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By

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A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Psychology in the Graduate Division of the University of California, Berkeley

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Abstract

Executive Functions in Young Adult Females with and without ADHD: Longitudinal Development and Associations with Impairment

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Attention-deficit/hyperactivity disorder (ADHD) is a male predominant neurodevelopmental disorder, with the unfortunate consequence that boys and men constitute the focus of the bulk of the extant research (Gaub & Carlson, 1997; Hinshaw & Blachman, 2005). Many studies include entirely male samples; others include too few females to conduct meaningful analyses within all-female subsamples. Thus, very little research has focused specifically on girls with this disorder, particularly with respect to neuropsychological variables. It is important to understand these topics in females, including specific neuropsychological mechanisms underlying both typical and atypical development, in order to determine core underlying mechanisms as well as to guide diagnostic and treatment-development efforts. In the present study, I utilized data from a longitudinal study of girls with and without ADHD. This investigation of a large, well-characterized, and diverse female sample currently consists of data from three time points, the first collected in childhood (ages 6-12); the second collected during adolescence (ages 12-18); and the third collected during late adolescence/young adulthood (ages 17-25). This investigation had three main aims: (1) to determine whether girls with and without childhood-defined ADHD show improvements in neuropsychological functioning over time (from childhood to adolescence to young adulthood) and whether the developmental trajectory is different for girls with ADHD versus comparison girls; (2) to assess differences in neuropsychological functioning in those whose ADHD symptoms have persisted into young adulthood versus those whose ADHD symptoms have remitted; and (3) to determine whether neuropsychological performance in adolescence mediates associations between childhood ADHD symptoms and young adult functional outcomes. Results indicated that individuals with childhood-diagnosed ADHD – who had the greatest EF impairments in childhood – showed the greatest improvement from childhood to adolescence to young adulthood relative to comparisons on some measures of EF, but similar or slower rates of development on others, controlling for key baseline comorbidities. The ability of ADHD persistent-remitted status to predict change in EF abilities was lacking, and there was no evidence of any association between improvement in EF abilities and remitted ADHD status. Mediation analyses indicated that adolescent EF mediated associations between ADHD symptoms and young adult academic achievement abilities, but no other outcomes. Such findings suggest the potential importance of EF abilities as a treatment target in ADHD in order to prevent academic difficulties.
Executive Functions in Young Adult Females with and without ADHD: Longitudinal Development and Associations with Impairment

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neurodevelopmental disorder characterized by developmentally extreme levels of (a) inattention-disorganization and/or (b) hyperactivity-impulsivity (American Psychiatric Association, 2000). Neuropsychological deficits are common in individuals with ADHD, particularly those abilities that fall within the executive function (EF) domain (e.g., Berlin, Bohlin, & Rydell, 2003; Scheres et al., 2004; Thorell, 2007). EF is generally conceptualized as an umbrella term that involves the ability to “effortfully guide behavior toward a goal” (Banich, 2009, p. 89) and encompasses skills such as planning, organization, response inhibition, sustained attention, set shifting, working memory, and reasoning. Performance of these abilities relies on the prefrontal cortex (PFC) and its extensive interconnections with other brain regions (Tranel, Anderson, & Benton, 1994). There is some debate over exactly which abilities constitute the EF construct, and more recent cognitive neuroscience terms encompassing similar skills have emerged (i.e., “cognitive control”). Regardless, deficits in abilities generally thought to be components of the EF construct have been found consistently across multiple studies of children and adolescents with ADHD (e.g., Hinshaw, Carte, Fan, Jassy, & Owens, 2007; Hinshaw, Carte, Sami, Treuting, & Zupan, 2002; Rapport, Alderson, Kofler, Sarver, Bolden, & Sims, 2008; Re, De Franchis, & Cornoldi, 2010; for a review, see Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). EF deficits have also been documented in adults with ADHD (e.g., Miller, Ho, & Hinshaw, 2012; Rohlf et al., 2011; for a review, see Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005), but far less research has focused on adults with this disorder.

Multiple theories have attempted to characterize the nature of EF deficits in individuals with ADHD, and the literature reflects the variable profile of EF impairment in ADHD. Many have pinpointed dysfunction in the PFC as being central to the development of EF deficits in ADHD and/or symptoms related to the ADHD syndrome (Barkley, 1997; Benson, 1991; Pennington & Ozonoff, 1996). Alternatively, others have posited that ADHD results primarily from noncortical dysfunction (e.g., in subcortical regions related to attention and impulsivity), and that prefrontally-mediated mechanisms account for ADHD symptom reduction and improvements in EF across development (Halperin & Schulz, 2006). Although the exact mechanisms by which EF deficits develop and/or improve over time are unclear, having intact EF abilities appears important for success across multiple domains of functioning, including academic, social, and global (Biederman et al., 2004; Miller & Hinshaw, 2010; Miller, Nevada, & Hinshaw, 2012b). Still, there is a dearth of knowledge about EF deficits in females with ADHD, particularly with regard to developmental trajectories and associations between EF problems and change in ADHD status over time.

At the outset, I note that EF deficits are not specific to ADHD but rather are common to a range of neurodevelopmental disorders including autism spectrum disorders, conduct disorder, and Tourette syndrome (Pennington & Ozonoff, 1996; Willeutt, Doyle, Nigg, Faraone, & Pennington, 2005), among others. Additionally, EF deficits are not found in all individuals with ADHD but may instead characterize subgroups of this population. However, in those youth with ADHD who display clear EF impairments, these deficits appear to persist through adolescence (Fischer, Barkley, Smallish, & Fletcher, 2005; Hinshaw et al., 2007) and into young adulthood (Miller et al., 2012a), with linkages to difficulties in other life domains (Miller & Hinshaw, 2010; Miller et al., 2012b).
Many recent investigations have shown that EF deficits are salient in at least a subgroup of individuals with ADHD (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005; Hinshaw et al., 2002; Hinshaw et al., 2007; Miller et al., 2012a; Nigg et al., 2002; Seidman, Valera, & Makris, 2005; Seidman et al., 2006; Willcutt et al., 2005), although patterns of impairment tend to vary across studies. EF abilities have been linked to the successful performance of a wide range of tasks, including academic performance as well as social/interpersonal skills, across a range of populations including ADHD, autism spectrum disorders, and typically developing individuals (Biederman et al., 2004; Clark, Prior, & Kinsella, 2002; Clark, Pritchard, & Woodward, 2010; McEvoy, Rogers, & Pennington, 1992; Miller & Hinshaw, 2010). However, little is known about these long-term prospective associations in females with ADHD.

Children with ADHD who exhibit EF deficits are likely to require intensive academic intervention in order to prevent academic failure or school dropout (Barry, Lyman, & Klinger, 2002; Biederman et al., 2004; Massetti et al., 2007). Examination of EF-academic achievement associations at a 5-year follow-up, into adolescence, of an all female sample (the one investigated in the current study) indicated that lower EF scores in childhood predicted lower academic achievement scores in adolescence across the entire sample, regardless of diagnostic group (Miller & Hinshaw, 2010). A recent examination of associations between childhood EF and young adult academic achievement in this same sample revealed similar results, indicating that childhood EF – particularly measures of global EF and working memory – continued to predict academic achievement in young adulthood (Miller et al., 2012b). Additionally, diagnostic status (ADHD versus comparison) moderated the association between (a) working memory and reading achievement and (b) a measure of global EF and suspensions/expulsions. That is, in the ADHD group but not the comparison group, low working memory scores predicted poor reading scores in young adulthood, and low global EF scores predicted a higher number of suspensions/expulsions (Miller et al., 2012b).

As for social functioning, some studies have found linkages between EF skills and social abilities (Clark et al., 2002; Diamantopoulou et al., 2007), whereas others have not (Biederman et al., 2004). Extremely little relevant research has focused on girls with ADHD. A recent investigation into such associations in the present sample of females revealed that childhood EF (sustained attention, response inhibition) predicted teacher-rated social preference in adolescence across the sample (Miller & Hinshaw, 2010). Additionally, a measure of global EF predicted a measure of “positive adjustment” in the domain of social functioning in adolescence. These whole-sample predictions suggest that both inhibiting behavior and paying attention are important to relationships and social interactions with respect to peer regard.

Other areas of functioning become prominent during late adolescence/young adulthood. In particular, suicide risk increases in young adulthood (Centers for Disease Control, 2010), and girls diagnosed with ADHD in childhood have been shown to be at particularly high risk for suicidal ideation and attempts through adolescence (Chronis-Tuscano et al., 2010; Hinshaw et al., 2012), making this an especially salient outcome in samples of females with ADHD. Females with ADHD also exhibit high rates of self-harm behavior in adolescence (Rucklidge & Tannock, 2001) and young adulthood (Hinshaw et al., 2012), and EF impairments have been found in adolescents exhibiting non-suicidal self-injury (Fikke, Melinder, & Landro, 2010). Given the role of EF in self-regulatory processes, including inhibitory control and emotion regulation (Barkley, 2001; Zelazo &
Cunningham, 2007), early EF abilities may also be predictive of later suicide attempts and self-injury. Previous investigations of the present sample found that a global measure of EF predicted self-injury/suicide attempts over and above IQ but not diagnostic group status in young adulthood (Miller et al., 2012b). Additionally, a measure of response inhibition was predictive of young adult self-injury/suicide attempts when controlling for IQ.

Occupational functioning also becomes a highly relevant domain to assess during young adulthood. Recently, Barkley and Fischer (2011) found that self-ratings of EF (and EF tests themselves, to a lesser extent) were associated with occupational functioning in a sample of individuals with ADHD followed into adulthood. This sample consisted largely of males, so that sex-specific associations could not be addressed. A recent investigation evaluated such associations in the present all-female sample, finding that childhood EF scores were indeed predictive of occupational attainment in young adulthood, over and above either diagnostic group status or IQ, entered separately (Miller et al., 2012b).

Global functioning is also a crucial outcome measure. Findings are limited and mixed in terms of the associations between EF deficits and global impairments in ADHD. One study did not find such linkages (Biederman et al., 2004), although sex differences were not assessed. Determining childhood predictors of later global functioning in females with ADHD is an especially important area of research, because this population appears to be at risk for particularly negative outcomes across many domains in young adulthood (Hinshaw et al., 2012). Indeed, understanding the associations between childhood EF and later global functioning could prove especially important in determining who may be at risk for becoming generally maladjusted later in life. Such examinations in the present sample at the 5-year follow-up were suggestive of significant associations in the ADHD group but not in the comparison group (Miller & Hinshaw, 2010). However, recent examinations at the 10-year follow-up of the present sample did not find predicative associations between childhood EF measures and global functioning over and above childhood diagnostic group status (Miller et al., 2012b). This discrepancy in findings may be attributable, in part, to the parent-reported nature of the global functioning measure used.

Not only have EF abilities been linked to outcomes, but ADHD symptoms themselves are strong predictors of functioning across multiple domains. Loya, Guelzow, & Hinshaw (2012) found that childhood symptoms of ADHD predicted negative outcomes in young adulthood in females across the domains of internalizing symptoms, functional impairments, and substance use, with symptoms of inattention serving as stronger predictors than hyperactive-impulsive symptoms. Others have found associations between inattention and/or hyperactive-impulsive symptoms and substance use (Molina & Pelham, 2003), nicotine use and dependence (Fuemmeler, Kollins, & McClernon, 2007), and peer dislike (Diamantopoulou, Henricsson, & Rydell, 2005), among other outcomes. Additionally, many studies have documented negative outcomes in individuals with ADHD without specifically examining the independent contributions of inattentive versus hyperactive-impulsive symptoms (e.g., Biederman et al., 2010; Bussing, Mason, Bell, Porter, & Garvan, 2010; Chronis-Tuscano et al., 2010; Hinshaw et al., 2012).

Overall, EF abilities are associated with a range of functional outcomes, both in males and females with (and without) ADHD, and ADHD symptoms themselves are strongly linked with negative outcomes. However, it remains unclear whether and how deficits in EF make a contribution to the impact of ADHD symptoms on a range of functional domains. In a community-based sample of kindergartners, Thorell (2007) showed that EF scores mediated the
relationship between symptoms of inattention and academic skills, including reading and math. Replicating this finding across developmental periods, along with assessing neuropsychological mediation of other ADHD symptom-functional domain associations, could provide insight into the mechanisms by which childhood ADHD symptoms influence functional outcomes.

*Development of Neuropsychological Abilities and Associations with ADHD Status*

Longitudinal studies of boys with ADHD suggest that EF deficits persist from childhood into adolescence and adulthood (e.g., Biederman et al., 2007), although persisting neurocognitive deficits may not be restricted to EF domains (Boonstra et al., 2005). However, as mentioned throughout, extremely few longitudinal studies focus on girls with ADHD. Previous work in the present longitudinal sample has shown that EF deficits are present cross-sectionally in females with ADHD during childhood (Hinshaw et al., 2002), adolescence (Hinshaw et al., 2007), and more recently, young adulthood (Miller et al., 2012a). In all, data are quite limited with regard to both cross-sectional assessments of EF in childhood-diagnosed young adults and, in particular, developmental trajectories of neuropsychological functioning in females with childhood-diagnosed ADHD. Understanding female manifestations of ADHD and the development of deficits in this population is important, as it is unclear whether studies from males with ADHD readily apply to girls with this syndrome. What is clear is that females with ADHD exhibit significant impairment (Biederman et al., 2008; Biederman et al., 2010; Hinshaw, 2002; Hinshaw et al., 2002; Hinshaw, Owens, Sami, & Fargeon, 2006; Hinshaw et al., 2012), yet our knowledge continues to be lacking with respect to the longitudinal course of ADHD in females.

A major question concerns whether individuals with childhood ADHD exhibit long-lasting deviation from comparison groups in terms of neuropsychological development or whether these abilities are delayed but improve over time, as suggested by neuroimaging work from Shaw et al. (2007) and behavioral studies of neuropsychological abilities (e.g., Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005). In other words, does the *pattern* of development differ between those with and without childhood ADHD across development? This is a question that has largely been unexplored using methods that can statistically model growth trajectories longitudinally. This is a key area of emphasis for the present investigation, with a specific focus on females. A more thorough understanding of female manifestations of ADHD, including crucial aspects of developmental neuropsychology, has critical diagnostic and treatment implications for this impaired and understudied diagnostic group.

ADHD subtype differences are also largely unexplored using longitudinal designs, particularly in female samples. Individuals with the ADHD-Inattentive subtype (ADHD-I) exhibit significant symptoms of inattention but not hyperactivity/impulsivity whereas individuals with the ADHD-Hyperactive/Impulsive subtype (ADHD-HI) exhibit the opposite, although studies rarely focus on the ADHD-HI subtype except for in the preschool years. Those with ADHD-Combined subtype (ADHD-C) display both inattentive and hyperactive/impulsive symptoms. One study examining working memory – an aspect of EF – in an adult ADHD sample found no differences between the ADHD-C and ADHD-I subtypes (Schweitzer, Hanford, & Medoff, 2006). Several studies examining subtype differences on EF tasks in children with ADHD have also found more commonalities than differences (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2005; Hinshaw et al., 2002; Hinshaw et al., 2007; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002; Pasini, Paloscia, Alessandrelli, Porfirió, & Curatolo, 2007). As a result of these and additional findings, there is considerable controversy regarding the validity of
ADHD subtypes, particularly in adults (McGough & Barkley, 2004). The presence of age-related variations in the manifestation of symptoms (e.g., decreases in hyperactivity-impulsivity with age, differential expression of hyperactive-impulsive symptoms in adulthood) also make continuities between childhood- and adulthood-defined ADHD subtypes questionable. Indeed, it remains unclear whether DSM-5 will retain ADHD subtypes given the many studies that fail to find meaningful differences between them. Overall, little is known regarding whether childhood ADHD subtypes predict the longitudinal development of neuropsychological abilities.

There are also few studies examining the relationship between EF improvement and change in ADHD status. In a longitudinal neuroimaging study of boys and girls with ADHD, Shaw et al. (2006) found that children with ADHD who had worse clinical outcomes at follow-up showed “fixed” thinning of the left medial PFC, a region involved in EF, whereas children with ADHD and better clinical outcomes showed normalization of the right parietal region. Similarly, Halperin and Schulz (2006) suggested that improvement in ADHD symptoms is related to developmental changes in the PFC. Indeed associations between ADHD symptoms and neuropsychological variables have been suggested (Nigg, 2005; Seidman, 2006). One study that examined differences in “ADHD persistor” vs. “ADHD remitter” status found that only those whose ADHD persisted from childhood into adolescence showed deficits on measures of EF (Halperin, Trampush, Miller, Marks, & Newcorn, 2008), supporting the theory that improvements in symptoms over development are associated with improvements in EF abilities. However, a recent longitudinal study consisting largely of male participants did not find associations between improvements in neuropsychological functioning and change in ADHD symptoms (Vaughn et al., 2011). Thus, findings are mixed and whether such developmental trajectories and associations are observable at a clinical, behavioral level (i.e., EF measures) remains unknown, particularly in all-female samples. Relevant data could help identify vulnerable subgroups of children with ADHD at risk for particularly poor outcomes over time.

**Summary**

Overall, studies of the female ADHD phenotype are becoming more common but are still limited, particularly in young adulthood and especially using prospective designs. Moreover, the developmental course of neuropsychological deficits in female samples is not well characterized. Finally, very few studies have focused on longitudinal associations among ADHD symptoms, EF abilities, and functional outcomes within a design that can support mediation models. A more thorough understanding of female manifestations of ADHD has crucial diagnostic and treatment implications for this clearly impaired and understudied group. In particular, understanding the development of neuropsychological abilities over time, from childhood through adolescence to young adulthood, will provide particularly important information regarding the developmental course of EF in a female ADHD sample, potentially pinpointing critical periods for intervention. Evaluating how such neuropsychological changes are related to changes in ADHD status could lead to research aimed at developing treatments that address EF impairments with the goal of improving ADHD symptoms. Overall, findings could suggest critical or sensitive periods for implementing such interventions to be examined in future studies. Finally, assessing the mediating effects of EF abilities could provide insight into the mechanisms underlying associations between ADHD symptoms and functional outcomes, potentially highlighting a specific target for future treatment development efforts.
Present Investigation and Hypotheses

Initial EF data were collected on a large, well-characterized, and diverse sample of preadolescent girls with ADHD and a matched comparison sample, ages 6-12 years. In childhood, the ADHD group showed clear EF deficits relative to the comparison group with stringent statistical control of demographic variables, comorbid disorders, and Full-Scale IQ (FSIQ). Comparisons between ADHD-C and ADHD-I subtypes were rarely significant (Hinshaw et al., 2002). This sample was then followed prospectively into adolescence with similar findings: The childhood-defined ADHD group again showed clear EF deficits relative to comparisons under statistical control of demographic variables and comorbid disorders (but not with the addition of FSIQ); subtype differences were again minimal (Hinshaw et al., 2007). Most recently, this sample was evaluated in young adulthood. Parallel to findings from childhood and adolescence, the young adult females with childhood-diagnosed ADHD displayed medium to large deficits in EF relative to comparisons at follow-up, even with statistical control of baseline demographic and comorbidity variables (Miller et al., 2012a). Comparisons between ADHD subtypes yielded non-significant results with small effect sizes. EF impairments were evident in participants whose ADHD diagnoses persisted and in those whose ADHD symptoms had remitted to a non-diagnosable level; both subgroups had greater EF impairments than those who did not meet criteria for ADHD in either childhood or young adulthood (Miller et al., 2012a). EF abilities in childhood predicted functional outcomes in adolescence (Miller & Hinshaw, 2010) and in young adulthood (Miller et al., 2012b), as did ADHD symptoms (Loya et al., 2012).

The present investigation has three main aims. First, I sought to determine whether girls with and without childhood-defined ADHD show improvements in neuropsychological functioning over time (from childhood to adolescence to young adulthood) and whether developmental trajectories are different for girls with ADHD versus comparison girls. Using growth curve modeling – which allows examination of (1) individual change, (2) average change, and (3) predictors of individual differences in change over time – I expected to find improvement in all participants from childhood to adolescence to young adulthood. I also predicted that girls with childhood-diagnosed ADHD would continue to perform worse than those without ADHD at each time point, and that the pattern of change over time would be similar across both groups. Subtype differences were explored.

Second, I sought to assess differences in neuropsychological functioning in those whose ADHD symptoms had persisted into young adulthood versus those whose ADHD symptoms had remitted. As noted previously, a longitudinal neuroimaging study of boys and girls with ADHD found that children with ADHD who had worse clinical outcomes at follow-up showed “fixed” thinning of the left medial PFC (Shaw et al., 2006). Similarly, Halperin and Schulz (2006) suggested that improvement in ADHD symptoms may be related to developmental changes in the PFC, and evidence exists in support of this theory (Halperin et al., 2008). Based on this model, and given that EF measures are a proxy of PFC functioning, I expected that those whose ADHD symptoms remitted would display greater change in EF scores over time than those whose ADHD symptoms persisted.

Finally, I sought to determine whether neuropsychological performance in adolescence mediated associations between childhood ADHD symptoms and young adult functional outcomes. Based on results of Thorell (2007), who found that EF abilities mediated the relationship between ADHD inattentive symptoms and academic achievement, it was expected that associations between childhood ADHD symptoms and young adult functional outcomes
(social, academic achievement, global) would be mediated by EF variables in adolescence.

Method

Overview of Procedure

The present study utilizes data from a longitudinal study of behavioral, neuropsychological, social, and family functioning in 228 girls, 140 with rigorously diagnosed childhood ADHD and 88 matched comparison girls. All participated in summer research programs and extensive testing during childhood (ages 6-12) and were followed prospectively into adolescence (ages 11-18) and late adolescence/young adulthood (ages 17-25), completing extensive evaluations at each time point. During the baseline summer programs, multi-domain evaluation of key areas of relevance to childhood functioning were emphasized, and an extensive neuropsychological battery – including EF, language, and motor speed measures – was performed when any medicated participants were off medication. Well-trained graduate students and bachelor’s-level research assistants, all of whom were closely supervised by a licensed clinical psychologist, administered the assessments and tests. Initial and follow-up assessments had received full approval from UC Berkeley’s Committee for the Protection of Human Subjects.

For the 5-year follow up assessments (adolescence), 209 out of 228 girls were retained (92%) for extensive individual and family evaluation. This level of participant retention was a function of considerable efforts to contact families who had moved or relocated. As indicated in Hinshaw et al. (2006), the 209 girls in the follow-up sample and the 19 lost to attrition were statistically indistinguishable with respect to nearly all baseline variables examined. The key goal was to appraise, via multi-informant and multi-method procedures, levels of symptomatology and adjustment/impairment in key domains of psychiatric, academic, and social functioning. Any medicated participants were off stimulant medication for at least 24 hours prior to completing the neuropsychological battery.

At the 10-year follow-up (young adulthood), the goal was again to evaluate levels of symptomatology and adjustment/impairment in key domains of psychiatric, academic, neuropsychological, relational, and occupational functioning. For this follow-up, 216 out of 228 girls (95% overall; 93% of the ADHD group, 98% of the comparison group) were retained. Participants in this follow-up sample and those lost to attrition were statistically indistinguishable with respect to 18 out of 23 baseline demographic variables examined, but the non-retained sample had lower family incomes and FSIQ scores and higher baseline rates of teacher-rated ADHD, externalizing, and internalizing symptoms. Attrition was slightly higher in the ADHD groups than the comparison group (7% vs. 2%). At young adulthood, 97% of ADHD participants were off stimulant medication for at least 24 hours prior to completing the neuropsychological battery.

Participants

A multi-gated procedure was used to recruit participants from pediatric practices, school referrals, and community advertisements to participate in free summer enrichment programs. Those in the ADHD group had to surpass sex-specific thresholds for the Swanson, Nolan, and Pelham scale (SNAP-IV; Swanson, 1992) and meet full DSM-IV criteria for ADHD based on the Diagnostic Interview Schedule for Children – Parent version (4th ed., DISC-IV; Shaffer, Fisher,
Dulcan, & Schwab-Stone, 2000). Those in the comparison group could not meet SNAP-IV or DISC-IV criteria for ADHD; neither group could have a history of neurological damage, psychosis, pervasive developmental disorder, IQ less than 70, or medical conditions precluding participation in a summer camp. The comparison sample was matched, at a group level, with the clinical group in terms of age and ethnicity.

The overall sample is both socioeconomically and ethnically diverse (family incomes ranging from public assistance to upper-middle class; 53% White, 27% African-American, 11% Latina, 9% Asian-American). At baseline, these 228 girls had a mean age of 9.6 years. The mean age of the comparison group was 113.2 months ($SD = 19.8$, range = 80-153), for the ADHD-I group was 118.0 months ($SD = 20.2$, range = 80-161), and for the ADHD-C group was 114.4 months ($SD = 20.2$, range = 79-160). In childhood, both the ADHD-I and ADHD-C groups had significantly lower FSIQ scores than the comparison group. At baseline, mean FSIQ for the comparison group was 112.0 ($SD = 12.7$, range = 72-140), for the ADHD-I group was 99.8 ($SD = 14.3$, range = 72-122), and for the ADHD-C group was 99.6 ($SD = 13.2$, range = 74-134).

At the 5-year follow-up, the 209 retained girls were 11 to 18 years of age ($M = 14.2$ years), and at the 10-year follow-up, the mean age of the 216 retained young women was 19.6 years. In some cases, follow-up assessments occurred via home visits or telephone interviews; in other cases, measures were missing because of fatigue or refusal; and in other instances, computer failures occurred. Thus, data loss for neuropsychological variables was higher than the overall attrition rate.

Diagnostic Classification and Measures of ADHD Symptoms

The main diagnostic measure was the DISC-IV (Shaffer et al., 2000), including the child and parent versions at baseline and adolescent follow-up, and the young adult version and parent versions at the young adult follow-up. In addition, the SNAP-IV (Swanson, 1992) rating scale was used at all time points, yielding dimensional counts of ADHD symptoms. Persistent ADHD versus remitted ADHD status was determined by comparing childhood DISC-IV ADHD diagnoses to young adult DISC-IV ADHD diagnoses: Those who met criteria in childhood and young adulthood were classified as having “persistent ADHD;” those who met criteria in childhood but not in young adulthood were classified as having “remitted ADHD.”

Measures of EF

Cancel Underline (CUL). The CUL was administered at each time point and is a modified version of the Underlining Task (Rourke & Orr, 1977). It measures the EF component of inhibitory control and rapid, accurate visual discrimination, abilities that recruit anterior cingulate and prefrontal regions (Cabeza & Nyberg, 1997). Participants are instructed to underline targets (shape or consonant sequences) and cancel out nontargets (ratio of 1:5). Analyses are based on correct minus incorrect responses. Previous research has shown medium-sized differences between ADHD and comparison individuals on this measure, with those with ADHD performing worse (Hinshaw et al., 2002, 2007; Miller et al., 2012a; Nigg, Hinshaw, Carte, & Treuting, 1998). Lower scores indicate greater impairment.

Conners’ Continuous Performance Task (CPT; Conners, 1995). The CPT was administered at each time point and is a computerized visual task of attentional processing and response inhibition that requires the participant to press the spacebar when target letters appear
on the screen (all letters except ‘X’), and not respond to the letter ‘X’. The 14-minute task consists of trials that are presented in six blocks (interstimulus intervals: 1s, 2s, and 4s); stimuli are displayed for 250ms. This task differs from other commonly-used continuous performance tasks by featuring frequent display of target stimuli (requiring response) and relatively infrequent display of non-targets (requiring non-response), so that response inhibition rather than detection of rare stimuli is featured. Neuroimaging studies indicate involvement of a neural network including frontal, cingulate, parietal, occipital, and temporal regions as well as the basal ganglia and cerebellum in the performance of this task (Ogg et al., 2008). Two scores were utilized in analyses: percentage of omission errors and percentage of commission errors. Prior research in this sample has shown significantly higher percentages of both error types in the ADHD group at baseline and follow-up, with effect sizes in the medium range (Hinshaw et al., 2002, Hinshaw et al., 2007; Miller et al., 2012a). Conners (1995) provided criterion-related validity data for omission and commission errors based on known-groups differentiation. Higher scores indicate greater impairment.

Rey Osterrieth Complex Figure (ROCF; Osterrieth, 1944). The ROCF was administered in childhood and young adulthood and is a complex cognitive task that requires an individual to copy and later recall a complex figure composed of 64 segments. The Copy condition of this task was used, in which participants draw the figure with no delay. This measure appears to tap multiple domains of EF, such as planning, inhibitory control, attention to detail, and organization. Intriguingly, only this condition differentiated the girls with ADHD from our comparison sample at baseline (Sami, Carte, Hinshaw, & Zupan, 2003), and was the most predictive of outcomes in adolescence (Miller & Hinshaw, 2010) and young adulthood (Miller et al., 2012b). The ROCF has been successfully used to distinguish patients with frontal lobe lesions from those without (Lezak, 1995), as well as children with ADHD from those without (Carte, Nigg, & Hinshaw, 1996; Nigg et al., 1998; Sami et al., 2003). Scores from various methods of scoring the ROCF are significantly correlated with other measures of EF (Troyer & Wishart, 1997; Somerville, Tremont, & Stern, 2000; Watanabe et al., 2005), indicating that the ROCF is indeed assessing one or more aspects of EF.

In the present investigation, the error proportion score (EPS) was used, a validated method of scoring the ROCF developed by Sami et al. (2003). The EPS is a ratio (number of errors/total number of segments drawn) and is a measure of efficiency. Intraclass correlations between pairs of the three primary scorers for the EPS at W1 ranged from .91 to .94 (drawings n = 84-195 across rater pairs); at W3 the intraclass correlations between pairs of the two primary scorers was .91 on a sample of 70 drawings. Among all of the EF measures in the battery, this EPS showed the largest effect size (d = .90) in differentiating the girls with ADHD from the comparison sample during childhood (Hinshaw et al., 2002; Sami et al., 2003). Higher scores indicate greater impairment.

Taylor Complex Figure Test (TCFT; Taylor, 1969). This measure was administered during adolescence and served as a parallel form of the ROCF, measuring the same constructs. The TCFT is the only major alternative to the ROCF in a test-retest situation (Helmes, 2000). As with the ROCF, the copy condition of the TCFT was utilized, again using the EPS. The intraclass correlations between pairs of the three scorers ranged from .77-.94, with a mean of .84 on a subsample of 60 drawings. As with the ROCF, higher scores indicate greater impairment.

WISC-III Digit Span - Backward (Wechsler, 1991). The WISC-III Digit Span was administered at each time point and is a widely used measure of auditory working memory that requires participants to immediately recall digit sequences of increasing length either in their
original presentation order (digits forward) or in their reverse presentation order (digits backward). These abilities rely on frontostriatal and cerebellar regions (Martinussen et al., 2005). Given the importance of manipulation of information to the construct of working memory, the ‘backward’ condition of the digit span was analyzed, using raw scores. Lower scores indicate greater impairment.

**Adolescent Mediator Variables**

The following EF variables (described in detail above) comprised the mediators in adolescence: Cancel Underline, Conners’ CPT percentage of omission errors and commission errors, Taylor Complex Figure Task, and WISC-III Digit Span (backward). These measures were converted to z-scores and averaged to obtain a composite measure of adolescent EF.

**Young Adult Outcome Measures**

**Columbia Impairment Scale (CIS; Bird et al., 1993)**. The CIS is a 13-item parent-reported scale that assesses functioning across the domains of interpersonal relations, broad psychopathological domains, school/job functioning, and use of leisure time. Parents rated their child’s impairment for each item using a 5-point scale, yielding an index of global impairment. The CIS has been used extensively in investigations of child and adolescent psychopathology and treatment response, and is used in the present study as a measure of global functioning.

**Adult Self Report: Friends Adaptive Functioning Scale (Achenbach & Rescorla, 2005)**. The Adult Self Report is a self-report form that covers a range of symptom domains and includes normed scales for adaptive functioning, empirically based syndromes, and DSM-oriented scales. The Friends adaptive functioning scale was employed as a measure of social functioning.

**Substance Use Questionnaire (Molina & Pelham, 2003)**. The Substance Use Questionnaire is a paper-and-pencil task in which participants answer questions regarding current and lifetime use of substances including illicit drugs and inappropriate use of prescription drugs. Additional information collected includes age of first use and frequency/quantity of use. A standardized “severity” score was created that incorporates both variety of substances used and the frequency of substances that were used over the past 12 months.

**Suicide Attempts/Self-Injury**. Information was collected from participants and their families covering a range of domains over the years since they were last evaluated. Participants and/or their parents noted the absence or presence of particular behaviors or events in each of the years since their last visit. For example, a participant might note that she attempted suicide in the first and third years, but not the second, fourth, or fifth years. This information was summed for each participant and a continuous variable was created to indicate the number of suicide attempts and the number of NSSI “episodes” that had occurred since their last visit; these two variables were summed.

**Wechsler Individual Achievement Test (WIAT; Wechsler, 1992)**. The WIAT is a psychometrically sound assessment of academic achievement, with both internal consistency and test-retest reliability estimates at above .85 for most composite scores (Wechsler, 1992). Both the Basic Reading and Math Reasoning composite scores were used as measures of academic functioning at W3.
Covariates

In growth curve analyses, baseline age and relevant comorbidities were included in level-2 models. Comorbidities were ascertained from the DISC-IV and included (1) Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD), and (2) depression/dysthymic disorder or anxiety disorder, each dummy coded as 1 vs. 0 for their presence vs. absence. In these models, IQ was intentionally not included as a covariate because IQ deficits are likely to be associated with EF impairments (see Barkley, 1997; Dennis et al., 2009; Vaughn et al., 2011).

For mediation analyses, the FSIQ score from the Wechsler Intelligence Scale for Children – Third Edition (WISC-III, Wechsler, 1991) was used to indicate intelligence, which was administered in total to all participants at baseline. Mediation analyses were conducted with and without IQ as a covariate, per Barkley’s (1997) suggestion.

Data Analytic Plan

Neuropsychological Development. Change in EF abilities over the three time points was modeled using growth curves, a strongly-recommended approach to analyzing repeated-measures data and documenting developmental patterns (Boyle & Williams, 2001; Willett, Ayoub, & Robinson, 1991). This method allows examination of (1) individual change, (2) average change, and (3) predictors of individual differences in change over time. In the present investigation, hierarchical linear models were evaluated using HLM software, version 6.08 (Raudenbush, Bryk, & Congdon, 2004). A two-step process ensued: First, the data were modeled unconditionally (without predictors) to examine individual and group-level EF as a linear function of time (childhood, adolescence, young adulthood), for each EF variable. Second, predictors of variance were added to the models in the EF growth curve slopes and intercepts. In each of the participants, a trajectory or growth curve was represented by a slope (rate of change) and an intercept (level of EF at baseline). An average growth curve was generated and then predictors of variance around the slope and intercept of this average curve were examined. Three separate models were examined using a time variable (childhood = 0, adolescence = 1, young adulthood = 2), with the following predictors: baseline diagnostic status (ADHD = 1 vs. comparison = 0), baseline ADHD subtype (ADHD-C = 1, ADHD-I = 0), and persistent-remitted ADHD status (persistent ADHD = 1, remitted ADHD = 0). Both intercepts and slopes were allowed to vary in unconditional models, as individual variability was predicted to be high. The main indicator of interest was the slope rather than the intercept, given my interest in rate of change, although both were evaluated in each model. Baseline age and relevant baseline comorbidities were included as covariates (ODD/CD, internalizing disorders). IQ was intentionally not included as a covariate in these analyses because IQ deficits are likely partially associated with EF impairments, and removing IQ-associated variance would likely diminish differences on EF measures (see Barkley, 1997; Dennis et al., 2009; Vaughn et al., 2011).

Mediation Analyses. Five EF variables ascertained in adolescence (TCFT, CPT omissions, CPT commissions, Digits Backward, CUL) were converted to z-scores and averaged to create a composite score of EF in adolescence. Mediation analyses were conducted as suggested by Baron and Kenny (1986) and Judd and Kenny (1981). First, using multiple regression, relations between childhood ADHD symptoms (inattention, hyperactivity-impulsivity) and young adult functional outcomes were assessed. Second, the relations between childhood ADHD symptoms
and the composite adolescent EF variable were assessed. Third, the relations between the adolescent EF variable and young adult functional outcomes were assessed, controlling for childhood ADHD symptoms. Finally, when all 3 paths above were significant, the Sobel test (Sobel, 1982) was used to assess partial mediation by determining whether the effect of childhood ADHD symptoms on young adult functional outcomes was significantly less when taking into account the effect of adolescent EF. Thus, I inferred partial mediation when (a) all paths were significant, (b) the effect of childhood ADHD symptoms on young adult outcomes was larger when adolescent EF scores were not partialled than when they were partialled, and (c) the Sobel test was significant (MacKinnon, 2008).

Results

Neuropsychological Development

Unconditional models. Descriptive statistics are presented in Table 1. Figure 1a displays the estimated mean growth curve for ROCF/TCFT error proportion scores from baseline to young adult follow-up, revealing improvement between childhood and young adulthood. As can be seen, average ROCF/TCFT scores decreased over time, signifying fewer errors. The linear slope of the estimated mean growth curve was -.0591 and its intercept (i.e., the average ROCF score at baseline) was .2918. Both of these values were significantly different from zero, and were moderately reliable (.40 for slope estimate and .74 for intercept estimate). The correlation between slope and intercept was \( \tau = -.99 \), indicating a strong association between higher (worse) baseline ROCF scores and rate of improvement. The variances around the average slope and intercept were also significant (.0217 for intercept, \( \chi^2_{214} = 849.71, p = .000 \); .0032 for slope, \( \chi^2_{214} = 364.29, p = .000 \)), indicating variability in participants’ trajectories and suggesting that predictors of this variance should be determined.

Figure 1b displays the estimated mean growth curve for CPT omissions. Again, average CPT omission scores decreased over time. The linear slope of the estimated mean growth curve was -3.11 and its intercept was 8.57. Both of these values were significantly different from zero and were moderately reliable (.56 for slope estimate and .36 for intercept estimate). The correlation between slope and intercept was \( \tau = -.98 \), indicating a strong association between higher (worse) baseline CPT omission scores and rate of improvement. The variances around the average slope and intercept were also significant (71.79 for intercept, \( \chi^2_{198} = 476.81, p = .000 \); 24.09 for slope, \( \chi^2_{198} = 308.35, p = .000 \)), suggesting that predictors of variability in participants’ trajectories should be sought.

Figure 1c displays the estimated mean growth curve for CPT commissions. Average CPT commission scores decreased over time, as expected. The linear slope of the estimated mean growth curve was -11.23 and its intercept was 54.44. Both of these values were significantly different from zero; the intercept was moderately reliable (.45) but the slope was less reliable (.10). The correlation between slope and intercept was \( \tau = -.34 \), indicating a small relation between higher (worse) baseline CPT commission scores and rate of improvement. The variance around the intercept was significant (191.38, \( \chi^2_{198} = 347.04, p = .000 \)), but the variance around the slope was not (18.46, \( \chi^2_{198} = 221.20, p = .124 \)), indicating that predictors may not need to be explored.
Figure 1d displays the mean growth curve for Digit Span Backwards. Average scores increased over time, which was expected because, unlike the three previous variables, higher scores indicate better performance. The linear slope of the estimated mean growth curve was .9188 and its intercept was 4.61. Both of these values were significantly different from zero. As with CPT commissions, the intercept was moderately reliable (.53) but the slope was less reliable (.27). The correlation between slope and intercept was $\tau = -.03$, indicating that very little association existed between baseline Digit Span Backwards scores and rate of improvement. The variances around the average slope and intercept were significant ($1.82$ for intercept, $\chi^2_{213} = 464.12$, $p = .000$; $.3586$ for slope, $\chi^2_{213} = 291.93$, $p = .000$), suggesting that predictors should be evaluated.

Finally, Figure 1e displays the mean growth curve for CUL. Average scores increased over time (here, again, higher scores indicate better performance). The linear slope of the estimated mean growth curve was 15.43 and its intercept was 6.32. Both of these values were significantly different from zero but only the slope was reliable (.65) while the intercept was not (.02). The correlation between slope and intercept was $\tau = .97$, indicating a large association between lower (better) baseline CUL scores and rate of improvement. The variances around the average intercept were not significant for the intercept ($0.5833$, $\chi^2_{2} = 128.76$, $p > .500$) but were for the slope ($0.3613$ for slope, $\chi^2_{2} = 557.69$, $p = .000$), indicating that predictors for the intercept may not need to be explored but could be evaluated for the slope with a fixed intercept in subsequent analyses.

Based on the results of the unconditional models, the following four variables were retained for subsequent analyses involving level-2 predictor variables and covariates: ROCF/TCFT (global EF), CPT omissions (sustained attention), Digit Span Backwards (working memory), and CUL (inhibitory control). CPT commissions was omitted, given that the variances around intercept and slope were not significant for this variable.

**Baseline ADHD status (ADHD vs. comparison).** Baseline diagnostic status (ADHD vs. comparison) was entered as a predictor of the variance around the slope and intercept. Baseline age and two key baseline comorbidities (presence of ODD/CD, presence of any internalizing disorder) were also included as predictors in the models, after baseline ADHD status. Graphs of the estimated growth curves by group are included in Figures 2a-2d.

For ROCF/TCFT, baseline diagnostic status was a significant predictor of both the intercept (coefficient $= .1170$, $se = .0248$, $t_{223} = 4.72$, $p = .000$) and the slope (coefficient $= -.0352$, $se = .0133$, $t_{223} = -2.64$, $p = .009$). For CPT omissions, group status was again significantly predictive of both the intercept (coefficient $= 5.71$, $se = 1.74$, $t_{222} = 3.28$, $p = .002$) and the slope (coefficient $= -2.91$, $se = 1.27$, $t_{222} = -2.30$, $p = .023$). For Digit Span Backwards, baseline group status was significantly predictive of the intercept (coefficient $= -1.09$, $se = .2847$, $t_{218} = -3.82$, $p = .000$), but not the slope (coefficient $= .0249$, $se = .1861$, $t_{218} = .13$, $p = .894$). Finally, for CUL, the intercept was set as fixed and only predictors of the slope were evaluated. In this case, baseline diagnostic status was a significant predictor of the slope (coefficient $= -4.08$, $se = 1.31$, $t_{223} = -3.07$, $p = .003$). For ROCF/TCFT and CPT omissions, the ADHD group performed worse during childhood and showed a higher rate of improvement (i.e., steeper slope) over time than the comparison group. For the CUL, the intercept was fixed based on findings from the unconditional model, and the ADHD group showed a slower rate of improvement than the comparison group.
Baseline ADHD subtype (ADHD-I vs. ADHD-C). To evaluate whether there were differences in EF trajectories based on childhood ADHD subtype, the analyses above were repeated with baseline ADHD subtype (ADHD-I, ADHD-C) as the predictor, again including age and relevant comorbidities as covariates. Graphs of the estimated growth curves by subtype are included in Figures 3a-3d. For ROCF/TCFT, baseline ADHD subtype was a marginally significant predictor of the intercept (coefficient = .0522, se = .0284, t135 = 1.83, p = .068) and a significant predictor of the slope (coefficient = -.0378, se = .0152, t135 = -2.48, p = .015). For CPT omissions, baseline subtype was neither predictive of the intercept (coefficient = 1.63, se = 2.27, t134 = .72, p = .475) or the slope (coefficient = -2.41, se = 1.65, t134 = -1.47, p = .145). Similarly, for Digit Span Backwards, baseline subtype was not predictive of the intercept (coefficient = -.1534, se = .3091, t131 = -.50, p = .620) or the slope (coefficient = .1334, se = .1991, t131 = .67, p = .504). Finally, for CUL (with a fixed intercept), baseline ADHD subtype was also not a significant predictor of the slope (coefficient = 1.05, se = 1.59, t135 = .66, p = .511).

For ROCF/TCFT, the ADHD-C group showed the greatest improvement (i.e., steepest rate of change) over time relative to the ADHD-I group.

Persistent-remitted ADHD status (persistent ADHD vs. remitted ADHD). Finally, to evaluate whether improvements in EF over time occurred to a greater degree in those whose ADHD symptoms remitted to a non-diagnosable level, ADHD persistent-remitted status (persistent ADHD, remitted ADHD) was entered as the predictor, again including baseline age and relevant baseline comorbidities. Graphs of the estimated growth curves by persistent-remitted ADHD status are included in Figures 4a-4d. For ROCF/TCFT, persistent-remitted ADHD status was not predictive of the intercept (coefficient = .0273, se = .0289, t122 = .94, p = .348) or the slope (coefficient = -.0199, se = .0151, t122 = -1.31, p = .191). For CPT omissions, persistent-remitted status was again not predictive of the intercept (coefficient = -2.25, se = 2.05, t121 = -1.10, p = .275) or the slope (coefficient = -.45, se = 1.58, t121 = -.29, p = .773). For Digit Span Backwards, persistent-remitted status was marginally significantly predictive of the intercept (coefficient = .58, se = .3069, t122 = 1.88, p = .061), but not the slope (coefficient = -.1558, se = .1956, t122 = -.80, p = .427). Finally, for CUL, with the intercept set as fixed, persistent-remitted status was not predictive of the slope (coefficient = 1.90, se = 1.53, t122 = 1.24, p = .217).

Summary. The ADHD group showed greater improvement in scores (i.e., steeper slope) than the comparison group for the ROCF/TCFT and CPT omissions, but showed a slower rate of improvement on the CUL. When using baseline subtype as the predictor, the ADHD-C group showed the greatest improvement in scores on the ROCF/TCFT compared to the ADHD-I group, but the two groups did not differ on any other measures. Finally, when persistent-remitted status was used as the predictor, the persistent ADHD group and remitted ADHD group did not differ on any EF variable.

Mediation Analyses

For models including childhood inattention symptoms as the independent variable, initial regression analyses revealed that at least one path in the models for young adult substance use and young adult suicide/self-injury was non-significant. Therefore, mediation was not considered and follow-up Sobel tests were not conducted for these outcomes. Whereas all paths in the
models including young adult global functioning and young adult social functioning as the dependent variables were significant, Sobel tests were not indicative of mediation ($z = -1.37, p > .05$ and $z = -1.33, p > .05$, respectively). For the final models regarding academic performance, adolescent EF partially mediated the association between childhood inattention symptoms and young adult reading scores ($z = -3.61, p < .001$) and math scores ($z = -3.74, p < .001$). These significant mediation models are shown in Figures 5a and 5b.

For models including childhood hyperactive-impulsive symptoms as the independent variable, initial regression analyses revealed that at least one path in the models for young adult substance use and young adult suicide/self-injury was non-significant. Therefore, mediation was not considered and follow-up Sobel tests were not conducted. Although all paths in the model including young adult global functioning and young adult social functioning as the dependent variables were significant, Sobel tests were not indicative of mediation ($z = -1.51, p > .05$ and $z = -1.18, p > .05$, respectively). Parallel to childhood inattention symptoms, results using childhood hyperactive-impulsive symptoms as the independent variable indicated partial mediation for academic performance. Specifically, adolescent EF partially mediated associations between childhood hyperactive-impulsive symptoms and young adult reading scores ($z = -3.66, p < .001$) and math scores ($z = -3.95, p < .001$). These significant mediation models are shown in Figures 6a and 6b.

When including childhood FSIQ as a covariate, findings were virtually identical to those without FSIQ as a covariate with one exception: Adolescent EF fully mediated the association between childhood hyperactive-impulsive symptoms and young adult math achievement scores ($z = -2.14, p < .05$). However, given controversies around using IQ as a covariate in studies of cognitive abilities in neurodevelopmental disorders (e.g., Dennis et al., 2009), and given that results did not substantially differ, the results from analyses without IQ as a covariate are emphasized.

Overall, results of mediation analyses indicated that adolescent EF partially mediated associations between childhood ADHD symptoms (both inattentive and hyperactive-impulsive) and young adult academic achievement (both reading and math). There was a suggestion that adolescent EF fully mediated the association between childhood hyperactive-impulsive symptoms and young adult math scores when including childhood IQ as a covariate. There was no suggestion of mediation by adolescent EF in associations between childhood ADHD symptoms and young adult global functioning, social functioning, substance use severity, or suicide/self-injury.

Discussion

Overall, in the present study I found that childhood ADHD status (ADHD versus comparison) was predictive of the rate at which EF abilities improved from childhood to adolescence to young adulthood in females, controlling for key baseline comorbidities. ADHD subtypes (ADHD-I versus ADHD-C) rarely differed in terms of patterns of change. ADHD persistent-remitted status showed no predictive utility in terms of change in EF abilities, showing no evidence of associations between improvement in EF abilities and remitted ADHD status. Mediation analyses indicated that adolescent EF partially or fully mediated associations between ADHD symptoms and young adult academic achievement abilities.

Growth curve analyses indicated that the developmental trajectory of certain neuropsychological variables differed between girls who were diagnosed with ADHD in
childhood versus comparisons, as those with childhood diagnoses of ADHD showed greater improvement (i.e., steeper slopes) than comparison participants on two measures of EF, one a more “global” EF measure (ROCF/TCFT), and the other a measure of sustained attention (CPT omissions). However, on a measure of inhibitory control (CUL), the ADHD group showed less improvement over time than the comparison group, suggesting that there may be differences in developmental patterns of inhibitory control compared to other EF abilities. Findings were similar but less consistent when using baseline ADHD subtype (ADHD-I versus ADHD-C) as the predictor, with the ADHD-C group showing the greatest improvement compared to the ADHD-I group on the ROCF/TCFT. Additionally, those whose ADHD symptoms had persisted showed equivalent improvement on all variables to those whose ADHD symptoms had remitted. Overall, those with the most impairment on EF variables in childhood generally showed the greatest improvement over time, which could be an artifact of regression toward the mean. That is, because the ADHD groups had greatest impairment in childhood, they had more room to improve in their scores. However, on one measure of inhibitory control for which the intercept was fixed, the ADHD group did show a slower rate of improvement over time. Continued follow-up of the present sample will allow for a more complete understanding of these developmental trajectories, and potential differences in patterns between aspects of EF (e.g., inhibitory control versus sustained attention).

Previous longitudinal studies have shown that EF impairments persist from childhood through adolescence and into adulthood (Biederman et al., 2007; Hinshaw et al., 2002; Hinshaw et al., 2007; Miller et al. 2012a). However, most of these studies have examined EF abilities using cross-sectional designs or statistical methods that focus on evaluating mean differences rather than rates of change. The present study adds to such findings by showing that the rate of change (i.e., improvement) in EF abilities in females with childhood diagnoses of ADHD appears to be greater, in general, than for comparisons. A common issue that exists regarding neurodevelopmental processes in ADHD is whether individuals with ADHD show a delay in brain maturation compared to those without ADHD, or whether there is actual deviance in the neurodevelopmental course. Previous neuroimaging studies have contributed to the notion that there is a delay in brain development in individuals with ADHD (Shaw et al., 2007) rather than a fundamental difference in the way in which the brain develops, with such delays ranging from 3-5 years depending upon brain region. Given the current finding of steeper slopes in the ADHD group on some measures of EF, the present data partially support the delay model of ADHD in this all-female sample. However, on one measure of inhibitory control, the females with ADHD showed slower rates of improvement than the comparison group, although did still show improvements.

Whereas developmental trajectories of these EF abilities show improvement over time in individuals with ADHD, an important question persists regarding whether and when individuals with ADHD “catch up” to those without ADHD. Indeed, it should be noted that a recent cross-sectional investigation in the present sample found that childhood-diagnosed females with ADHD continue to show significant EF impairments relative to comparisons in young adulthood (Miller et al., 2012a), a time during which the PFC is reaching its developmental endpoint. Additionally, in the present growth curve models, group status was not predictive of the slopes of several variables (working memory, response inhibition), indicating that both the ADHD group and the comparison group showed comparable rates of change on these measures. Moreover, on one measure of inhibitory control, the ADHD group actually showed a slower rate of improvement. This latter finding of equal or slower rates of change the ADHD group on some
variables, coupled with work showing that – even in adulthood – individuals with ADHD show considerable impairments on some measures of EF, could be interpreted as reflecting a fundamental difference in developmental trajectories of EF abilities between the two groups (i.e., “deviance”). Thus, a persistent issue is whether the development of some aspects of EF is “delayed” in ADHD while other aspects of EF exhibit signs of “deviant” development.

In terms of ADHD subtypes, the present findings do not suggest predictive utility of childhood ADHD subtype (ADHD-I versus ADHD-C). Findings were more robust when using a dichotomous childhood ADHD variable rather than childhood ADHD subtype. Both predictor variables were associated with improvement in a global EF measure (ROCF/TCFT), but the dichotomous childhood ADHD variable was predictive of additional measures of EF. Additionally, the literature reflects mixed findings in terms of differing outcomes and neuropsychological profiles between the ADHD subtypes, and there are considerable concerns regarding the utility and stability of subtypes over development (e.g., Lahey, Pelham, Loney, Lee, & Willcutt, 2005; Valo & Tannock, 2010). Indeed, in the present all-female sample, little evidence of subtype differences has been found with respect to neuropsychological variables (Hinshaw et al., 2002; Hinshaw et al., 2007; Miller et al., 2012a).

Finally, the dichotomous variable of persistent versus remitted ADHD status was least predictive of change in EF performance over time. More specifically, the rate of change in EF scores was similar between the persistent ADHD and remitted ADHD groups. This finding is in contrast to the theory that improvement in ADHD symptoms may be related to developmental changes in the PFC (Halperin & Schulz, 2006), suggesting that this argument may be weak. Instead, the present findings are more in line with the longitudinal study by Vaughn et al. (2011), which did not find associations between improvements in neuropsychological functioning and change in ADHD symptoms. The current investigation extends such findings to females with ADHD. Indeed, a recent cross-sectional evaluation of young adult females whose ADHD persisted versus those whose symptoms had remitted did not find differences in EF profiles between these two groups, although both groups showed greater EF impairment than those who had never been diagnosed with ADHD (Miller et al., 2012a). Thus, in the current all-female sample, profiles of EF development did not appear to differ among these three groups. A future focus on associations between change in EF scores and change in dimensional measures of ADHD symptoms may provide more meaningful information regarding the relationships among these variables and mechanisms underlying symptom improvement. Additionally, current diagnostic classification systems for ADHD do not readily apply to adults and may contribute to inaccurate diagnosis (see McGough & Barkley, 2004). Development of appropriate diagnostic criteria for adults with ADHD is warranted, and use of such criteria in the present investigation may have resulted in alternative findings. Current proposals for DSM-5 criteria partially address these concerns by requiring a reduced number of symptoms for individuals age 17 and up, but symptom descriptions continue to lack integration with developmental science. Furthermore, the DSM-5 may propose an enriched set of impulsivity-related symptoms, which may be essential for capturing this critical domain of functioning, both symptomatically and neuropsychologically.

In each set of significant growth curve models, one variable emerged as being the most informative. The ROCF/TCFT, a more global measure of EF, was best predicted by diagnostic group in models using childhood ADHD status or subtype compared to other, more focused measures of specific EF abilities. This pattern may occur because it assesses multiple aspects of EF within one measure (in addition to visuospatial and motor abilities), and better captures the neuropsychological deficits that are common in individuals with ADHD. Previous investigations
of group differences in EF measures in this female sample have found the ROCF to be particularly good at distinguishing the ADHD group from the comparison group in childhood (Hinshaw et al., 2002; Sami et al., 2003), adolescence (Hinshaw et al., 2007), and young adulthood (Miller et al., 2012a), consistently yielding some of the largest effect sizes in the neuropsychological battery. This variable has also emerged as the most strongly predictive of outcomes in adolescence (Miller & Hinshaw, 2010) and young adulthood (Miller et al., 2012b).

The results of the growth curve modeling suggest that EF abilities improve over time across the entire sample. Previous investigations in the present sample and in others have shown that both ADHD symptoms and EF abilities are predictive of a range of outcomes (Chang, Lichtenstein, & Larsson, 2012; Diamantopoulou et al., 2007; Loya et al., 2012; Miller & Hinshaw, 2010; Miller et al., 2012b). Yet whether EF abilities mediate associations between ADHD symptoms and outcomes has largely been unexplored (particularly in females) because studies often lack the longitudinal design to appropriately test such models. In the present study, mediation analyses revealed that adolescent EF abilities partially mediated associations between childhood ADHD symptoms (both inattention and hyperactive-impulsive) and young adult reading and math achievement. The present findings are consistent with work by Thorell (2007), who found that EF abilities act as a mediator between inattention and both language skills and mathematics in a community sample of kindergartener. They also expand on this work by finding similar associations when examining hyperactive-impulsive symptoms. Such findings indicate that EF abilities may act as one pathway to the development of lower academic achievement in individuals with significant symptoms of ADHD, suggesting the importance of considering EF abilities as potential treatment targets. However, because adolescent EF did not fully mediate such associations, these findings also suggest that these skills are not independently essential to these pathways, that other mediators likely also play a role, and that ADHD symptoms continue to have a direct effect on outcomes even after EF abilities are taken into account. Overall, children who have significant symptoms of inattention and/or hyperactivity-impulsivity (e.g., children with ADHD) and also have impairments in EF may be at especially high risk of academic failure, as both symptom domains and EF abilities made independent contributions to academic achievement in young adulthood.

It is of interest that adolescent EF did not mediate associations between childhood ADHD symptoms and young adult outcomes in any domain other than those related to academic achievement. Whereas both childhood ADHD symptoms and adolescent EF abilities were often independently related to young adult outcomes in the present investigation, difficulties in effortfully guiding behavior toward a goal in adolescence do not appear to be the path by which ADHD symptoms impact non-academic young adult outcomes (i.e., social functioning, global functioning, substance use severity, suicide/self-injury). Rather, it seems that EF abilities mediated associations between symptoms and outcomes that were cognitive in nature (i.e., academic achievement). Further work examining other potential adolescent mediators of the associations between ADHD symptoms and outcomes is warranted, along with future work examining EF abilities as mediators of such outcomes during earlier developmental periods and with more frequent assessments.

Although few studies have prospectively followed large samples of females with ADHD, the present growth curve findings are generally consistent with cross-sectional studies of individuals with ADHD that demonstrate consistent impairments across development (e.g., Biederman et al., 2007; Hinshaw et al., 2002; Hinshaw et al., 2007; Miller et al., 2012a; Nigg et al., 2002; Seidman et al., 2006), but they extend these findings by using a longitudinal design in
order to examine trajectories and by focusing on the understudied population of females with childhood-diagnosed ADHD. Additionally, the current results from mediation analyses are in line with other studies that have focused on community samples of boys and girls (Thorell, 2007). These findings converge to highlight the importance of understanding the development of EF abilities in ADHD and how they contribute to outcomes in individuals who have or are at risk for developing ADHD. A continued focus on the female ADHD phenotype and its developmental course across various symptom and functioning domains is of great importance, given potential unique risks for this group (Hinshaw & Blachman, 2005; Hinshaw et al., 2011; Rucklidge, 2010). Future work should focus on (a) continuing to examine predictors and mediators of outcomes in longitudinal designs with more frequent assessments, (b) evaluating differences in patterns of change between various EF abilities in those with and without ADHD, (c) determining how developmental trajectories of EF abilities relate to changes in dimensional measures of ADHD symptoms over time, (d) performing brain imaging work that focuses on ADHD in females and sex differences, and (e) refining ADHD subtypes and developing valid diagnostic criteria for ADHD in adulthood.

Limitations of this study include that the sample was clinically-ascertained, and it is not clear whether our results would be similar in a community sample of females with ADHD. Additionally, because the sample is entirely female, comparisons between sexes are impossible. Investigations of sex differences in this population are warranted in future research. Although the retention rates for both the adolescent and young adult follow-up assessments were very high, home visits, equipment failure, and missed tests for some participants reduced the amount of neuropsychological data available at both the adolescent and young adult follow-up. Other limitations center on the construct EF itself, particularly in terms of conceptual issues surrounding the definition of EF, having important implications for the selection of measures and interpretation of findings. Finally, the lack of developmentally appropriate diagnostic criteria for adults with ADHD may mask differences that would be present if valid adult-specific diagnostic criteria were available.

Overall, the present investigation (1) enhances our understanding of the development of EF abilities in females with ADHD, (2) provides insight into the female ADHD phenotype, and (3) clarifies potential mechanisms underlying outcomes. The growth curve modeling analyses provide important information regarding the developmental course of EF in a female sample and suggest that females with ADHD show variability in improvement of EF abilities over time, with greater improvement than comparisons on some measures and less improvement on others. Additionally, these findings suggest that change in EF does not appear to be associated with change in ADHD status. The present findings highlight the potential importance of EF abilities as a target for future treatment development efforts by showing that EF abilities may be one mechanism by which ADHD symptoms lead to impairments in academic achievement. Future treatment development efforts may do well to incorporate interventions that target EF abilities in order to assess whether such interventions impact the course of ADHD symptoms and prevent the development of later academic difficulties.
References


and Allied Disciplines, 46, 824-836.


Table 1. Means and SDs of neuropsychological variables at each time point by baseline diagnostic status.

<table>
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ADHD = Attention-Deficit/Hyperactivity Disorder; ROCF = Rey-Osterrieth Complex Figure; TCFT = Taylor Complex Figure; CPT = Continuous Performance Task, CUL = Cancel Underline.
Fig. 1a

\[ y = 0.2918 + (-0.0591 \times \text{time}) \]

Fig. 1b

\[ y = 8.57 + (-3.11 \times \text{time}) \]
Fig. 1c

\[ y = 55.44 - (11.23 \times \text{time}) \]

Fig. 1d

\[ y = 4.61 + (0.9188 \times \text{time}) \]
Figures 1a-1e. Unconditional growth curves for the five EF variables. Time 0 = childhood (intercept); Time 1 = adolescence, Time 2 = young adulthood; ROCF = Rey-Osterrieth Complex Figure; TCFT = Taylor Complex Figure; CPT = Continuous Performance Task; CUL = Cancel Underline.
Figures 2a-2d. Estimated growth curves for EF variables with significant unconditional models, including baseline diagnostic group (ADHD vs. comparison) as the predictor. The intercept for CUL was fixed. Time 0 = childhood (intercept), Time 1 = adolescence, Time 2 = young adulthood. ADHD = Attention-Deficit/Hyperactivity Disorder; ROCF = Rey-Osterrieth Complex Figure; TCFT = Taylor Complex Figure; CPT = Continuous Performance Task; CUL = Cancel Underline.
Figures 3a-3d. Estimated growth curves for EF variables with significant unconditional models, including baseline ADHD subtype as the predictor. The intercept for CUL was fixed. Time 0 = childhood (intercept), Time 1 = adolescence, Time 2 = young adulthood. ADHD-I = Attention-Deficit/Hyperactivity Disorder-Inattentive type; ADHD-C = Attention-Deficit/Hyperactivity Disorder-Combined type; ROCF = Rey-Osterrieth Complex Figure; TCFT = Taylor Complex Figure; CPT = Continuous Performance Task; CUL = Cancel Underline.
Figures 4a-4d. Estimated growth curves for EF variables with significant unconditional models, including persistent vs. remitted ADHD status as the predictor. The intercept for CUL was fixed. Time 0 = childhood (intercept), Time 1 = adolescence, Time 2 = young adulthood. ADHD = Attention-Deficit/Hyperactivity Disorder; ROCF = Rey-Osterrieth Complex Figure; TCFT = Taylor Complex Figure; CPT = Continuous Performance Task; CUL = Cancel Underline.
Figures 3a-3b. Models of the significant relationships between childhood inattention symptoms, adolescent executive function (EF), and young adult academic achievement scores. Numbers are standardized beat coefficients. Standardized coefficients after the slash indicate weight after inclusion of the mediator (adolescent EF).

* $p < .05$
** $p < .01$
*** $p < .001$
Figures 3c-3d. Models of the significant relationships between childhood hyperactive-impulsive symptoms, adolescent executive function (EF), and young adult academic achievement scores. Numbers are standardized beat coefficients. Standardized coefficients after the slash indicate weight after inclusion of the mediator (adolescent EF).

* $p < .05$
** $p < .01$
*** $p < .001$