Clinical, sociobiological, and cognitive predictors of ADHD persistence in children followed prospectively over time.

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Tara McAuley, Ph.D.
Department of Psychology, Centre for Mental Health Research
University of Waterloo
Jennifer Crosbie, Ph.D., Alice Charach, M.D., & Russell Schachar, M.D.
Department of Psychiatry Research
Hospital for Sick Children

Corresponding author: Tara McAuley, Department of Psychology, University of Waterloo, 200 University Ave West, Waterloo, Ontario, Canada N2L 3G1. E-mail: tara.mcauley@uwaterloo.ca. Phone: 519-888-4567 x31343. Fax: 519-746-8631.

Other author information: Jennifer Crosbie, Alice Charach, & Russell Schachar, Department of Psychiatry Research, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail: jennifer.crosbie@sickkids.ca, alice.charach@sickkids.ca, russell.schachar@sickkids.ca. Phone: 416-813-6564. Fax: 416-813-6565.

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Abstract

With increasing awareness that ADHD is chronically disabling, a burgeoning literature has examined childhood clinical indicators of ADHD persistence. This study investigates whether childhood factors reflecting biological risk and cognitive reserve have additive predictive value for the persistence of ADHD that is unique beyond childhood indicators of disorder severity. One-hundred thirty children with ADHD (mean age = 8.9 years, 75% male) were followed into adolescence (mean age = 14.0 years). Childhood ADHD and co-morbidities were assessed via interviews with parents and teachers; parental psychopathology was assessed via parent interview; exposure to neurobiological and psychosocial adversity were indexed by parent questionnaire; and cognitive reserve was evaluated through children's performance on measures of IQ and executive functioning. Univariate analyses identified childhood inattention and hyperactivity-impulsivity, co-morbid oppositional defiant disorder, overall impairment, and paternal anxiety and depression as more prevalent amongst adolescents with persistent compared with remitted ADHD. Only child-level predictors remained significant in a final multivariate model. These results suggest that children who are most likely to experience persistent ADHD have a more severe clinical presentation in childhood, reflected by increased levels of inattention, oppositional behavior, and impairment. They also are more likely to have fathers with internalizing concerns, but these concerns do not uniquely predict ADHD persistence beyond child-level factors. Contrary to expectations, childhood adversity and cognitive functioning did not predict the course of ADHD.
Clinical, sociobiological, and cognitive predictors of ADHD persistence in children followed prospectively over time

What do we know about the persistence of ADHD? Over the past several decades of study, we have come to understand that relatively few of the 5% of children who are diagnosed with ADHD meet strict diagnostic criteria for the disorder later in development; however, 70% continue to exhibit impairing traits in adolescence and 40 to 60% do so in adulthood (Faraone, Biederman, & Mick, 2006; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Though we have become increasingly aware that ADHD is a chronically disabling condition, we remain limited in our knowledge of childhood factors that predict the course of this disorder. Filling this knowledge gap is important, as it may elucidate pathophysiological mechanisms involved in the persistence of ADHD and facilitate clinical decision-making regarding the early identification and targeted intervention of ADHD children.

To date, the most oft-studied predictors of ADHD persistence have been clinical indicators of disorder severity. Children are more likely to experience persistence of ADHD if they initially present with a greater number of ADHD symptoms and more overall impairment, and if they have co-occurring oppositional and delinquent behavior and, to a lesser extent, anxiety and low mood (Hart et al. 1995; Kessler et al 2005; Biederman et al. 1996; Biederman et al. 2011; Hurtig et al. 2007; Lara et al. 2009; Mick et al. 2011). Familial factors also have been implicated in the persistence of ADHD, including parental history of the disorder and other clinical concerns, which may reflect a stronger genetic loading for ADHD in an affected child and/or point to a home environment characterized by less adept parenting, higher levels of familial conflict, and less routine/structure (Biederman et al. 1996; Faraone, Biederman, &

Comparatively little is known regarding the extent that other factors may predict ADHD persistence; however, the risk/reserve framework was initially formulated by neuropsychologists to account for heterogeneity in the onset of clinical symptoms following known or presumed brain insult and may be extended to examine inter-individual variation in the persistence of clinical symptoms that have already emerged (e.g., Dennis, Spiegler, & Hetherington, 2000; Satz, 1993). In this framework, biological risk refers to the amount of CNS plasticity that is available to promote adaptive change in response to events that may be normative or atypical in nature (e.g., acquisition of developmental milestones, incurring a traumatic brain injury), whereas cognitive reserve refers to compensatory mental resources – such as general intelligence and more specific problem-solving skills – that are shaped by one’s natural endowment, education, and extant life experience (Dennis et al., 2000). Biological risk and cognitive reserve are broad constructs that tend to be examined individually vis-a-vis neurobehavioral outcome, often using proxies consisting of formative and reflective measures of brain structure and function, respectively. Because an incredible range of factors may be evaluated as possible prognostic indicators of ADHD persistence, not all of which are feasible to include in a single study, we suggest that the risk/reserve framework provides a necessary theoretical impetus for the selection of childhood variables that may account for heterogeneity in the ontogenesis of ADHD above and beyond a child’s initial clinical presentation.

Several putative indicators of biological risk are more prevalent amongst ADHD children compared with their typically developing peers. Their mothers, for example, are more likely to have endured extreme emotional stress during pregnancy, smoked nicotine, consumed alcohol,
and/or used illicit substances whilst pregnant, and experienced medical complications around the time of their child’s birth (Sprich-Buckminster, Biederman, Milberger, Faraone, & Lehman, 1993; Thapar, Cooper, Eyre, & Langley, 2013). The families of these children also tend to be characterized by higher levels of conflict, financial hardship, and stressful life events – each of which increase the occurrence of ADHD in childhood and, when aggregated, do so in a dose-dependent manner (Biederman et al 1995; Scahill et al. 1999). Neurobiological and psychosocial adversities have known brain correlates (e.g., Charil, Laplante, Vaillancourt, & King, 2010; Roussotte, Soderberg, & Sowell, 2010; Gunnar & Quevedo, 2007) and are well-established risk factors for childhood ADHD, yet few studies have examined their potential role in predicting persistence of the disorder.

Childhood ADHD also has well-established cognitive correlates. Overall cognitive capacity is lower in children with ADHD compared with their typically developing peers (Frazier, Demaree, & Youngstrom, 2004) – though IQ has not predicted ADHD persistence in individuals followed over time (Biederman et al. 1996; Hart et al. 1995; Mick et al. 2011). Executive functioning (EF) refers to a more circumscribed set of cognitive skills that promote purposeful, goal-oriented behavior, including the maintenance of goal-relevant information (working memory; Baddeley 1992), suppression of prepotent but goal-inappropriate actions (response inhibition; Harnishfeger 1995; Nigg 2000), and ability to maintain consistent levels of performance during goal acquisition (response variability: Schmiedek, Oberauer, Wilhelm, Süß, & Wittmann, 2007; West, Murphy, Armilio, Craik, & Stuss, 2002). Deficits in these aspects of EF are evident in ADHD (Kofler et al. 2013; Lipszyc & Schachar 2010; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), may be influenced by drugs used to alleviate ADHD symptoms (Swanson, Baler, & Volkow, 2011), are supported by neural networks that have been
implicated in ADHD (Krain & Castellanos 2006), and are related to genetic risk for the disorder (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010). Some evidence suggests that adult levels of EF may be worse in individuals with persistent compared with remitted ADHD (Bedard, Trampush, Newcorn, & Halperin, 2010; Halperin, Trampush, Miller, Marks, & Newcorn, 2008), though other evidence has demonstrated that these groups evidence comparable rates of change in EF over time (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014; McAuley, Crosbie, Charach, & Schachar, 2014). As noted in a recent review of this literature (van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013), the extent that individual differences in childhood EF predict the persistence of ADHD has been examined in few studies and thus remains relatively unknown.

In sum, most attempts at identifying predictors of ADHD persistence have focused on childhood indicators of disorder severity. Few studies have examined the predictive power of biological risk, fewer have examined cognitive reserve, and almost none have examined risk and reserve together in conjunction with other childhood factors. The simultaneous examination of multiple factors is essential if they are likely to be correlated, which permits elucidation of their relative importance vis-à-vis outcome, and to develop a more comprehensive prediction model than can be derived from any one factor examined in isolation. As such, the aim of our study was to simultaneously explore a wide range of childhood factors in relation to the persistence of ADHD. Our sample consisted of rigorously diagnosed children with ADHD who were followed into adolescence. We included childhood clinical measures to replicate previous findings regarding the association of core symptoms and clinical correlates of ADHD to remission status. To extend these findings, we also drew upon the constructs of biological risk and cognitive reserve to examine whether other childhood measures that have been associated with the
emergence of ADHD added incremental predictive validity to our baseline armamentarium. Compared with adolescents who remitted from ADHD, we hypothesized that adolescents with persistent ADHD would (1) present with more ADHD symptoms and impairment as children, (2) have more co-morbid mental-health concerns in childhood (particularly oppositional behavior) and, somewhat more guardedly, a stronger parental history of ADHD and other psychopathologies (especially depression), and (3) be exposed to more neurobiological and psychosocial adversity in childhood and evidence lower levels of EF as children. Because little research has examined the prognostic utility of these latter childhood factors in relation to ADHD persistence, the last set of hypotheses were necessarily speculative.

Method

Participants

Our ascertainment procedure is depicted in Figure 1. Children were recruited from an outpatient clinic for youth with attention, learning, and/or behavioural difficulties. ADHD was diagnosed when a child exhibited six or more impairing symptoms of inattention or hyperactivity-impulsivity per the report of either the parent or teacher and, to ensure pervasiveness across settings, 4 or more impairing symptoms of inattention or hyperactivity-impulsivity per the report of the other informant. At baseline, our sample included 323 children diagnosed with ADHD who did not also have a diagnosis of a pervasive developmental disorder or evidence of psychosis, history of traumatic brain injury with loss of consciousness, uncorrected hearing or visual impairment, low intellectual function (i.e., verbal and performance IQ below 80), and treatment with a medication that could not ethically be withdrawn within 24 hours of testing. One hundred seventy-one of these families were contacted approximately 5 years after baseline, at which point 138 were re-assessed and 41 declined re-assessment. One
hundred forty-four families did not respond to our call or were lost to follow-up. Compared with children who were not re-assessed, re-assessed children had more baseline inattention, \( t(176) = -1.95, d = -.30, p = .05 \), and impairment, \( t(176) = -2.50, d = -.30, p = .02 \), but were comparable on other clinical and demographic variables (\( ps > .10 \)). Within our sample of children with ADHD who were followed into adolescence, 25% were primarily inattentive in childhood, 17% were primarily hyperactive-impulsive, and 58% were combined.

As described in our previous work (McAuley et al., 2014), adolescents were categorized into one of four diagnostic groups at follow-up based on symptoms and impairment associated with ADHD. A symptom was considered to be present if it was endorsed by the parent or adolescent at a clinically significant threshold (based on frequency, intensity, and developmental atypicality – for example, an adolescent who often left classes to wander the hallways of his school because he was not able to remain seated during lessons). Impairment was assessed by the clinician. Of the 130 adolescents who were re-assessed, 64 continued to meet full DSM-IV diagnostic criteria for ADHD and were considered to be fully persistent for the disorder, 22 had threshold symptoms but remitted impairment, 20 had remitted symptoms but continued to be impaired, and 24 were considered to be fully remitted from the disorder. Childhood characteristics of the adolescent groups are presented in Table 1.

[Insert Figure 1 and Table 1]

Procedure

Details of the protocol have appeared elsewhere and will be reviewed only briefly (e.g., McAuley et al., 2014). Informed consent was initially obtained from the child and his/her parent. The child then underwent intellectual, academic, and cognitive testing and completed self-report questionnaires. At the same time, the parent completed a clinical interview with a well-trained
individual who had an advanced degree in developmental psychopathology (e.g., MD, PhD clinical psychologist, MSW). The child’s teacher was interviewed separately by phone. The follow-up protocol was conceptually similar, except that information regarding mental health was obtained from both the parent and adolescent, the parent provided information about the adolescent’s treatment history, teachers were not interviewed, and intellectual and academic tests were not re-administered. Ethics approval was granted by the Research Ethics Board at the Hospital for Sick Children in Toronto, Canada.

Measures

Clinical Evaluation of Child/Adolescent. Baseline information regarding children’s mental health was obtained from parents using the Parent Interview for Child Symptoms (PICS: Ickowicz et al., 2006) and from teachers using the Teacher Telephone Interview (TTI: Tannock, Hum, Masellis, Humphries, & Schachar, 2002), which cover DSM-IV criteria for ADHD, Conduct Disorder, and Oppositional Defiant Disorder. The PICS also covers DSM-IV criteria for other Axis-I disorders, which are screened by the TTI. Comparable clinical information was obtained from adolescents and parents at follow-up using the Kiddie-Sads-Present and Lifetime Version (KSADS-PL: Kaufman et al., 1997). Symptoms of inattention and hyperactivity-impulsivity were calculated at baseline and follow-up using criteria described above. At both time points, impairment was determined by the clinician using the Children’s Global Assessment Scale (CGAS: Shaffer et al., 1983). Scores range from 1 (most impaired) to 100 (least impaired), with a cutoff below 60 considered to be indicative of clinically significant impairment (Bird et al., 1990). The Services for Children and Adolescents – Parent Interview (SCAPI: Jensen et al., 2004) was administered at follow-up to obtain information regarding mental-health services accessed by the adolescent and his/her family, including use of medication, educational
interventions, and psychosocial treatment. All of these clinical tools are well-validated and have established psychometric properties – including high inter-rater agreement (e.g., ICC or $\kappa > .80$: Hoagwood et al., 2004; Ickowicz et al. 2006; Kaufman et al., 1997; Shaffer et al., 1983; Tannock et al., 2002). Diagnoses at baseline and at follow-up were based on DSM-IV diagnostic criteria (American Psychiatric Association, 1994) and were made by a child psychiatrist and/or clinical psychologist per information obtained in the clinical interviews, as described above, as well as behavioral observations of child/adolescent during the assessment. Diagnoses were scored as 0 (absent) or 1 (present).

Clinical Evaluation of Parent. Information regarding family mental-health was obtained using an in-house clinical interview that was conducted by a PhD-level clinical psychologist with the child’s parent. The parent was asked questions about Axis-I concerns per diagnostic criteria in DSM-IV (American Psychiatric Association, 1994) in each of the child’s first degree relatives. Parents were considered to have a probable history of ADHD when they provided clear evidence of inattentive and/or hyperactive-impulsive symptoms and associated impairment (e.g., school-related difficulties, peer problems) in their childhood. Paternal and maternal history of ADHD were coded as 0 (absent) or 1 (present). Other parental mental-health concerns were coded in a similar manner.

Childhood Adversity. Childhood adversity was assessed using the Family and Household Form from the Ontario Child Health Study, which was developed in collaboration with Statistics Canada to examine the health and well-being of Ontario’s children (OCHS; Boyle et al., 1987). The Family and Household Form is one component of the larger survey and consists of 59 items that are completed by the child’s parent/guardian. Neurobiological risk factors included having a mother who experienced prenatal and/or delivery complications (e.g., severe nausea, planned or
emergency c-section), was perceived to have endured extreme emotional stress during pregnancy, smoked or used drugs/alcohol whilst pregnant, and had a child with low birth weight (< 5.5 lbs). Psychosocial risk factors included characteristics of the family (e.g., single parent household, parent with less than a high school education, parent with long-term medical condition), family conflict (e.g., yelling and/or physical fighting amongst parents, spanking or other physical discipline of child), housing problems (e.g., subsidized housing, overcrowded housing), and the occurrence of stressful events in the past year (e.g., loss of job, self-perceived financial problems). Responses to each question were scored as 0 (absent) or 1 (present) and summed to create separate indices of neurobiological and psychosocial adversity, which each demonstrated acceptable internal consistency (α = .88 and .79 in our sample, respectively).

*Childhood Intellectual Functioning.* Intellectual functioning was assessed using the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III; Wechsler, 1991). For each subtest, raw scores were converted into T scores using normative data from same-age children and were summed to compute a Full Scale IQ (α = .86 in our sample).

*Childhood Working Memory.* Verbal and spatial working memory were assessed using the digit span and spatial span tasks from the WISC-III (Wechsler, 1991) and WISC-III PI (Kaplan, Fein, Kramer, Delis, & Moris, 1999), respectively. In both tasks, children recalled orally presented numbers or locations on a block board in serial order (forward condition) and reverse order (backward condition). In both conditions, presentation began with two items and increased by 1 until both trials at a given level of difficulty were incorrectly recalled. Total raw score in the backward conditions of the tasks served as an index of verbal/spatial working memory. The digit span and spatial span tasks had acceptable internal consistency (α = .85 and .76 in our sample, respectively).
**Childhood Inhibition and Response Variability.** Inhibition and response variability were assessed using the stop signal task (Logan & Cowan, 1984). In this task, children made speeded keypress responses to Xs and Os that appeared at a central location on a computer screen. On 25% of trials, appearance of the letter was followed by an auditory tone that signaled children to inhibit their response. Timing of the tone was determined using a dynamic tracking algorithm, such that children were able to inhibit their response on approximately 50% of trials. Reaction times (RTs) were measured in milliseconds. Variability in the average latency to respond to letters (GoRTSD; \( \alpha = .78 \) in our sample) served as an index of response variability. Stop signal reaction time, calculated as the difference between the mean delay of the stop signal and the average latency to respond to the letters (SSRT; \( \alpha = .89 \) in our sample), served as an index of response inhibition.

**Analytic Approach**

Clinical data were missing from 8 family history interviews, 2 OCHS questionnaires, and 2 CGAS evaluations. Cognitive data were missing from 10 children on the stop signal task (due to invalid data), 18 on digit span (due to recent administration of the WISC), and 28 on spatial span (which was added to the baseline battery after their enrollment). Missing data were not associated with any observed variables in the dataset and were assumed to be missing at random (i.e., not related to the underlying measure). Replacement of missing values was conducted with multiple imputation (SPSS version 22.0).

Multinomial logistic regression analyses were used to determine whether childhood measures differentiated amongst the four adolescent groups that were created based on remission status at follow-up (i.e., fully remitted, remitted symptoms, remitted impairment, persistent). Given the number of predictors we sought to examine relative to our sample size, we followed established guidelines for model fitting using a build-up procedure (Hosmer & Lemeshow,
This procedure entailed running univariate analyses in which continuous and categorical predictors were individually examined, creating a multivariate model using predictors that demonstrated a relaxed statistical threshold of \( p < .10 \), eliminating predictors from the multivariate model that were not significant based on inspection of the Wald statistic, re-running this refined model with excluded predictors from the univariate analyses added one at a time to determine whether any made a significant contribution to clinical outcome in the presence of other variables, and lastly checking the assumption of linearity for continuous predictors in the final model. The final multivariate model enabled us to determine which childhood variables uniquely contributed to ADHD remission status at adolescent follow-up. In all analyses, adolescents with remitted ADHD served as the group against which the other 3 were compared.

Because our study entailed a secondary analysis of data that were already collected, we conducted a sensitivity analysis to ascertain the effect size that was detectable using our statistical approach given a sample size of 130 youth, significance level of .05, and desired statistical power of .80 (G*Power version 3.1.9.2: Faul, Erdfelder, Lang, & Buchner, 2007). Results indicated that our analyses were capable of detecting effects that were at least moderately sized for continuous and categorical predictors examined individually and in tandem, the latter of which assumes a low association amongst predictors in the model (\( R^2 = .10 \)).

Results

There was no significant effect of parental history of ADHD, childhood adversity, or childhood cognitive functioning on remission status at follow-up (\( ps > .10 \)). Omnibus model fit was significant or approached significance for inattentive and hyperactive-impulsive symptoms (\( p = .014 \) and .104, respectively), co-morbid ODD (\( p = .058 \)), overall impairment (\( p < .001 \)), lifetime medication use (\( p < .001 \)), as well as paternal anxiety and depression (\( p = .092 \) and .048,
respectively). In the final model, all of these predictors remained significant or approached significance with the exception of childhood hyperactivity-impulsivity and paternal psychopathology (ps >.10). These results indicate that adolescents who remitted from ADHD had a different childhood profile than adolescents who did not remit from the disorder: as children, they had fewer inattentive symptoms than adolescents who were fully persistent or who had remitted impairment (OR = 1.62, p = .015 and OR = 1.46, p = .089, respectively), less co-morbid ODD than adolescents who were fully persistent (OR = .23, p = .018), and were less impaired than adolescents who were fully persistent or who had remitted symptoms (OR = .92, p = .015 and OR = .91, p = .03 respectively). Neither sex nor age at diagnosis moderated the relationship between variables in the final model and adolescent remission status (ps > .10). Results are presented in Table 2.

[Insert Table 2]

Discussion

With increasing awareness that ADHD is chronically disabling for most diagnosed children, a burgeoning literature has examined the prevalence and correlates of persistent ADHD. The first objective of our study was to replicate findings regarding the predictive role of ADHD severity vis-à-vis persistence of the disorder. Consistent with our hypothesis, ADHD status in adolescence was predicted by clinical features of the disorder in childhood: when

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1 Because paternal anxiety and depression were moderately correlated (r = .54), we re-ran multivariate models including one and not the other. Doing so revealed a unique effect of paternal depression (p = .051). Further exploratory analyses also revealed a significant interaction between paternal depression and childhood ODD (p = .001).
compared with adolescents in the remitted comparison group, adolescents who exhibited persistence of inattention and/or impairment also exhibited higher levels of these traits in childhood. Considered as a function of baseline symptomatology, 18% of children with all 9 inattentive symptoms compared with 58% of children with 5 or fewer inattentive symptoms exhibited below-threshold inattention at adolescent follow-up. Similarly, 20% of the most impaired children (i.e., CGAS < 41) compared with 40% of more moderately impaired children (i.e., CGAS = 51 to 60) exhibited minimal to no impairment at adolescent follow-up (i.e., CGAS > 60). These findings suggest that it is the children who are most adversely affected by ADHD who are most likely to persist over time – perhaps because they must experience more change relative to their less affected peers in order to ‘outgrow’ the disorder. Compared with adolescents who remitted from ADHD, it also is worth noting that adolescents in each of the other subgroups were more likely to have had some experience with the use of medication for treatment of ADHD by the time of follow-up, though we lacked detailed information regarding access to other supportive services such as educational interventions and psychosocial treatments.

ADHD symptoms and overall impairment have emerged as the most robust predictors of remission status, but specific findings have varied across studies and hint at possible moderators of this association. For example, longitudinal studies have found that the 4-year persistence of ADHD is predicted by initial levels of inattention and impairment in males and by hyperactivity-impulsivity in females (Biederman et al., 1996; Mick et al., 2011).² At an 11-year follow-up,

²A 4-year follow-up of ADHD boys found that childhood hyperactivity-impulsivity and conduct disorder (CD) predicted ADHD persistence; however, these boys were recruited due to their
baseline impairment (but not inattention) continues to differentiate males with persistent and remitted ADHD but neither ADHD symptoms nor impairment predict remission status in females (Biederman et al., 2011; Biederman et al., 2012). These findings suggest that age and gender may moderate the association between a child’s initial clinical presentation and the course of the disorder. Though our pattern of results did not vary with age or gender, the narrow age range of our participants and relatively small number of females in our sample may have rendered such comparisons underpowered. Future studies may seek to elucidate non-additive effects of these demographic characteristics in relation to childhood predictors of ADHD persistence by oversampling females who receive an ADHD diagnosis and recruiting males and females with ADHD across a broad age range.

The second objective of our study was to explore whether other aspects of a child’s clinical presentation were related to adolescent remission status. Consistent with our hypothesis, adolescents with persistent ADHD were more likely than adolescents with remitted ADHD to have co-morbid ODD as children – though this was demonstrated only in adolescents in the fully persistent subgroup and not in adolescents who had either persistent ADHD symptoms or persistent impairment but not both. Childhood ODD has conferred risk for ADHD persistence in other longitudinal studies, though generally in males – and not females – who have been diagnosed with ADHD and followed over time (Biederman et al., 1996; Biederman et al., 2011; Mick et al., 2011; Biederman et al., 2012). A clear explanation of this association is currently lacking. However, compared with ADHD children who do not have clinically significant highly disruptive behavior and evidenced high rates of co-morbid CD, thus may not be representative of boys with ADHD more generally (Hart et al. 1995).
behavioral concerns, children who have both ADHD and ODD may have a distinct genetic etiology for ADHD, more disrupted neurodevelopment, more dysfunctional parent-child interactions, and/or more impairments in other domains of functioning – any of which may have implications for ADHD persistence. These ideas are speculative and require further research. There have also been indications that ADHD persistence is more common in the context of co-morbid anxiety and depression; however, these findings should be interpreted cautiously given the use of retrospective self-report to assess childhood mental-health concerns (Hurtig et al., 2007; Lara et al., 2009) and relatively large number of psychiatric referrals in these samples (e.g., Biederman et al., 1996; Biederman et al., 2011). Aside from ODD, no other childhood diagnoses predicted remission status in our adolescents.

Related to our second objective, parental history of ADHD was examined because of its high heritability (Thapar, Langley, Owen, & O’Donovan, 2007) and possible implications for a child’s genetic risk and/or home environment (Biederman et al., 1996; Faraone et al., 2000). Whilst roughly half of our children had a positive history of ADHD in a parent, parental history of ADHD did not differentiate children who did and did not remit from the disorder. Similar null results have been reported elsewhere (see below), though there have been exceptions. One longitudinal study found that males with persistent ADHD were somewhat more likely than males with remitted ADHD to have a parent with a positive ADHD history as determined by clinical interview (Biederman et al., 1996), but this trend-level finding did not approach significance at longer follow-ups (Biederman et al., 2010) and was not replicated in females.

3 Given that mood difficulties can present as irritability, we re-ran our analyses controlling for scores on the Children’s Depression Inventory. ODD remained a predictor of ADHD persistence.
Predictors of ADHD persistence

(Mick et al., 2005). Parental attention difficulties on an ADHD rating scale did predict ADHD persistence in an epidemiological study of adolescents (Hurtig et al., 2007); however, it is uncertain whether these difficulties occurred in the context of ADHD given that attention problems are featured in other psychological disorders (e.g., depression). Clarity regarding the predictive role of parental ADHD could be achieved in future studies via comprehensive clinical interviews (rather than ADHD-specific rating scales) that are conducted with both parents, when possible, who report upon their own symptomatology and that of their partner. This approach would facilitate differential diagnoses – thereby increasing confidence that ADHD symptoms are occurring in the context of ADHD proper, and would permit the synthesis of multi-informant ratings of ADHD symptomatology in either parent, thereby increasing the reliability of this information.

Parental anxiety and depression were two additional parent-level factors selected for inclusion in our study. Consistent with our hypothesis, adolescents with persistent ADHD were more likely to have a parent (namely fathers) with concerns related to anxiety and depression compared with adolescents who remitted from ADHD. The predictive role of parental psychopathology has been supported in previous work demonstrating an increased likelihood of ADHD persistence (most notably in males) in the context of familial mood-related difficulties, paternal internalizing concerns, and antisocial personality traits in either parent (Biederman et al., 1996; Biederman et al., 2010; Lara et al., 2009). These findings, and those of our univariate analyses, suggest that children are less likely to remit from ADHD when they have fathers or other close family members with mental-health problems, particularly depression. In light of our aforementioned finding that adolescents with persistent ADHD had the highest rate of co-morbid ODD in childhood, it is worth noting that parental depression is known to exert a deleterious
impact on the development of ADHD children – especially those with oppositional behavior (Johnston & Mash, 2001). Our post-hoc finding of a significant interaction between paternal depression and childhood ODD vis-à-vis ADHD persistence is one that hints at parent-child dynamics as potentially playing an important role in ADHD outcomes – a speculation supported by longitudinal work indicating that change in ADHD symptomatology is mediated by non-shared environmental influences that remain unspecified (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005; Larsson, Larsson, & Lichtenstein, 2004). This speculation also requires further empirical study.

The final objective of our study was to determine whether childhood indicators of biological risk and cognitive reserve predicted ADHD remission above and beyond a child’s initial clinical presentation. Early exposure to neurobiological and psychosocial adversity have been implicated in a wide range of children’s mental-health concerns, including ADHD (Blanz, Schmidt, & Esser, 1991; Rutter, Cox, Tupling, Berger, & Yule, 1975; Taylor & Rogers, 2005). Given that adverse clinical outcomes are more prevalent in the context of increased biological risk (e.g., Brown et al., 2008; Thompson et al., 1994), we speculated that childhood exposure to neurobiological and psychosocial adversity would differentiate ADHD children who did and did not remit from the disorder. Contrary to our hypothesis, individual differences in these aspects of childhood adversity did not predict adolescent remission status. Other studies examining the predictive role of overall risk aggregates and individual risk indicators have also produced mostly null results (Biederman et al., 1996; Biederman et al., 2011; Kessler et al., 2005; Lara et al., 2009; Mick et al., 2011) – with the exception of parental psychopathology described above. Of note, we are not aware of any studies that have explored the possibility of a non-monotonic relationship between early adversity and the course of ADHD, perhaps owing to the relatively
low levels of adversity exposure in many samples (including that of our own). To explore the idea that ADHD persistence is more likely to occur in the context of high childhood adversity, future studies may consider examining the persistence of ADHD in individuals for whom childhood adversity is high. This could include children with in utero exposure to teratogens, congenital brain abnormalities or brain issues acquired early in life, trauma histories, and/or impoverished socioeconomic backgrounds. Examining the interaction of neurobiological and psychosocial adversity could also be informative, as they tend to be correlated in higher risk populations and are thought to predict a broad range of health-related outcomes in children (e.g., Bradley & Corwyn, 2002).

Regarding childhood cognitive function, we were particularly interested in the predictive role of childhood EF. Previous work has demonstrated that adult-levels of EF are better in individuals with remitted compared with persistent ADHD, leading to the suggestion that individual differences in EF may confer a strategic advantage that enables some children to outgrow the disorder (Bedard et al., 2010; Halperin et al., 2008). Subsequent work has shown that individuals with remitted and persistent ADHD evidence comparable rates of change in EF over time (Coghill et al., 2014; McAuley et al., 2014); however, the association between childhood EF and ADHD persistence has been largely unexamined (van Lieshout et al., 2013). Interestingly, longitudinal work with non-clinical samples has demonstrated that childhood EF predicts externalizing concerns that emerge later in development, including ADHD, even when EF is assessed as early as the preschool years (Berlin, Bohlin, & Rydell, 2003; Riggs, Blair, & Greenberg, 2004; Thorell & Wahlstedt, 2006). By extension, we speculated that individual differences in childhood EF would predict ADHD remission status, such that performance on baseline measures of working memory, response inhibition, and response variability would be
better amongst adolescents who remitted from ADHD compared with those who experienced persistence of the disorder. Contrary to our prediction, there was no significant association between childhood EF and adolescent remission status. Given our use of performance-based measures of EF, in which a child’s EF is assessed directly via tasks administered in the lab, our null findings may not generalize to informant ratings of EF, which indicate how well a child applies his or her executive skills in the more naturalist context of everyday life (Toplak, West, & Stanovich, 2013). The inclusion of parent and/or teacher questionnaires that measure children’s EF in relation to ADHD persistence would be an interesting avenue for future studies.

In conclusion, ADHD is a persistently impairing condition associated with adversity in adulthood (Murphy & Barkley, 1996; Young, 2000). The ability to identify risk and resilience factors associated with the course of ADHD thus has important implications for the early intervention and long-term monitoring of ADHD children. Our results do not support the notion that childhood measures of biological risk and cognitive reserve play a predictive role in ADHD persistence; however, they do join others in suggesting that children are more likely to experience persistent ADHD when they present with more impairing ADHD symptoms, co-morbid ODD, and have fathers with anxiety and depression. Good clinical practice thus suggests that clinicians be alert not only to a child’s presenting level of ADHD symptomatology, but also explore potential co-morbid behavioural concerns in their initial assessment of the child and, when possible, solicit information pertaining to the psychological well-being of the child’s parents – as each of these factors may lead to an elevated risk of ADHD persistence amongst children who are diagnosed with this disorder as they transition into adolescence and adulthood.
The strengths of our study include having a relatively large and representative sample of boys and girls with rigorously diagnosed ADHD, prospective follow-up of these children into adolescence, and the simultaneous inspection of different childhood measures that were inspired by a risk/reserve framework, which provides a compelling theoretical rationale for examining the myriad factors that may moderate changes in the expression of ADHD that occur over time. Our results should nonetheless be interpreted in the context of several limitations: our sample was not sufficiently large to permit powerful comparisons of age and gender subgroups or to detect effect sizes that were small in magnitude, low overall levels of childhood adversity precluded us from examining possible threshold effects, our performance-based measures of EF may not capture a child’s application of executive skills in naturalistic settings, and neither parenting skills nor parent-child interactions were directly assessed – though our results hint that they may be important to consider. In spite of these limitations, our study adds to a growing literature on childhood predictors of ADHD persistence, provides suggestions for examining additional predictors and moderating influences in future work, and will hopefully inspire this field to move toward the elucidation of underlying mechanisms that explain why certain childhood factors predict the long-term course of ADHD.
Compliance with Ethical Standards

This work received ethics approval from the Research Ethics Board at the Hospital for Sick Children. All procedures were in accordance with the ethical standards of this institutional committee and national research committees and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all participants in the study.
Acknowledgements

The authors extend their sincerest appreciation to the youth and families who have participated in clinical research studies of ADHD conducted by the Neuropsychiatry Clinic at the Hospital for Sick Children, as well as the dedication of support staff who have made this undertaking possible.
Conflicts of Interest

Tara McAuley has received an honorarium for a clinical trial involving Cogmed. Russell Schachar is a consultant for Highland Therapeutics, Purdue Pharma, Lilly Corp., and ehave and has equity in ehave. The other authors have no conflicts of interest to disclose.
References


Table 1. Baseline characteristics of ADHD children as a function of adolescent remission status.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Remittent (n = 24)</th>
<th>Remitted Impairment (n = 22)</th>
<th>Remitted Symptoms (n = 20)</th>
<th>Persistent (n = 64)</th>
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<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>n (%)</td>
<td>M (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Child Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>16 (73)</td>
<td>16 (80)</td>
<td>50 (78)</td>
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<td>14.10 (1.76)</td>
<td>13.73 (1.49)</td>
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Predictors of ADHD persistence

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<tr>
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<th>Mean (SD)</th>
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<td>Paternal Depression</td>
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<td>2 (9)</td>
<td>3 (15)</td>
<td>19 (30)</td>
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Table 2. Multinomial logistic regression analyses of childhood predictors of adolescent ADHD remission status.

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<th>Model $\chi^2$ (p-level)</th>
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Predictors of ADHD persistence

<table>
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<th>p</th>
<th>B</th>
<th>SE</th>
<th>t</th>
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**Final Multivariate Model**

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<td>-1.45</td>
<td>.23</td>
</tr>
</tbody>
</table>

Note: Fully remittent ADHD is the reference group.

**p < .001, *p < .05, ′p < .10}
Figure Caption

*Figure 1.* Ascertainment procedure for children diagnosed with ADHD and followed prospectively into adolescence.
Predictors of ADHD persistence

Baseline ADHD Sample
n = 323

Response to follow-up request?

- Reascertained
  n = 138*

- Declined
  n = 41

- No Answer
  n = 144

6 or more ADHD symptoms?

- Yes
  6 or more ADHD symptoms?
    - Yes
      Fully Persistent
      n = 64
    - No
      Remitted Impairment
      n = 22

- No
  CGAS below 60?
    - Yes
      Remitted Symptoms
      n = 20
    - No
      Remitted
      n = 24

*Eight participants did not complete interviews and so diagnostic status was not re-ascertained