analyses.

The CANTAB task was selected to be consistent with the types of tasks used frequently in the ADHD literature and for which moderate to large effects have been found (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt et al., 2012). Although often referred to as a measure of spatial working memory, it is likely that it primarily taps visual short-term memory maintenance, rather than updating/serial memory search processes, an important distinction in some models that we address further in the Discussion.

Delayed Reward Valuation—Delayed reward valuation was assessed using a computerized delay discounting questionnaire, based on the task described by Mitchell (1999) and Wilson, Mitchell, Musser, Schmitt, and Nigg (2011). The task design is consistent with tasks that show acceptable test-retest reliability (Beck & Triplett, 2009; Matusiewicz, Carter, Landes, & Yi, 2013; Weafer et al., 2013) and identify meaningful individual differences in children, adolescents, and adults (Daugherty & Brase, 2010; Duckworth & Seligman, 2005), including studies that have examined developmental improvements from childhood to adulthood in typically-developing populations (Green, Fry, & Myerson, 1994; Steinberg et al., 2009). Prior publication in a subset of the current sample identified relationships between performance on this task and functional connectivity of the nucleus accumbens, lending further support to the validity of the task in this age range (Dias et al., 2015).

[1]An anonymous reviewer noted that stop signal delay (SSD) has been proposed as an alternative outcome measure for this task (e.g., Alderson, Rapport, & Kofler, 2007). A check in our data indicated an inconsistent developmental pattern for stop signal delay with no clear polynomial trend and poor fitting models. The observed patterns in the raw data were difficult to align with well-established, age-dependent improvement in response inhibition. For this reason, and to be consistent with the majority of cognitive and ADHD research, we retain stop signal reaction time as our focus. We can provide results for SSD on request to the first author.

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Children were presented a series of 91 questions. Specific answers had no effect on the overall duration of the task; however, children's response time affected task length because the next question was not presented until the previous question was answered. For each question, children chose between (1) a varying amount of hypothetical money now and (2) a hypothetical $10.00 after a varying delay (e.g., $6.50 now or $10 in 30 days). Participants indicated whether they preferred the immediate or delayed alternative using the computer mouse to choose their answer. The immediate money varied from $0–$10.50 in $0.50 increments, presented in random order. The delayed money (always $10.00) was available after one of four hypothetical delays (7, 30, 90, or 180 days). A delayed and an immediate item were selected to form each question so that each delayed alternative was paired with each immediate alternative, and presented in a random sequence. Three additional questions were used to assess attention to the task ($10 in 0 days vs. $10.50, $9.50, and $9.00 now). The task took approximately 12 minutes.

Valuation of delayed rewards was quantified as the discounting gradient, or rate at which the delayed outcome was discounted. A hyperbolic equation was fitted to each participant's indifference points (Mazur, 1987) using the Solver subroutine in Microsoft Excel 2007 as follows: $V = M/(1+kD)$. V represents the subjective value of the delayed item, as indexed by the indifference point. M represents the objective value of the delayed item ($10). D represents the delay length associated with receiving $10. The free parameter, k, represents the gradient of the discounting function.

Three validity criteria were applied: 1) Criterion 1 proposed by Johnson & Bickel (2008): an indifference point for a specific delay could not be greater than the preceding-delay indifference point by more than 20% ($2); 2) modified from Criterion 2 of Johnson & Bickel (2008): the final (180 day) indifference point was required to be less than the first (0 day) indifference point, indicating evidence of variation in subjective value of rewards across delays; and 3) the first (0 day) indifference point was required to be at least 9.25. Lower values for the 0-day indifference point indicate that the child chose multiple times to have a smaller reward *now* over a larger reward *now*, suggesting misunderstanding or poor task engagement. Data that did not meet validity criteria were treated as missing in analyses. Our stringent criteria, resulted in exclusion of 18% of children at Year 1, 12% of children at Year 2, and 8% of children at Year 3. These data were treated as missing.

The gradient of the discounting function (k) was used as the final outcome variable because prior publication indicated this best differentiates ADHD and control performance (Mitchell, Wilson, & Karalunas, 2015). To address non-normality, the k values were log-transformed, such that more positive values indicate a steeper gradient (i.e., a greater preference for immediate rewards).

ADHD Symptom Change—ADHD symptoms for growth models were obtained at all data collection time-points using a) parent report on the KSAD as scored by the clinical interviewer (coded as present or absent) and b) teacher report on the ADHD-RS (also coded as present or absent, with ratings of "often" or "very often" counted as present). Parent and teacher reports of each symptom domains were treated separately in all analyses resulting in

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four total symptom models: a) parent inattention, b) parent hyperactivity-impulsivity, c) teacher inattention, and d) teacher hyperactivity-impulsivity.

Analytic Strategy

The current study utilized an accelerated longitudinal design to model change from age 7 to 13 years (Graham, Taylor, & Cumsville, 2001). Observations were binned according to the age at which the child completed the assessment such that bins were centered on whole age years (e.g., children ages 7.5–8.49 years at the time of assessment were grouped as "age 8" observations, children age 8.5–9.49 years at the time of assessment were grouped as "age 9" observations, etc.). Results were generally the same when an individual-varying times of observation analytic approach was applied, and are available in the supplemental material (Section I, Tables S1–S4).

Overview of Analytic Plan—For each neurocognitive process of interest there were two types of analyses conducted: 1) conditional latent growth curve models (LCMs) and 2) latent class growth analyses (LCGAs). Each analysis is described in detail below. Conceptually, the LCM models established the shape of the growth trajectory in the full sample (e.g., linear, quadratic) (Bollen & Curran, 2006) and were used to test for diagnostic group differences in the overall trajectory. LCM analyses assume that individuals in each diagnostic group follow a similar trajectory. The LCGA models then directly addressed the question of heterogeneity within diagnostic groups. LCGAs tested whether each diagnostic group was best described by a single trajectory class or by multiple subgroups following unique trajectories. As our last step, we ran four additional LCM models on the parent and teacher reported symptom scores to characterize baseline symptom severity and rate of change in each ADHD symptom domain. The factor scores for each child were used as dimensional measures that could be compared between the neurocognitive groups.

Covariates—Sex, family income, and child race were initially included as covariates in the LCM models. None were significantly associated with the neurocognitive slopes. For response inhibition models all $p > .30$ and for delayed reward discounting models all $p > .31$. For VWM models, all $p > .25$, except for sex, which was marginally associated with slope ($p=.083$). VWM models with and without sex as a covariate yielded essentially identical results. To be consistent with other models (and because the sex covariate did not rise to statistical significance) we report the results without sex as a covariate. IQ significantly differed between ADHD and control groups; however, covarying IQ in studies of cognitive function potentially removes variation of interest, so it was not covaried. For the within-group LCGA models, sex and medication status (coded as yes/no indicating whether child was on any type of psychotropic medication, even if on stimulant washout) were used as covariates.

Latent growth curve models (LCM)—Separate LCMs were fit in the full sample for response inhibition, VWM, and delayed reward discounting. The intercept and the slope were regressed on the child's ADHD status to test for between-group differences. See Figure 1 for a visual depiction of these models. Both linear and quadratic trends were examined; the best fitting model was determined via chi-squared difference tests and examination of: a)

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comparative fit index (CFI, Bentler, 1990), b) Tucker-Lewis index (TLI, Tucker & Lewis, 1973), and c) the root mean squared error of approximation (RMSEA, Browne & Cudeck, 1993). In the case of the delayed reward valuation task, piecewise models were also examined based on visual inspection of the raw data, which suggested the presence of two separate linear slopes (the piecewise model is depicted in Figure 1b). For our primary analyses, the intercept of each growth curve was defined at age 7. However, we also computed each model with the intercept defined at age 13 (and in the case of the piecewise model, at both age 13 and at the empirically determined knot), in order to determine if children with and without ADHD differed significantly from one another at the end of the age period examined for the current study.

Latent class growth analyses (LCGA)—Next, LCGAs (one for each neurocognitive measure) were fit separately in the ADHD and typically-developing sample (Jung & Wickrama, 2008). Groups were examined separately to focus on within-group variation. One- through ten-class LCGA models were considered and the best-fitting model was selected based on Bayesian information criterion (BIC), convergence (entropy), and the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR LRT), which assesses whether the k-class model significantly improves on the k – 1 class model (Asparouhov & Muthén, 2012). In each of the models, child medication status and child sex were included as covariates, and regressed onto the intercept and slope of the neurocognitive measures. However, the delayed reward valuation models with child sex and medication status did not converge, and thus the models without covariates are presented.

Relationship between Neurocognitive Group and Symptom Change—Finally, we conducted a second set of LCM analyses for: a) parent inattention, b) parent hyperactivity-impulsivity, c) teacher inattention, and d) teacher hyperactivity impulsivity. Factor scores for the intercepts and slopes from each model were exported using M*plus*' *savedata* and *fscores* commands, so that each child had scores for each symptom domain indicating their baseline symptoms and rate of change based on parent and teacher report. Factor scores were used as dimensional measures of baseline symptom severity and symptom change, respectively, and were compared between neurocognitive subgroups using standard t-test / ANOVAs.

Missing Data and Clustering—LCMs and LCGAs were parameterized using the M*plus* 7.2 software package and the robust maximum likelihood estimator (Muthén & Muthén, 1998–2012). Full information maximum likelihood was used to handle missing data (Arbuckle, Marcoulides, & Schumacker, 1996). Non-independence of observations (i.e., the nesting of children within families) was handled using M*plus*'s *cluster* command. Planned missingness was accommodated by setting the covariance coverage in M*plus* to 0 in all analyses.

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Results

Group level Neurocognitive Trajectories (LCM models)

LCM models established the shape of the growth trajectory in the full sample (e.g., linear, quadratic) and tested for diagnostic group level differences in trajectories. Results are summarized in Table 2 and depicted visually in Figure 2A. Fit statistics for all LCM models are in the supplemental material in Table S5.

Response inhibition—In the full sample, a linear model provided the best fit for change in response inhibition between ages 7–13 years (see Table S5 for model fit statistics). Children with ADHD exhibited slower response inhibition than non-ADHD controls at age 7 (group difference = 62.85 ms, $p < .001$) and continued to show slower response inhibition at age 13 (group difference = 36.71 ms, $p < .001$). Consistent with the persistent group difference in performance, the effect of ADHD status on the slope of response inhibition was not significant (slope difference = −4.34 ms/year, $p = .18$), indicating that at the group level children with and without ADHD followed similar developmental trajectories.

VWM—In the full sample, a linear model provided the best fit for VWM development (see Table S5 for model fit statistics). At age 7, children with ADHD had poorer VWM than non-ADHD controls (group difference = −.68 items, $p = .003$), and the group level difference remained significant at age 13 (group difference = −1.66 items, $p < .001$). The effect of ADHD status on the slope of VWM change was significant (slope difference = −.16 items/year, $p = .03$); children with ADHD developed less rapidly (i.e., had a less steep slope) than their non-ADHD peers, suggesting they fell further behind their typically-developing peers with age.

Delayed Reward Valuation—A piecewise model with two linear splines and a knot defined at age 11 provided the best fit to the group level data (see Table S5 for model fit statistics). At age 7, children with ADHD had steeper discounting of delayed rewards than their typically-developing peers (group difference = 1.27, $p = .003$). There was a significant effect of ADHD status on the first slope of the delayed reward valuation task (slope 1 difference = −.30, $p = .03$), but not on the second slope of this task (slope 2 difference = .17, $p = .46$). That is, between the ages of 7 and 10 years, children with ADHD improved at twice the speed of controls, such that by age 11 the ADHD and control groups no longer differed from one another in delayed reward discounting (age 11 group difference = .09, $p = .71$ at age 11). Between ages 11 and 13, there was no difference in rate of development for delayed reward valuation.

Summary of group level results—At the group level, response inhibition and VWM were both persistently impaired in children with ADHD as compared to non-ADHD controls. In contrast, reward discounting was initially impaired for children with ADHD, but improved more quickly than for typically-developing children and normalized by late childhood.

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Within-group Heterogeneity in Neurocognitive Development

We next report results from the LCGAs, which directly address the question of heterogeneity within diagnostic groups. The intercept and slope values for each LCGA group are summarized in Table 3 (ADHD) and Table 4 (control). Fit statistics are detailed in Table 5.

Response inhibition—In the non-ADHD control group, a two-class solution provided the best fit for the data. Class 1, called “Control: normally developing,” included nearly all the children (n = 257; 95.2%). This group showed moderate improvement in response inhibition between ages 7 and 13. A much smaller second trajectory class in the control sample (n = 13; 4.8%), called “Control: impaired,” had impaired response inhibition at age 7 (group difference: t (268) = 36.74, p < .001) and more rapid improvement over time than the normally developing control group (slope difference: t (268) = −25.94, p < .001). There was partial normalization of response inhibition by age 13; however, the impaired control group still had slower response inhibition than the normally developing control group at age 13 (group difference: t (268) = −15.99, p < .001).

In the ADHD sample, a two-class solution also provided the best fit for the data. ADHD Class 1 (n = 364; 81.4%), labeled “ADHD: unimpaired,” included children who were unimpaired at age 7 and showed normal developmental improvements in response inhibition over time, as indicated by intercept and slope values very similar to those of the “Control: normally developing” group. ADHD Class 2 (n = 76; 18.6%), labeled “ADHD: impaired,” included children who had impaired response inhibition at age 7 compared to both the “Control: normally developing” (group difference: t (324) = 8.06, p < .001) and “ADHD: unimpaired” groups (group difference: t (438) = −53.85, p < .001), but who improved more quickly over time than either their unimpaired ADHD or “Control: normally developing” counterparts (all p < .001 for comparison of slope values). A faster rate of improvement resulted in partial normalization of response inhibition, but the “impaired” ADHD group continued to show significantly slower response inhibition than any of the other groups at age 13, including the “Control: impaired” group (all p < .001 for comparison of age 13 group differences). The trajectory classes are visually depicted in Figure 2B.

VWM—In the Control group, a two-class solution provided the best fit for the data. Control Class 1 (n = 197; 71.6%), called “Control: normally developing,” showed significant improvement between ages 7 and 13. A second class in the control sample (n = 78; 28.4%), called “Control: impaired” had impaired VWM at age 7 (group difference: t(273) = −35.96, p < .001) and a slower rate of development than the “Control: normally developing” group (slope difference: t (273) = −30.05, p < .001), resulting in persistently lower VWM at age 13 (group difference: t (273) = −33.87, p < .001).

In the ADHD group, a three-class solution provided the best fit to the data. ADHD Class 1 (n = 137; 30.2%), labeled “ADHD: impaired, recovering,” included children who had impaired VWM at age 7 compared to the “Control: normally developing” group (group difference: t(331) = −22.43), p < .001). This group also improved significantly faster over time than the normally developing controls (slope difference: t(331) = 3.77, p < .001) and normalized on VWM performance by age 13 (age 13 group difference compared to normally

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developing controls: $t(331) = 1.32$, $p = .19$). ADHD Class 2 ($n = 248$; 54.8%), labeled "ADHD: stably impaired" included children who also had impaired VWM at age 7 (group difference: $t(443) = -32.40$, $p < .001$) compared to the "Control: normally developing" group and did not significantly improve over time. A smaller group of children made up Class 3 ($n = 68$; 15.0%), which was labeled "ADHD: high VWM." This group of children showed no VWM impairment at age 7 and in fact had mean performance that exceeded the "Control: normally developing" group (group difference: $t(263) = 10.13$, $p < .001$). However, performance for this group did not significantly improve between ages 7 and 13 years, and VWM scores for this group at age 13 were lower than for the "Control: normally developing" group (group difference: $t(340) = 9.79$, $p < .001$).

Delayed reward valuation—A 1-class solution provided the best fit in the typically-developing sample, suggesting no distinct trajectory classes in the non-ADHD control sample in this age range.

In the ADHD sample, a 2-class solution provided the best fit to the data. Although the BIC for the three class solution was lower than that of the two-class solution, the VLMR LRT for the 3 vs. 2 class solution was not statistically significant, suggesting that the two-class solution may be preferable. Further, the third class was relatively small (5.56% of the sample) and was difficult to justify theoretically, adding evidence for selection of the 2-class solution.

ADHD Class 1 ($n = 229$; 57.83%), labeled "ADHD: impaired" included children who showed steeper discounting of delayed rewards at age 7 than non-ADHD controls (group difference: $t(468) = 90.88$, $p < .001$). This group also had more rapid improvement in delayed reward discounting between ages 7 and 11 than controls (slope difference: $t(468) = 44.25$, $p < .001$), but then no significant change between ages 11 and 13. This group continued to have worse performance (i.e., more discounting of delayed rewards) at age 13 as compared to controls (group difference: $t(468) = -39.13$, $p < .001$). ADHD Class 2 ($n = 167$; 42.17%), labeled "ADHD: unimpaired" showed delayed reward discounting similar to that of control children at age 7 (group difference: $t(406) = 34.86$, $p < .001$), and significantly faster improvement in delayed reward discounting between the ages of 7 and 11 than non-ADHD controls (slope difference: $t(406) = 46.49$, $p < .001$). The trajectory for this group also indicated some worsening of delayed reward discounting between the ages of 11 and 13 as they approached adolescence as compared to controls (slope difference: $t(406) = 19.18$, $p < .001$).

Summary of trajectory class results—Developmental heterogeneity in neurocognition was observed for both children with and without ADHD. For children with ADHD, heterogeneity was observed for all three neurocognitive processes. Both impaired and unimpaired classes were evident for response inhibition and delayed reward discounting; impaired groups did not normalize, although partial normalization was observed for the impaired response inhibition trajectory. Unimpaired and impaired classes were also evident for VWM, but here some children remained persistently impaired and while others' VWM normalized over time.

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Overlap in Trajectory Classes

The impaired delayed discounting class had lower income than the unimpaired class ($t(373) = -2.04$, $p = .04$). There were no other differences between any of the trajectory classes in proportion of males, child race, or family income (all $p > .18$), suggesting distinct patterns of neurocognitive development are not related to these demographic characteristics in our sample.

Chi-square tests were used to examine overlap of the neurocognitive trajectory classes. In the control sample, the trajectory classes for response inhibition and VWM did not overlap at rates greater than expected by chance ($p = .27$). In the ADHD sample, delayed reward discounting and VWM classes did not overlap at rates greater than expected by chance ($p = .17$). Children with ADHD in the impaired response inhibition trajectory class were marginally more likely to be in the impaired delayed reward discounting class (69% of children with impaired response inhibition were also in the impaired delayed reward discounting group, $p = .054$) and were significantly more like to be in the persistently impaired VWM class (74% of those with response inhibition impairment were in also in the persistently impaired VWM class, $p < .001$).

Differences in ADHD Symptom Change between Neurocognitive Classes

LCM symptom trajectories for parent and teacher reports are shown in Figure 3. Overall, both reporters indicated similar patterns of symptom change. Consistent with diagnosis, children with ADHD exhibited greater symptoms of hyperactivity-impulsivity (group difference= 5.75 symptoms for parent report and 4.38 for teacher report, all $p < .001$) and inattention (group difference = 6.83 symptoms for parent report and 5.44 for teacher report, all $p < .001$) at age 7 than their typically-developing peers. There was a significant decline in both inattention and hyperactivity-impulsivity for children with ADHD across the age range examined (parents report: −.16 symptoms per year for inattention and −.61 symptoms per year for hyperactivity-impulsivity; teacher report: −.46 symptoms per year for inattention and −.58 symptoms per year for hyperactivity-impulsivity). Within the ADHD group, baseline symptom severity at age 7 was not associated with rate of symptom change over time (covariance = −.33, $p = .14$ for parent report and covariance = .01, p = .98 for teacher report of hyperactivity-impulsivity; covariance = .04, $p = .80$ for parent report and −.01, $p = .97$ for teacher report of inattention).

Scores for baseline symptom severity (intercept) and change in symptoms (slope) in the ADHD children were compared between neurocognitive latent trajectory classes. Intercept and slope values for each of the ADHD neurocognitive trajectory classes are summarized in Table 3. (Note that similar analyses were not conducted for non-ADHD neurocognitive classes due to floor effects on symptoms.)

Response inhibition—The response inhibition classes did not differ from one another in parent reported baseline symptom severity (all $p > .10$) or parent reported slope of symptom change for either symptom domain (all $p > .29$). The classes also did not differ in teacher-reported baseline symptom severity for either domain (all $p > .10$) or in teacher reported slope of hyperactivity-impulsivity symptom change ($p = .30$). However, teacher report

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indicated that the "ADHD: Unimpaired" response inhibition class had more rapid decrease in inattention symptoms than the "ADHD: Impaired" class (slope difference: $t(430) = -2.14$, $p = .03$).

VWM—VWM classes did not differ in baseline hyperactivity-impulsivity symptoms, as reported by either parents or teachers (all $p > .05$). There were also no differences between classes in either parent or teacher reported change in hyperactivity-impulsivity symptoms (all $p > .44$).

Differences between classes were identified for inattention symptom change. The "ADHD: stably impaired" VWM class had significantly higher baseline inattention symptoms than the "ADHD: impaired, recovering" VWM class based on both parent and teacher report. "ADHD: stably impaired" VWM group also had higher baseline inattention symptoms than the "ADHD: high VWM" class based on teacher report. Regarding rates of symptom change, both parent and teacher report indicated that the "ADHD: stably impaired" VWM class had less improvement in inattention symptoms than the "ADHD: impaired, recovering" VWM class (slope difference: $t(383) = -2.22$, $p = .03$ for parent report and $t(375) = -2.63$, $p = .01$ for teacher report) or the "ADHD: high VWM" class (slope difference: $t(314) = 2.02$, $p = .04$ for parent report and slope difference: $t(309) = 1.97$, $p = .049$ for teacher report). The "ADHD: high VWM" and "ADHD: impaired, recovering" ADHD classes did not reliably differ from one another (slope difference: $t(203) = .26$, $p = .80$ for parent report and slope difference: $t(200) = -.11$, $p = .92$ for teacher report). Despite improvement in inattention symptoms, all of the ADHD VWM classes continued to have more symptoms of inattention than controls at age 13 (all $p < .001$).

Delayed reward valuation—The ADHD delayed reward valuation classes did not differ from one another in either baseline symptom severity or slope of change for either symptom domain, as reported by parents (all $p > .90$) or teachers (all $p > .08$).

Discussion

Neurocognitive endophenotypes for ADHD are considered extremely important to understanding the disorder (Gottesman & Gould, 2003; Insel et al., 2010; Kendler & Neale, 2010; Sonuga-Barke & Halperin, 2010), yet resolving their role has been difficult, in part, because their association with developmental change has been unclear. Clarifying this particular question for three leading candidate endophenotypes for ADHD was a key goal of the present study. Whereas developmental change in response inhibition and delayed reward valuation were unrelated to ADHD symptom changes, development of VWM was related to improvement in symptoms of inattention across early and middle childhood as confirmed in both parent and teacher reports. Consistent with research suggesting that neurocognitive impairments correlate more strongly with inattention than hyperactivity-impulsivity symptoms (Martel, Nikolas, & Nigg, 2007; Nigg, Stavro, et al., 2005), relationships between neurocognitive development and change in hyperactivity-impulsivity did not reach statistical significance. As children age, their clinical impairment is driven more heavily by symptoms of inattention than of hyperactivity-impulsivity (Willcutt et al., 2012); so the implications of current findings for clinical recovery are notable.

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Findings here are partly consistent with Halperin and Schultz's (2006) neurodevelopmental model of ADHD, which suggests that development in prefrontally-mediated executive functions contributes to symptom recovery by compensating for other, persistent impairments in subcortically-mediated processes. VWM normalization, which is associated with improving top-down control mediated by the dorsal lateral prefrontal cortex (Arnsten, 2009; Arnsten & Rubia, 2012), was observed for a subgroup of children with ADHD and was related to ADHD symptom improvement. In contrast, for children with impaired delayed reward discounting, which is thought to be relatively more reliant on subcortical reward networks (Arnsten & Rubia, 2012; Dias et al., 2013), there was no evidence of normalization and no relationship between changes in delayed reward discounting and symptom change. While we did not report neuroimaging data here, the pattern of results would potentially fit with a persistent alteration in basal ganglia/mid-brain dopamine reward valuation systems that are independent of symptom change, and thus may function as a liability marker, with compensation by prefrontally-mediated improvements in working memory as children age.

The picture is not quite so simple, however. While VWM improvements may contribute to symptom remission for some children and impaired delay discounting may operate as a liability marker for some children, these groups did not overlap at rates greater than chance, which does not support the hypothesis that the development in top-down control compensates for subcortically mediated impairments in this disorder. In addition, the recovering VWM class and those who already had high VWM at age 7 showed similar patterns of symptom remission over time. Further, the recovering ADHD cognitive subgroup did *not* fully normalized on inattention symptoms, despite performing nearly identically to normally developing controls on VWM by age 13. Taken together, VWM development as measured here contributed to but was not fully sufficient to explain symptom recovery.

Response inhibition partially normalized for those with initial impairment, but this normalization was not related to symptom change in ADHD. Instead, those who were unimpaired at baseline, showed some evidence of greater symptom improvement that those with initial impairment (although this was not consistent across parent and teacher reports). The patterns observed are not consistent with either liability or cognitive maturational accounts of its role in ADHD. Although often seen as a top down operation, response inhibition has a somewhat distinct neural implementation from that for working memory, with more involvement of inferior prefrontal rather than dorsolateral prefrontal cortical regions. Response inhibition may also have age dependent neuroimaging correlates, with basal ganglia activation playing a more prominent role for children than adults (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). The pattern of results suggests the hypothesis that symptom improvement relies on specific aspects of working memory but not top-down processes globally.

Impairment on response inhibition was also associated with having impairment on at least one other measure, suggesting it may simply be related to an overall more impaired neurocognitive profile in our sample. However, results in our sample are not reducible to a simple distinction between cognitively impaired and unimpaired ADHD groups. For example, as noted, impaired VWM and delay discounting trajectories did not overlap at rates

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greater than expected by chance. Overall, results are consistent with prior studies suggesting that distinct neurocognitive deficits may characterize different subgroups of children in ADHD (Karalunas & Huang-Pollock, 2011; Solanto et al., 2001; Sonuga-Barke, Bitsakou, & Thompson, 2010; Thorell, 2007), and further support the need to differentiate the roles of distinct aspects of neurocognitive functioning in understanding symptom change (Karalunas et al., 2016; Lee et al., 2013; Miyake et al., 2000).

Crucially, understanding the role of these neurocognitive phenotypes depends heavily on recognizing heterogeneity in development of ADHD symptoms and cognition. In the worst case, group level analyses yield an average result that does not correspond to any children in the sample. In the case of VWM, what appeared to be persistent, worsening impairment in the ADHD group as a whole was in fact driven by a subset of 50% of the ADHD group who remained impaired over time. The group data concealed the 30% of the ADHD children who had equally severe baseline VWM impairments, but showed accelerated development of VWM, such that abilities essentially normalized by age 13— and whose ADHD symptoms also improved. Failure to consider within-group heterogeneity would have resulted in incorrect conclusions about the relationship between VWM and ADHD symptoms over time.

Further, because both persistently impaired and recovering VWM groups had similar baseline VWM scores, the pattern of symptom recovery was not predictable from baseline functioning alone. This finding highlights the need for repeated assessment over time to evaluate change in cognitive effects with development. Determination of the importance of VWM in ADHD from cross sectional data must be qualified by careful consideration of children's age. In the present study, while a relatively large number of children with ADHD were impaired on VWM tasks at age 7, the proportion of children with impairment decreased as they developed. This is consistent with cross-sectional meta-analytic findings that ADHD effect sizes on working memory tasks decrease as children get older (Kasper et al., 2012). It suggests that a somewhat greater proportion of individuals with ADHD than previously thought may have impairments in working memory at some point in development, although a large group of children who are cognitively unimpaired also exists.

Group-level analysis of delayed reward discounting appeared to fit with the cognitive maturation hypothesis in which children with ADHD normalized over time. However, consideration of subgroups again modified the interpretation. In particular, apparent normalization between ages 7–11 years was driven by around 40% of children with ADHD who had normal baseline responses and rapid growth such that they actually had better delay tolerance than non-ADHD controls at age 13. A second group of around 60% of children with ADHD had baseline impairment in delayed reward discounting and remained impaired relative to non-ADHD controls at age 13 years. Both groups had similar rates of symptom improvement. Once again, the group average failed to accurately describe development for either subgroup of children.

The delay discounting trajectories also stood out from the other tasks in that performance plateaued for controls and one of the ADHD groups, and actually worsened for the other ADHD group, as children approached adolescence. Similar tasks as the one used here are

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frequently administered to adults, so the plateau is unlikely to reflect ceiling effects on this task. The pattern of worsening delayed reward discounting during adolescence is consistent with prior research that has similarly found that adolescents are more sensitive to reward cues than either children or adults (Cauffman et al., 2010; Figner, Mackinlay, Wilkening, & Weber, 2009).

Neurodevelopmental theory and data point to nonlinear development of reward response functions. Normatively, adolescents undergo rapid development of limbic systems (e.g., ventral striatum, amygdala) relative to prefrontal systems, resulting in increased salience of and responsivity to appetitive reward cues (Somerville, Jones, & Casey, 2010; Van Leijenhorst et al., 2010). This is supported by neuroimaging work demonstrating that adolescents have increased nucleus accumbens activity during reward tasks than either younger children or adults (Galvan et al., 2006). The pattern seen here seems to fit that picture. As the children in our sample continue into adolescence, we hypothesize that all groups would show some worsening in delayed reward tolerance during adolescence followed by improvement as they near adulthood. Our study is the first to longitudinally document this non-linear pattern for children with ADHD. Interestingly, pubertal changes have been strongly associated with this worsening of delayed reward discounting and examining these effects in relation to pubertal change may inform understanding of the non-linear trajectory (Steinberg, 2007). This is a future direction in our work.

Although heterogeneity within clinical diagnostic categories is now a major focus of psychopathology research, less attention has focused on heterogeneity in typically-developing populations. Current results, however, point to important variability in neurocognitive development for typically-developing children as well. In the case of response inhibition, similar subgroups were observed in both the ADHD and typically-developing samples, and the trajectories of neurocognitive change for impaired and unimpaired subgroups were similar regardless of diagnostic status. ADHD-related impairments in response inhibition appear to reflect a *quantitative* difference in the proportion of children on each developmental trajectory, but not a qualitative departure from normal developmental patterns. In contrast, *qualitatively* distinct trajectories were observed for VWM development in ADHD and non-ADHD children. This qualitative deviation from typical development may partially explain why VWM development predicts symptom change.

Limitations

Several limitations of the current work and areas for follow-up are notable. Working memory is viewed differently by different theorists. One model suggests that it has different components, such as the ability to hold multiple things in mind at once (maintenance), while mentally manipulating one or more of them (updating) (Baddeley, 2012). Other models suggest that there is short term memory and executive attention (Kane, Bleckley, Conway, & Engle, 2001; Unsworth & Engle, 2007). While the backward spatial span task probably requires some degree of executive attention, from the perspective of both Kane and Engle's and Baddeley's models it probably reflects only part of the complement of working memory functions (e.g., maintenance more than updating). It will be important in future work to

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clarify the importance of measures of updating, as well as more advanced executive attention tasks in which two competing tasks are performed at the same time. This is a future direction for our work as well.

The overall ADHD effect for response inhibition in our sample was consistent in magnitude with recent meta-analysis (d~ 0.50, Lipszyc & Schachar, 2010), but this effect was driven by a relatively small proportion of the ADHD sample. The relatively small size of this subgroup may have limited power to detect associations with symptom change for response inhibition. That said, the pattern for teacher reported symptoms in which ADHD children without initial impairment in response inhibition showed faster recovery than those who were impaired at baseline (despite the latter group showing more rapid improvement in response inhibition) does not align with either liability or maturational accounts.

We also used single indicators instead of latent variables to model change in neurocognition over time. While not without limitations (Willoughby, Holochwost, Blanton, & Blair, 2014), latent variable approaches provide important advantages, including improving measurement reliability and, potentially, isolating the executive processes of interest. We lacked the necessary data to consider such an approach here and it may be a valuable future direction as well.

By design, the ADHD and control samples differed in gender distribution here as they do in the population. While we did not examine development in boys and girls separately, sex of child was not related to the intercept or slope for any of the neurocognitive processes investigated; however, detailed consideration of sex differences will be important in future work.

Finally, while our study demonstrates the critical importance of neurocognitive heterogeneity and suggests and possible role for working memory development in ADHD symptom recovery, it does not directly test causal relationships. Future work examining potential third variables that may account for both reduced working memory growth and symptom persistence, as well as models that specifically differentiate between- and within-person associations over time may be useful for clarifying the likelihood that working memory trajectories or other cognitive processes play a causal role in ADHD symptom change. This is particularly needed given the growing efforts towards development of non-pharmacological cognitive interventions for treatment of ADHD, which are thus far unconvincing with respect to effects on core ADHD symptoms (Sonuga-Barke, Brandeis, Holtmann, & Cortese, 2014) perhaps because they do not target the best mechanism or the best age period.

Summary

Identifying developmentally-informed neurocognitive phenotypes can help clarify which neuropsychological measures are markers of ADHD liability (stable even when symptoms improve) and which may be candidate mechanisms related to clinical course. This was one of the largest studies to feature repeated measurement over time of three much-studied neurocognitive measures associated with ADHD. Here, it was striking that a pattern of recovery of VWM was associated with greater recovery (but not normalization) on

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inattention symptoms. Because these are the symptoms that primarily drive impairment in ADHD when they persist, the result suggests an important target for further study and intervention development. In contrast, impaired delayed reward discounting appeared to be a feature of many children with ADHD regardless of recovery, and recovery of response inhibition was not informative with regard to ADHD course. Findings demonstrate how consideration of neurocognitive heterogeneity may enable future risk prediction and treatment matching.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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General Scientific Summary

This study suggests that substantial variability in cognitive development exists for children both with and without ADHD. For children with ADHD, specifically, development of some cognitive processes, such as working memory maintenance, may be particularly informative for understanding how symptoms change during childhood.

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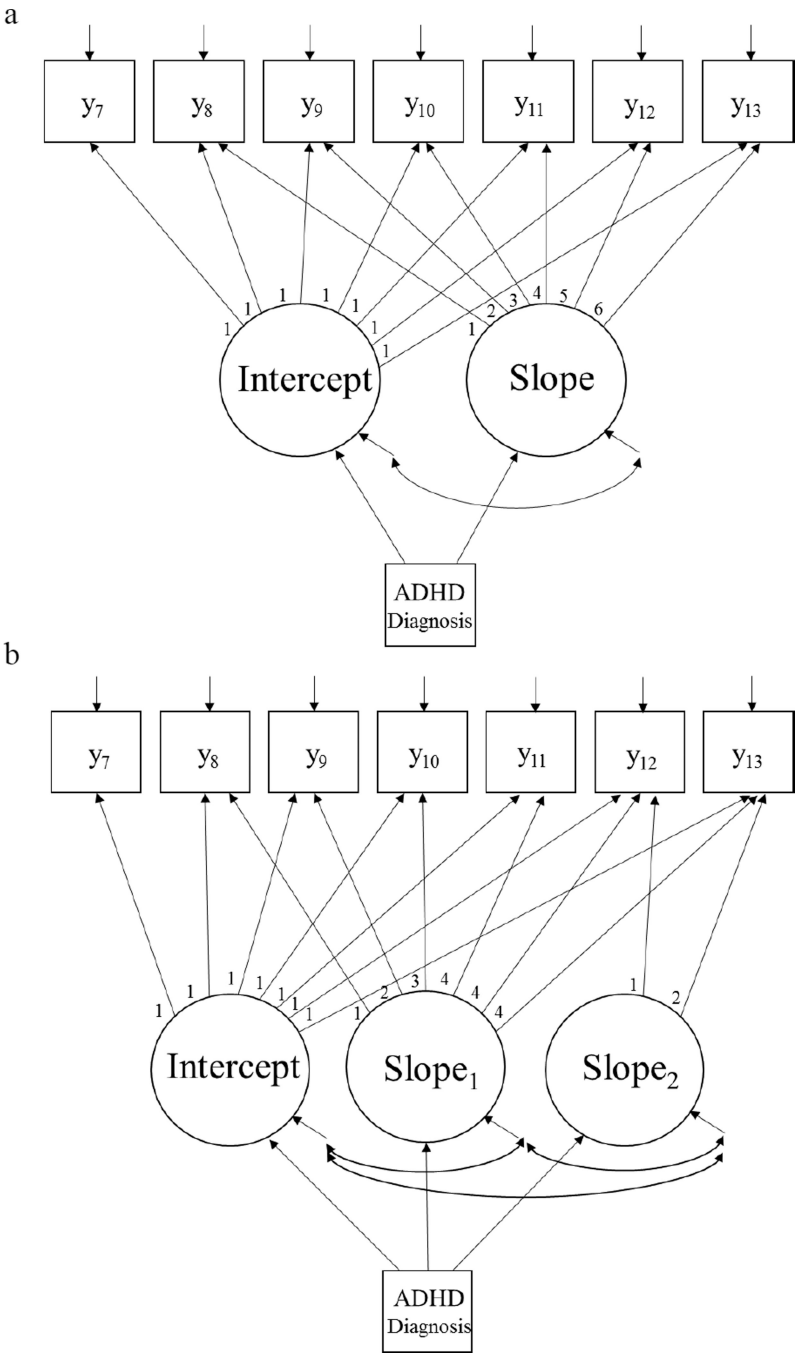

Figure 1.

Visual depiction of the conditional latent growth curve models used to examine change in stop signal reaction time, working memory, hyperactivity-impulsivity, and inattention (1a) and delay reward valuation (1b).

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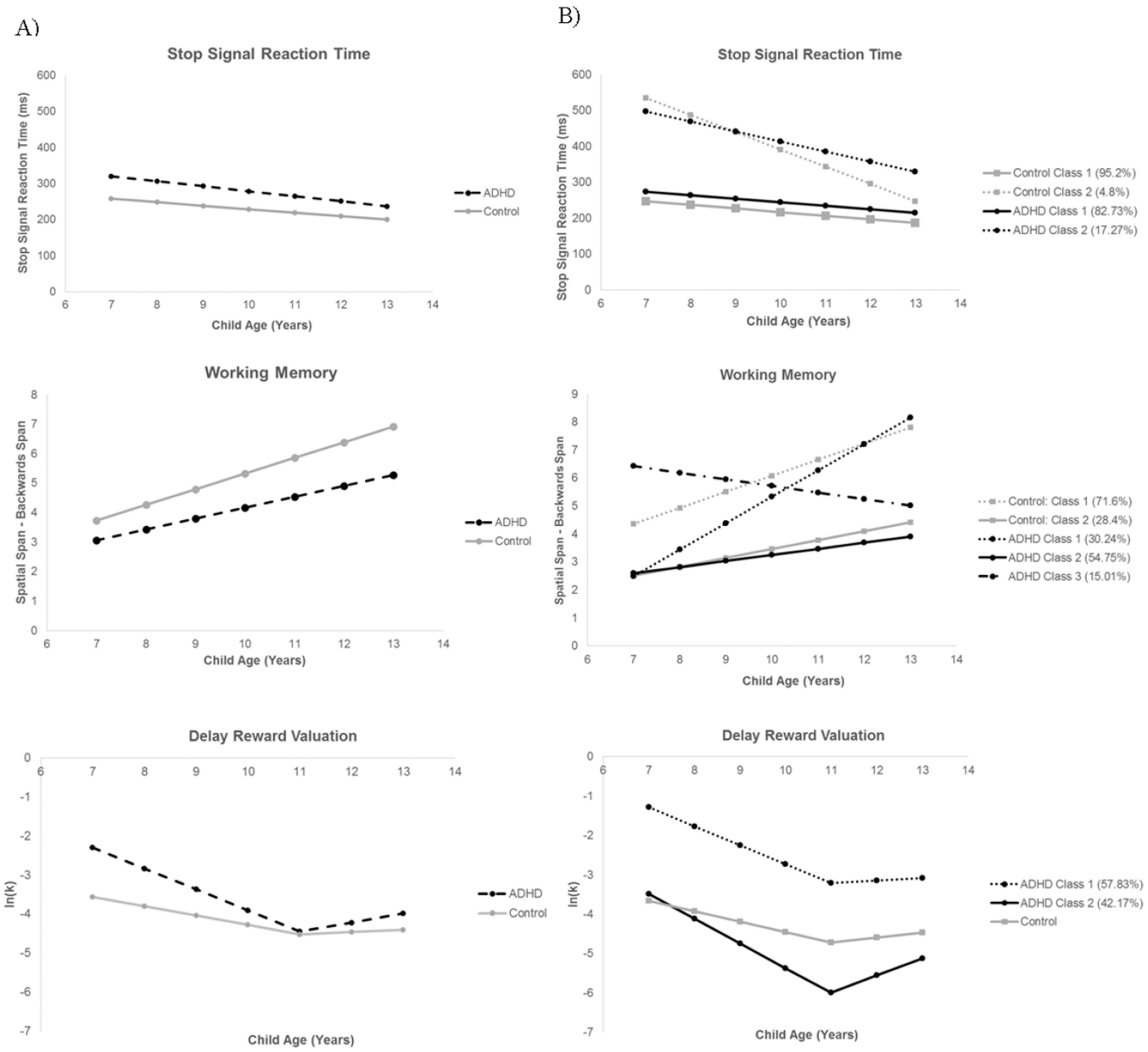

Figure 2.

Trajectories of neurocognitive development for children with and without ADHD. Panel A shows the group level trajectories based on the latent growth curve models (LCMs) and Panel B shows the subgroup trajectories based on the latent class growth analysis models (LCGAs).

Note. For the WMM panel, higher values indicate better performance. For both stop signal reaction time and delay reward discounting, lower values are associated with better performance.

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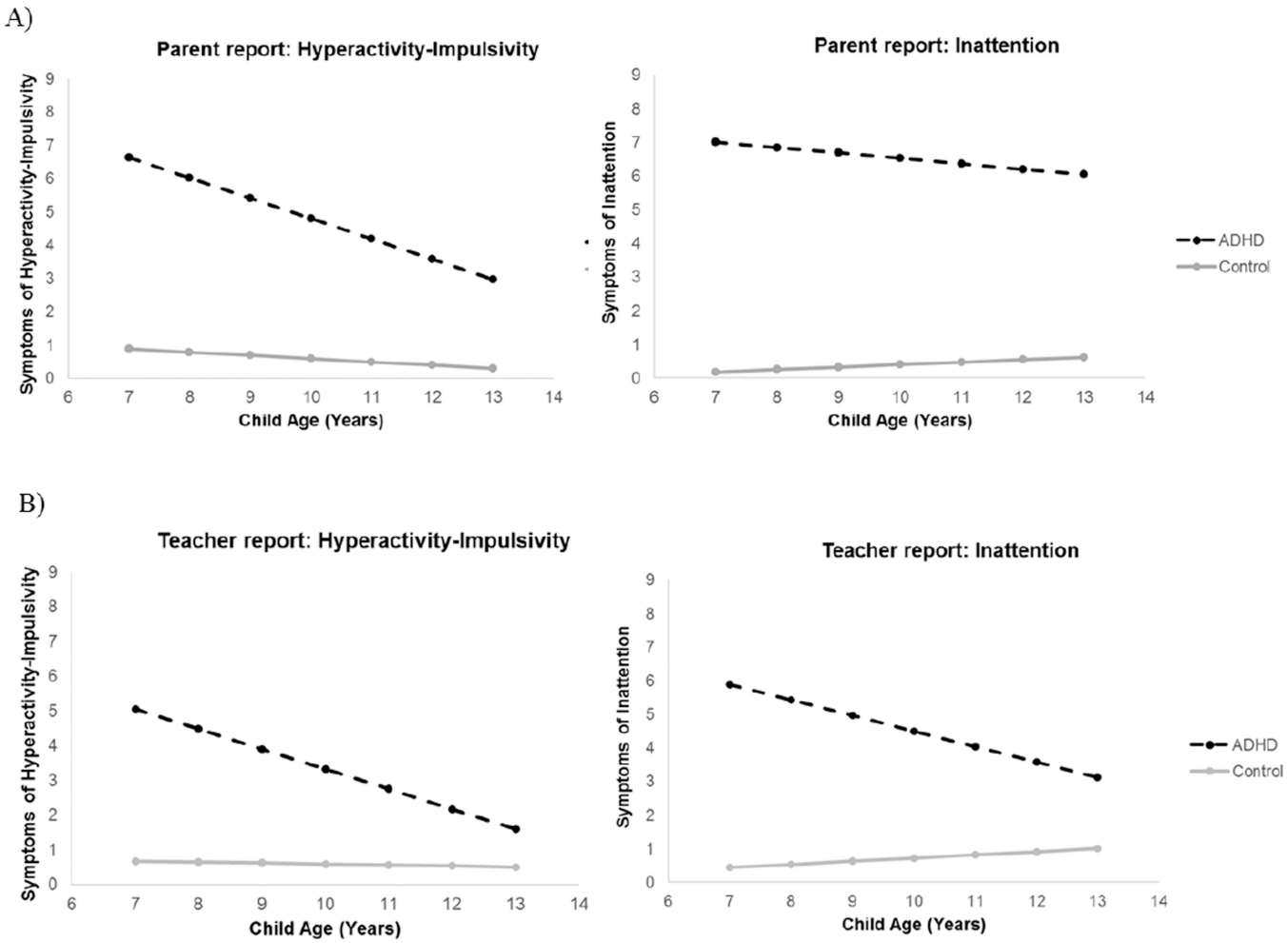

Figure 3.

Symptom trajectories for ADHD and typically-developing children based on latent growth curve models for A) parent report and B) teacher report.

Note: A linear model provided the best fit for trajectories of hyperactivity-impulsivity (parent report: χ^2 (33) = 88.75 p = .00, CFI = .96, TLI = .96, RMSEA = .05; teacher report: χ^2 (35) = 86.13 p = .00, CFI = .93, TLI = .92, RMSEA = .05) and inattention symptoms (parent report: χ^2 (33) = 35.14, p = .37, CFI = 1.00, TLI = 1.00, RMSEA = .01; teacher report: χ^2 (33) = 54.31, p = .01, CFI = .98, TLI = .97, RMSEA = .03).

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Table 1

Demographic Information for the ADHD and Control Groups

	ADHD (n = 437)	Control (n = 297)	
	M(SD) or %	M(SD) or %	
Child age at baseline	9.65 (1.52)	9.40 (1.60)	$t = -2.16$, $p = .03$
IQ	108.12 (13.98)	115.65 (12.18)	$t = 7.42$, $p < .001$
Child Sex (% male)	70.02%	49.46%	$\chi^2(1) = 31.04$, $p < .001$
Subtype (% H, I, C)	2.6%, 26.2%, 71.2%	---	
Annual Income			
Less than $25,000	10.96%	3.91%	
$25,000–$34,999	6.76%	6.25%	
$35,000–$49,999	12.59%	9.38%	
$50,000–$74,999	20.97%	21.09%	
$75,000–$99,999	20.97%	25.78%	
$100,000–$129,999	13.99%	17.19%	
$130,000–$149,999	5.36%	7.42%	
Higher than $150,000	8.39%	8.98%	$\chi^2(7) = 15.00$, $p = .04$
Race (% non-White or Hispanic)	20.3%	12.6%	$\chi^2(1) = 2.72$, $p = .10$
Baseline Comorbidities			
Mood Disorder	1.10%	0%	$\chi^2(1) = 3.07$, $p = .08$
Anxiety Disorder	19.82%	7.58%	$\chi^2(1) = 20.02$, $p < .001$
CD/ODD	18.28%	0.72%	$\chi^2(1) = 51.62$, $p < .001$
Baseline Symptoms (T scores)			
Parent Conner's – Hyp-Imp	71.62 (14.95)	47.14 (8.02)	$t = -25.12$, $p < .001$
Parent Conner's - Inattention	74.34 (11.52)	7.11 (11.52)	$t = -35.83$, $p < .001$
Teacher Conner's – Hyp-Imp	67.09 (10.83)	45.97 (6.69)	$t = -28.73$, $p < .001$
Teacher Conner's - Inattention	68.78 (15.88)	47.03 (6.60)	$t = -21.30$, $p < .001$

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Table 2

Results from conditional latent growth curve models (LCMs) for the neurocognitive measures

	Stop Signal Reaction Time		Working Memory		Delayed Reward Valuation	
	Estimate	**SE**	**Estimate**	**SE**	**Estimate**	**SE**
Intercept	257.37**	8.28	3.74**	.17	−3.56**	.29
Slope 1	−9.57**	2.12	.53**	.06	−.24**	.09
Slope 2	--	--	--	--	.06	.18
Direct Effects						
ADHD diagnosis → Intercept	62.85**	13.18	−.68**	.23	1.27**	.43
ADHD diagnosis → Slope 1	−4.34	3.26	−.16*	.07	−.30*	.14
ADHD diagnosis → Slope 2	--	--	--	--	.17	.23
Covariances						
Intercept with Slope 1	−829.28	758.53	.02	.21	−1.07	.75
Intercept with Slope 2	--	--	--	--	.80	3.37
Slope 1 with Slope 2	--	--	--	--	−.46	.85
χ^2 (df), *p* value	30.90 (28), *p* = .32		26.07 (28), *p* = .57		0 (23), *p* = 1.00	
CFI	.99		1.00		1.00	
TLI	.99		1.00		1.00	
RMSEA	.01		.00		.00	

Note:

* p < .05,

** p < .01.

ADHD diagnosis: 0 = control, 1 = ADHD; Child Sex: 0 = male, 1 = female.

Estimates presented here are unstandardized. All fit indices reveal good fitting models. Models for working memory and delayed reward valuation have “perfect” fit because the chi-square value is less than the model df.

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Table 3

Results of best-fitting LCGAs in the ADHD sample

Measure	**Stop Signal Reaction Time**				**Working Memory**						**Delayed Reward Valuation**			
Class	**Class 1**		**Class 2**		**Class 1**		**Class 2**		**Class 3**		**Class 1**		**Class 2**	
Class Label	**Unimpaired (*n* = 364)**		**Impaired (*n* = 76)**		**Impaired & Recovering (n=137)**		**Stably Impaired (*n*=248)**		**High Working Memory (n=68)**		**Impaired (*n* = 229)**		**Unimpaired (*n* = 167)**	
Parameter	Est	SE	Est	SE	Est	SE	Est	SE	Est	SE	Est	SE	Est	SE
Intercept	273.3**	14.6	497.5**	32.4	2.5**	0.6	2.6**	0.4	6.4**	0.5	−1.29*	0.65	−3.49**	0.72
Slope 1	−9.77**	3.3	−27.9**	7.7	0.9**	0.2	0.2	0.1	−0.2	0.2	−0.48**	0.16	−0.62**	0.17
Slope 2	--	--	--	--	--	--	--	--	--	--	0.07	0.21	0.44*	0.21
Direct Effects														
Sex → Intercept	−14.1	18.6	−14.1	18.6	−1.2**	0.3	−1.2**	0.31	−1.15**	0.31	--	--	--	--
Sex → Slope	1.8	4.1	0.7	4.1	0.4**	0.1	0.4**	0.10	0.35**	0.10	--	--	--	--
Medication → Intercept	1.6	17.3	1.6	17.3	0.03	0.3	0.03	0.3	0.03	0.30	--	--	--	--
Medication → Slope	0.7	3.9	1.8	3.9	−0.1	0.1	−0.1	0.1	−0.1	0.1	--	--	--	--
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Intercept Parent Hyp-Imp	6.37	1.86	6.66	1.71	6.47	1.75	6.52	1.78	6.06	2.19	6.40	1.90	6.41	1.80
Slope Parent Hyp-Imp	−0.59	0.19	−0.57	0.14	−0.58	0.19	−0.58	0.17	−0.60	0.18	−0.59	0.17	−0.59	0.19
Intercept Parent Int	7.05	1.21	7.28	1.01	6.91	1.27	7.24	1.03	6.95	1.38	7.05	1.20	7.06	1.18
Slope of Parent Int	−0.20	0.13	−0.18	0.12	−0.21	0.12	−0.18	0.12	−0.22	0.13	−0.20	0.13	−0.20	0.13
Intercept Teacher Hyp-Imp	4.67	1.17	4.85	0.99	4.70	1.12	4.74	1.10	4.54	1.27	4.66	1.17	4.72	1.15
Slope Teacher Hyp-Imp	−0.53	0.13	−0.51	0.12	−0.53	0.14	−0.52	0.13	−0.53	0.11	−0.52	0.12	−0.52	0.14
Intercept Teacher Int	5.62	1.02	5.80	1.07	5.54	0.88	5.77	1.08	5.43	1.06	5.66	1.05	5.54	1.03
Slope Teacher Int	−0.46	0.04	−0.45	0.04	−0.46	0.04	−0.45	0.04	−0.46	0.03	−0.45	0.04	−0.46	0.04
% male	70.1%		68.4%		69.8%		69.8%		67.7%		68.1%		70.7%	
% on meds	55.0%		64.5%		57.2%		59.7%		58.4%		55.0%		59.3%	

Note:

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* $p < .05$,

** $p < .01$.

Child Sex: 0 = male, 1 = female. Child Medication History: 0= no history of medication, 1= positive history of medication.

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Table 4

Results of best-fitting LCGAs in Typically-Developing sample

	Stop Signal Reaction Time				Working Memory			
	Class 1		Class 2		Class 1		Class 2	
	Normally Developing (*n* = 257)		Impaired (*n* = 13)		Normally Developing (*n* = 197)		Impaired (*n* = 78)	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	247.0**	9.3	535.8**	51.9	4.4**	0.3	2.5**	0.5
Slope	−10.0**	2.5	−48.0**	10.5	.6**	0.07	0.3*	0.1
Direct Effects								
Child Sex → Intercept	−16.5	14.6	−16.5	14.6	0.1	0.4	0.1	0.4
Child Sex → Slope	6.2	4.0	6.2	4.0	0.0	0.1	0.0	0.1
% male	51.0%		46.2%		51.8%		42.3%	

Note:

* $p < .05$,

** $p < .01$.

Child Sex: 0 = male, 1 = female.

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Table 5

Fit statistics for selection of LCGA models

	Stop Signal Reaction Time				Working Memory				Delayed Reward Valuation			
	ADHD		Controls		ADHD		Controls		ADHD		Controls	
	BIC	VLMR LRT *p value*	BIC	VLMR LRT *p value*	BIC	VLMR LRT *p value*	BIC	VLMR LRT *p value*	BIC	VLMR LRT *p value*	BIC	VLMR LRT *p value*
1 Class	10719.85	--	6158.07	--	4111.08	--	2519.68	--	3368.04	--	2090.30	--
2 Classes	10620.92	< .001	6141.99	< .001	4052.50	0.15	2485.12	0.00	3353.47	0.04	2069.40	0.37
3 Classes	10621.34	0.28	6146.82	0.11	4049.36	0.00	2492.12	0.28	3341.56	0.05	2053.78	0.12
4 Classes	10621.58	0.12	6154.83	0.05	4060.53	0.42	2503.96	0.28	3349.96	0.43	2057.73	0.08

Note: BIC = Bayesian information criterion, VLMR LRT = Vuong-Lo-Mendell-Rubin likelihood ratio test for the k vs. k - 1 class.

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